A STUDY OF PROGESTERONE RECEPTOR (PR) EXPRESSION IN MENINGIOMA, AND ITS CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS

Dissertation submitted in

partial fulfilment of the requirements for the degree of

M.D. (PATHOLOGY)

BRANCH - III

INSTITUTE OF PATHOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

THE TAMIL NADU

DR. M.G.R. MEDICAL UNIVERSITY

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APRIL 2017

CERTIFICATE

This is to certify that this Dissertation entitled **"A STUDY OF PROGESTERONE RECEPTOR (PR) EXPRESSION IN MENINGIOMA, AND ITS CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS."** is the bonafide original work of **Dr.SHENBAGAM.J.M**, in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2017.

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DECLARATION

I, **Dr. SHENBAGAM.J.M,** solemnly declare that the dissertation titled "**A STUDY OF PROGESTERONE RECEPTOR (PR) EXPRESSION IN MENINGIOMA, AND ITS CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS"** is the bonafide work done by me at the Institute of pathology, Madras Medical College under the expert guidance and supervision of **PROF. DR.PAPPATHI.S, M.D (Pathology)., D.C.H**., Professor of Pathology, Institute of child health, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place: Chennai

Date: **Dr. SHENBAGAM.J.M**

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
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Dear Dr.Shenbagam J.M.

The Institutional Ethics Committee has considered your request and approved your study titled **"A study of progesterone receptor (PR) expression in meningioma and its correlation with clinicopathological parameters" No.29082015.**

The following members of Ethics Committee were present in the meeting held on 04.08.2015 conducted at Madras Medical College, Chennai-3.

1.	Prof.C.Rajendran, M.D.,	: Chairperson
2.	Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3.	Prof.Sudha Seshayyan, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4.	Prof.B.Vasanthi, M.D., Professor Pharmacology, MMC	: Member
5.	Prof.A.Rajendran, M.S., Professor, Inst.of Surgery, MMC	: Member
6.	Prof.Saraswathy, M.D., Director, Inst. Of Pathology, MMC	: Member
7.	Prof.Srinivasagalu, Director, Inst.of Inter Med. MMC	: Member
8.	Tmt. J.Rajalakshmi, J.A.O. MMC, Ch-3	: Lay Person
9.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

11/8/15

Member Secretary, Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
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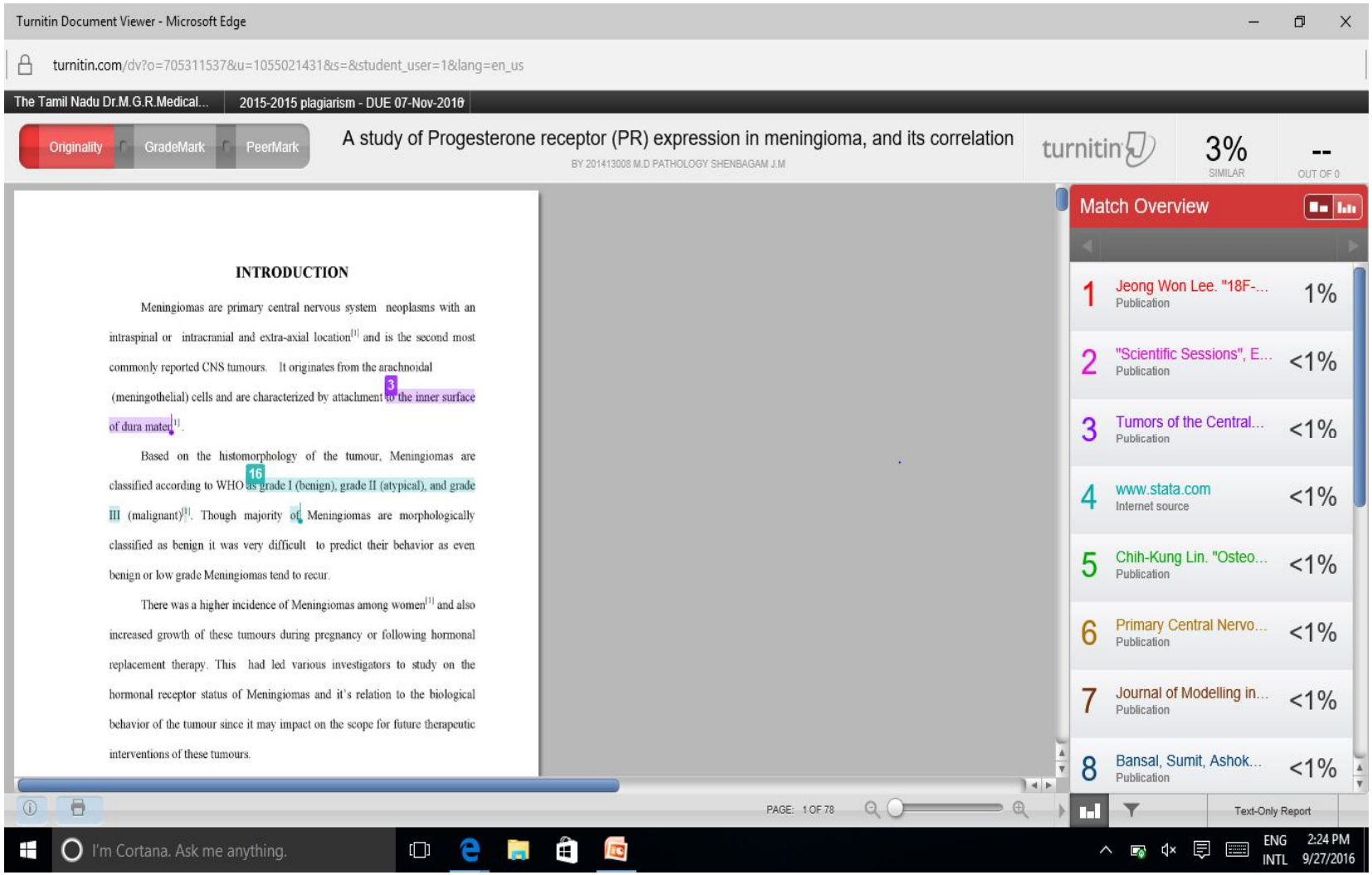
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INTRODUCTION
Meningiomas are primary central nervous system neoplasms with an intraspinal or intracranial and extra-axial location[1] and is the second most commonly reported CNS tumours. It originates from the arachnoidal (meningothelial) cells and are characterized by attachment to the inner surface of dura mater[1].
Based on the histomorphology of the tumour, Meningiomas are classified according to WHO as grade I (benign), grade II (atypical), and grade III (malignant)[1]. Though majority of Meningiomas are morphologically classified as benign it was very difficult to predict their behavior as even benign or low grade Meningiomas tend to recur.
There was a higher incidence of Meningiomas among women[1] and also increased growth of these tumours during pregnancy or following hormonal replacement therapy. This had led various investigators to study on the hormonal receptor status of Meningiomas and it's relation to the biological behavior of the tumour since it may impact on the scope for future therapeutic interventions of these tumours.
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INTRODUCTION

ABBREVIATIONS

CNS	-	Central nervous system
WHO	-	World Health Organisation
CBTRUS	-	Central Brain Tumor Registry of the United States
PR	-	Progesterone receptor
ER	-	Estrogen receptor
VEGF	-	Vascular endothelial growth factor
EGF	-	Epidermal growth factor
EMA	-	Epithelial membrane antigen
NCAM	-	Neural cell adhesion molecule
HPE	-	Histopathological examination

CONTENTS

INTRODUCTION

Meningiomas are primary central nervous system neoplasms with an intraspinal or intracranial and extra-axial location[1] and is the second most commonly reported CNS tumours. It originates from the arachnoidal (meningothelial) cells and are characterized by attachment to the inner surface of dura mater[1] .

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There was a higher incidence of Meningiomas among women[1] and also increased growth of these tumours during pregnancy or following hormonal replacement therapy. This had led various investigators to study on the hormonal receptor status of Meningiomas and it's relation to the biological behavior of the tumour since it may impact on the scope for future therapeutic interventions of these tumours.

It was well known that progesterone receptor (PR) expression was classically associated with breast & endometrial carcinomas. Many studies have then reported progesterone receptor expression in Meningiomas also[1] .

Some of these studies have demonstrated that the presence of progesterone receptor is a favorable prognostic factor in Meningiomas. It was said that Meningiomas of high grade tend to lose their progesterone receptor

positivity [1] and there was a positive association between the progesterone receptor (PR) negativity and increased tumour recurrence rates [1]. Numerous invitro and invivo experimental trials were done to study the effect of antiprogesterone agents on the growth of Meningiomas [1].

This particular study was done to analyze the biological behaviour of all the three WHO grades Meningiomas with respect to their progesterone receptor expression status and other clinical parameters.

AIMS AND OBJECTIVES

This study is done

1) To analyze the histopathological characteristics of large number of Meningioma cases consecutively operated during a period of three years.
2) To analyze the association of these histopathological features with the grading of Meningiomas.
3) To study the immunohistochemical incidence and distribution of progesterone receptor (PR) expression in Meningiomas.
4) To correlate the percentage of expression of PR with respect to the clinicopathological parameters.
5) To analyze the role of PR expression in prognosis of Meningiomas.

REVIEW OF LITERATURE

ANATOMY AND HISTOLOGY OF MENINGES:

Meninges are three layered (pia mater, arachnoid mater and dura mater) supporting tissue that surrounds the brain and the spinal cord[2]. The pia mater, a delicate layer covering the surface of CNS contains fine elastic fibres, collagen fibres and few fibroblasts. The arachnoid mater is a thick fibrous layer that over lies the pia mater. These two layers are considered together as a unit and are called as pia-arachnoid or the leptomeninges[2].

Subarachnoid space is seen between the pia and the arachnoid mater which is connected to the ventricular system by three foramina that aids in the CSF circulation. Flattened arachnoidal cells line the surface of the subarachnoid space and it contains small meningeal vessels and delicate fibrous strands that connects pia and arachnoid mater. All the veins and arteries that passes through the subarachnoid space from and to the CNS are surrounded by a layer of subarachnoid meningothelium and the pia mater[2].

Dura mater is a thick fibroelastic layer forming the outer most layer of meninges seen external to the arachnoid mater. It is lined by flat cells on it's inner surface. Subdural space is a potential space seen between the arachnoid and the dura mater. Dural folds extend in to brain space and are also attached to the periosteum of the skull. Dura forms two large folds, the falx and the tentorium that supports the brain and aids in it's venous drainage[2].

EMBRYOLOGY:-

Gagan JR et al said that meninges has it's origin from neural crest cells that forms a pleuripotent cellular network (meningeal mesenchyme) between the brain and skin[3].This is called as the meninx primitiva that gives rise to 2 distinct layers- the outer ectomeninx (gives rise to dura and bones of neurocranium) and the inner endomeninx (which forms the pia and arachnoid).

EPIDEMIOLOGY:

Meningiomas comprises of about for 24–30% of all primary intracranial neoplasms and is the second most commonly reported CNS tumor [4]. According to CBTRUS(Central Brain Tumor Registry of the United States),the prevalence of histopathologically confirmed Meningiomas were approximately found to be 97.5/100,000[5]. Though majority of Meningiomas are benign, they lead to significant morbidity and mortality.

Meningiomas occurs most commonly in middle-aged and elderly patients. Meningiomas rarely occur in children and if they occur they tend to be more aggressive. There is a higher incidence of these tumours among female patients with the female:male ratio being 1.7:1 [4] among middle-aged patients and at 3.5:1 [6] in the patients 40–44 years of age . Spinal Meningiomas accounts for about 25% of tumours in this location [1] and accounted for about 10% of all Meningiomas. Spinal Meningiomas show increased predilection for

occurrence in females and some studies showed as much as 90% female predominance [1] .

The incidence of subclinical Meningiomas (those diagnosed incidentally by autopsy and imaging studies) accounts for up to 2.8% [7,8] . Atypical and malignant Meningiomas shows a slight higher male predominance [9] .The atypical Meningiomas accounts for 4.7% to 7.2% of Meningiomas, although the incidence rises upto 20% on using the current WHO 2007 definitions. As said by willis J et al malignant / anaplastic Meningiomas comprises between 1.0% and 2.8% [10] and an annual incidence of about 0.17 per 1,00,000 population has been reported. The 10 year relative survival rate for malignant meningioma is 85.6%[5] .

MOLECULAR GENETICS:

The most common mutation associated with Meningiomas are inactivation and deletion of NF2 on chromosome 22. Those Meningiomas seen associated with NF2 tend to be multiple , occur at younger age and most often of fibroblastic variant [11].

The other genomic alterations that are recurrently seen in Meningiomas includes loss of chromosomes such as 1p, 9p, 6q,10q,14q, and 18q [11,12] and Angel Maillo et al said these chromosomal losses were linked with a shorter recurrence free survival and aggressive nature of the tumour [13] .

As the grade of Meningiomas increases the complexity of genetic defects also increases. Several familial cancer predisposition syndromes that

includes NF1, VHL, PTCH, PTEN, and CDKN2A genes are associated with the occurrence of Meningiomas [14] .

Increased telomerase activity in Meningiomas were strongly correlated with poor outcome [15]. Telomerase activity detected in various studies was as follows:- it was found in 3% to 21% of grade I Meningiomas, 58% to 92% in grade II Meningiomas and 100% in grade III Meningiomas [15]. But the role of these genetic abnormalities in the development of Meningiomas are still not known.

RISK FACTORS AND ETIOLOGY:

1) IONIZING RADIATION:

Exposure to ionizing radiation is the primary and the important risk factor associated with the development of Meningiomas. The risk of development of Meningiomas increases by 6 to 10 folds upon radiation exposure [16] .

Radiation therapy for treatment of intra-cranial tumours (for example:- whole brain irradiation done in cases of acute lymphoblastic leukemia) has been shown to be associated with the risk of development of Meningiomas. Those Meningiomas developing after exposure to radiation have very aggressive nature with younger age at presentation with increased tendency of multiplicity, rapid tumour progression, increased recurrence rate, MIB-1 labelling index and malignant potential [17].

2) HORMONES:

Hormones are involved in growth and differentiation of 2 major cancers in our body- breast and prostate cancers. Meningiomas have been found to have hormonal influence in their growth as explained by various immunohistochemical and molecular studies. It is said by korhonen K et al that 40%, 88% and 39% of Meningiomas have estrogen receptors(ER), progesterone receptors(PR), and androgen receptors(AR) respectively[18].

Although Meningiomas arises from a tissue that is not normally a target tissue for progesterone and estrogen, Meningiomas shows various clinical and epidemiological features that suggests the role of female sex hormones in their development. For example, females show an increased incidence of Meningiomas and it occurs rarely before puberty or after menopause, corresponding to the reproductive years with time of maximal hormonal activity . There is a regression or decrease in size of these tumours on cessation of hormonal replacement therapy[9] .

Wahab M et al said that some women suffers increase of symptoms during the luteal phase of menstrual cycle due to presence of functional progesterone rather than estrogen receptors in majority of Meningiomas [19].

According to Sroan milenkovic et al these fluctuations in symptoms is due to increase in tumor size occurring because of direct effects of sex hormones over Meningioma cells or steroid-induced vascular engorgement of tumor [20] .

Despite the evidence that majority of Meningiomas are estrogen receptor negative and progesterone receptor positive, it is proposed that estradiol used in hormonal therapy has significant effect on tumour growth as said by Borghei-Razavi et al., in their study [21].

3) PREGNANCY AND MENINGIOMAS:

It has been documented both radiologically and clinically that Meningiomas exhibit a rapid growth rate during pregnancy, with spontaneous regression during postpartum . Those women with a history of Meningiomas during pregnancy should be given strict birth control measures to prevent the recurrence of tumour in subsequent pregnancies [22]

4) OBESITY AND MENINGIOMAS:

There has been an increased occurrence of these tumours in obese patients which may be due to excessive peripheral aromatization (conversion of androstenedione to estrone) by adipocytes leading to rise in blood levels of estrogen [20].

5) HEAD TRAUMA:

Head trauma in both men and women has been suggested to be associated with meningiom risk, however no consistent results were obtained across various studies [9] .

6) ASSOCIATION OF MENINGIOMAS WITH BREAST CANCER:

Several studies that assessed the risk of occurrence of breast cancer in female patients with Meningiomas, and vice versa, stated that there is no causal relationship between the two tumours, rather these tumours shared the same risk factors such as hormone factors ,gender and age [23].

7) CELL PHONE USAGE:

It is a question of great interest if development of Meningiomas were associated with usage of cell phones. At present only a few studies highlights the presence of such an association because the sample sizes with regard to Meningiomas were quite small, the method of measurement of the extent of cell-phone usage was somewhat crude and the follow-up of the study subjects from the beginning of cell-phone usage was so difficult [24,25]. However the relationship between the risk of acquiring Meningiomas and usage of cell phones was a mystery for decades and therefore it deserves a still more detailed analysis and work up.

CLINICAL FEATURES OF MENINGIOMAS:

Meningiomas are slow growing tumours and produce focal neurological deficit's due to compression of adjacent structures. Specific neurological symptoms and signs depends on the site, size and growth rate of the tumour. Seizures, hearing loss, visual changes, paresis, and headache with obstructive hydrocephalus can occur in patients with Meningiomas. Due to their slow

growth rate they may sometimes be asymptomatic being diagnosed incidentally or during autopsy [26].

LOCATION OF MENINGIOMAS:

More than 80% of Meningiomas are supratentorial in location. Dural attachment of Meningiomas helps in their recognition. The most common sites are falx cerebri, parasagittal, over cerebral convexities, sphenoid ridge, olfactory groove, para and suprasellar region, tentorium cerebelli, foramen magnum, spinal canal and cerebellopontine angle [27].

Less common sites includes those arising from the choroid plexus and CNS parenchyma itself [28]. The diagnostically challenging ones are central pontine angle, spinal , choroid plexus and intraparenchymal Meningiomas as they resemble other tumours occuring in these locations, and Meningiomas may totally be forgotten as a differential. Spinal Meningiomas most commonly occurs in the thoracic region. Malignant Meningiomas most often metastasizes to liver, bone, lung and pleura [29].

RADIOLOGY OF MENINGIOMAS:

One of the important characteristics of Meningiomas are presence of dural tail surrounding the perimeter of dura around the mass. This familiar imaging sign indicates a rim of reactive fibrovascular tissue .On Magnetic resonance imaging, Meningiomas are typically contrast-enhancing isodense, dural masses. Some variants, such as microcystic Meningiomas, shows only

little contrast enhancement on CT and MRI. CT scan best demonstrates calcification seen in Meningiomas.

Numerous studies were done to look for correlation between the histopathology of Meningiomas and their radiological features in terms of number of lesions, location, and presence or absence of secondary changes[30].

According to study done by New et al in 1982, imaging features such as central areas of tumour necrosis, bony destruction, indistinct brain and tumour interface (interdigitation of tumour with brain) and mushrooming(prominent tumour or pannus, extending away from the globoid tumour mass with extensive perifocal oedema) have been described to be associated with aggressive nature of tumour pointing to their malignant behaviour [31].

Presence of peritumoral odema suggests aggressive nature of the intracranial tumours. But WHO grade I Meningiomas such as Angiomatous & Microcystic Meningiomas have similar degree of peritumoural odema as compared to grade II &III Meningiomas[32]. Peritumoual odema has also been associated with the secretory variant of meningioma [32] . Hence measurement of peritumoural odema cannot reliably distinguish between high grade and low grade Meningiomas as a good number of grade I Meningiomas tend to have appreciable levels of peritumoral odema [32].

Another important factor that predicts the histopathological grade of Meningiomas are tumour location. For example tumours in non-skull base location is important risk factor for high grade Meningiomas. Kim et al. in 2008 [33] found that around 58% of intraventricular Meningiomas were either atypical (grade II) or malignant (grade III) grade. They frequently showed intratumoral necrosis and irregular lobation. These findings support the association between location of Meningiomas and their grade which in turn influences the extent of secondary changes.

Presence of secondary changes such as necrosis, haemorrhage, and cystic change gives a heterogeneous pattern on contrast enhancement on imaging in high grade Meningiomas as compared to the homogenous pattern seen in benign Meningiomas [30] .

HISTOPATHOLOGY OF MENINGIOMAS:

Most of the Meningiomas are well-demarcated, firm and rubbery, sometimes presents as lobulated and rounded masses with broad based dural attachment [29] . Some Meningiomas have a gritty appearance, indicating the presence of psammoma bodies. Bone formation is very rare.

It is quite common for meningiomas to invade the underlying dura and the dural sinuses. Occasionally meningiomas invade the skull through the dura, where they induce the characteristic hyperostosis of the skull and such changes are highly in favour of skull invasion[29].

Meningiomas may encase or attach to cerebral arteries, but only rarely cause infiltration of arterial walls. Very rarely they cause infiltration of skin and extracranial compartments like orbit. Adjacent brain is compressed but rarely shows parenchymal infiltration. In some sites, such as sphenoid wing, meningiomas grow as carpet-like flat mass, a pattern characteristically termed as “en plaque meningioma.”

Atypical and anaplastic Meningiomas are larger than their benign counterparts and may have necrotic changes [29].

CLASSIFICATION:

According to WHO, Meningiomas are classified as benign (grade I), atypical (grade II) and anaplastic (grade III). The 2000 revision of 1993 WHO classification of Meningiomas made the definitions for grade II and grade III Meningiomas more objective and reproducible [9]. This resulted in a great shift in the number of cases diagnosed as grade II Meningiomas from 5 to 7 % by 1993 classification to 20 to 38 % by 2000 classification [10] .

The previous WHO classification (2000) of Meningiomas were little changed and recently updated in 2007. The major difference that was made was brain infiltration is considered now as a criteria for classifying a tumour as grade II or III. Those tumours that otherwise possessed benign morphology but had brain infiltration would now be graded as grade II [29] .

WHO classification of Meningiomas (2007), is the most commonly used recent system for classification and grading of Meningiomas and is given in annexure I.

GRADE I MENINGIOMAS:

Criteria for diagnosis for grade I Meningiomas are given in annexure II. Majority of Meningiomas fall under grade I accounting for about 80 to 90 %. The most common types among these are meningothelial, transitional and fibrous Meningiomas.

Grade I Meningiomas exhibit a relatively low rates of recurrence (7 to 20%) and are less aggressive in behaviour. On the other hand, site of the tumour has a major impact on the prognosis of Meningiomas. For example:- convexity Meningiomas are completely curable by surgical resection where as those situated at skull base such as petroclival area have a slow but invasive and destructive growth causing erosion of bony structures.

Grade I Meningiomas may remain histologically benign for long time or transform to higher grades over years [29]. Though these tumours have benign cytological features they have tendency to invade brain, dura and it's sinuses, skull, and rarely orbit, skin and soft tissues [14].

MENINGOTHELIAL MENINGIOMA:

This is the classical and the most common variant. The tumor cells resembles the normal arachnoidal cap (meningothelial) cells and are arranged

in the form of lobules. Within the lobules the cells are arranged in the form of syncytium which in large lobules should not be mistaken for sheet like pattern seen in high grade Meningiomas. The cells are uniform, with oval nuclei having fine chromatin that may exhibit central clearing or intranuclear cytoplasmic inclusions. Psamomma bodies are seen but are not as well formed as seen in psammomatous, transitional or fibrous subtypes[14, 29].

FIBROBLASTIC/ FIBROUS MENINGIOMA:

This variant has spindle cells arranged in fascicles, interlacing bundles and storiform pattern in a reticulin and collagen rich matrix [14,29].

TRANSTITIONAL MENINGIOMA:

This has features of both meningothelial and fibrous types. Tightly set whorls and psamomma bodies intermingled with fascicles[14,29].

PSAMOMMATOUS MENINGIOMA:

This has predominance of psamomma bodies compared to the tumour cells. Psamomma bodies are hyalinised irregular concentric calcified mass. The neoplastic cells are transtitional type in most cases[14]. Psammomatous meningioma occurs more commonly in middle aged women in thoracic spinal region.

ANGIOMATOUS MENINGIOMA:

This tumour has preponderance of blood vessels over tumour cells. The vascular channels may be thick or thin walled and most often the blood vessels are small with hyalinized walls.

Angiomatous Meningiomas have been classified based on the size of vessels in to macrovascular (>50% of vessels with more than 30 µm in diameter) and microvascular(> 50% of vessels with less than 30 µm in diameter) types.

Many a times foamy cells can be seen in cases of angiomatous meningioma. These can occur due to leakage of plasma lipids through thin walled blood vessels. The microvascular type of blood vessels when seen in association with foamy cells creates a suspicion of hemangioblastoma where immunohistochemistry can be done to confirm the diagnosis of meningioma [34]. Angiomatous meningioma have peritumoral oedema but are not aggressive in behaviour.

Hemangioblastoma and hemangiomapericytoma can be confused with angiomatous meningioma [35]. Hemangioblastoma radiologically presents as a mural nodule with in a cystic mass. Microscopically they have numerous thin walled blood vessels and polygonal stromal cells having foamy vacuolated cytoplasm. The stromal cells are immunoreactive for vimentin, S100, Glial fibrillary acidic protein, neuron-specific enolase, and calponin but are negative EMA [35]. Hemangiopericytomas are dural enhancing lesions with similar

radiological findings as that of Meningiomas. They have characteristic staghorn blood vessels with tumour cells having ill-defined cytoplasmic borders. These cells are positive for CD34 and vimentin with negativity for EMA as against Meningiomas which are EMA and vimentin positive [35].

MICROCYSTIC MENINGIOMA:

These tumours have numerous microcysts or extracellular spaces containing odematous fluid. The tumour cells have long cytoplasmic processes with stellate or vacuolated cytoplasm. The extracellular accumulation of fluid has been thought to be due to some vascular changes, degenerative process, secretory activity of tumour cells or CSF penetration in to the tumour[36].

Microcystic Meningiomas are confused with pleomorphic xanthoastrocytoma due to presence of xanthomatous type of cells, microcystic spaces and hyalinised vessels. Banstola S et al said that age of occurrence in children, presence of multinucleated giant neoplastic astrocytes, eosinophilic granular bodies, pericellular reticulin and GFAP positivity helps to distinguish pleomorphic xanthoastrocytoma from microcystic meningioma [36].

SECRETORY MENINGIOMA:

This type of meningioma has intercellular lumina (focal epithelial differentiation positive for CEA) with PAS positive eosinophilic inclusion. They have mast cells and exhibit significant peritumoral oedema[37] .

LYMPHOPLASMACYTE RICH MENINGIOMA:

This is the rarest type of Meningiomas. Most of the tumour comprises of chronic infllammatory infiltrate obscuring the meningothelial component[38] .

Various lesions occurring at these meningeal location with extensive lymphocytic infiltrate such as inflammatory pseudo tumour, plasma cell granuloma, meningeal sinus histiocytosis and chordoid meningioma mimics lymphoplasmacyte rich Meningioma. Radiological correlation with immunohistochemical study with EMA and vimentin helps in arriving at the correct diagnosis [39] .

METAPLASTIC MENINGIOMA:

These are Meningiomas seen associated with mesenchymal components such as cartilaginous, lipomatous, osteoblastic, myxoid or xanthomatous elements. These mesenchymal elements may be seen in single or in combination and may be focal or widespread [29].

GRADE II MENINGIOMAS:

Criteria for diagnosis for grade II Meningiomas are given in annexure II.

ATYPICAL MENINGIOMA:

It comprises 5 to 15% of cases. They exhibit increased cytological atypia, mitoses of > 4/ 10 HPF (high power field), and higher recurrence rates (30 to 40%) compared to the benign Meningiomas [29, 40]. When a patient is

diagnosed with Atypical Meningioma, strict postsurgical follow up must be considered.

CHORDOID MENINGIOMA:

These are usually large supratentorial tumours with poor prognosis and increased rates of recurrence. Histologically they resemble chordoma with the tumour cells arranged in characteristic cords and trabeculae. The cells have abundant eosinophilic vacuolated cytoplasm (resembles physaliferous cells seen in chordoma) set in a mucoid rich matrix.

They are rarely seen in pure form and often have intermingled areas of meningothelial cells and chronic inflammatory cells. An unbalanced translocation involving chromosome 1 and 3 (t(1,3)) have been noted in the chordoid variant of meningioma [14].

CLEAR CELL MENINGIOMA:

These variant of meningioma exhibit's pattern less sheets of arrangement of polygonal cells with glycogen rich(PAS positive diastase sensitive) clear cytoplasm and abundant interstitial and perivascular collagen. They occur more commonly in young adults with prospensity to Cauda equina and cerebellopontine angle.

These Meningiomas have aggressive behaviour, increased tendency to recur and rarely cause CSF seeding of tumour cells [41] . Metastatic renal cell

carcinoma (positive for cytokeratins) is a close differential for a clear cell meningioma.

GRADE III MENINGIOMAS:

Criteria for diagnosis for grade III Meningiomas are given in annexure II.

ANAPLASTIC MENINGIOMA:

Anaplastic / Malignant Meningiomas exhibit's features of frank malignancy with greater degrees of atypia, high mitotic rate above 20/ 10 HPF and increased recurrence rates (50 to 80%) than grade II Meningiomas.

The cytological features are so bizarre that metastatic carcinomas, sarcomas and melanoma comes under the differential diagnosis for an Anaplastic Meningioma[29] where immunohistochemical analysis helps in confirming the diagnosis.

Deborah L et al said that in some rare cases of hemangiopericytoma does not show the classical staghorn vessels where the increased cellularity leads to confusion with Anaplastic Meningioma [42] . Immunohistochemical and ultra structural features helps in arriving at the diagnosis. The characteristic ultrastructural feature for meningothelial differentiation in Meningiomas are the presence of intercellular junctions and interdigitating processes whereas basal lamina like material is seen in cases of hemangiopericytomas [42].

PAPILLARY MENINGIOMA:

They have characteristic perivascular pseudo papillary pattern of arrangement of tumour cells. They occur at younger age including children and are more common in males with a lower female to male ratio when compared to low grade Meningiomas [43]. They are very rare subtype of Meningiomas having aggressive behaviour and increased rates of recurrence (55%) with tendency to cause brain invasion (75%), diffuse cerebrospinal metastasis and metastasis to other sites (20%) such as pleura, liver and lung [43].

Markus J Riemenschneider et al said the preponderance of this variant of Meningiomas in children and the presence of perivascular pseudorosette like pattern of arrangement of tumour cells, they can be confused with ependymoma [14] . Immunohistochemistry and radiological features helps in the confirmation of the diagnosis.

RHABDOID MENINGIOMA:

This is a very rare and aggressive type of meningioma having sheets of plump rhabdoid cells with eccentric nuclei having open chromatin, prominent nucleoli and eosinophilic inclusion like fibrillar cytoplasm [44].

Various other rare presentations of Meningiomas are as follows:-

INTRAPARENCHYMAL MENINGIOMA:

Primary intraparenchymal Meningiomas are very rare in occurrence and are very challenging to diagnose as they mimic other intracranial lesions such as cavernous malformation, ependymoma, glioma and metastasis[45].

Intraparenchymal meningioma arise in brain tissue without any evidence of dural attachment. Their etiology is unclear. Some authors suggests that they arise from arachnoid cells of piamater that enters the brain tissue at sites of perforating vessels or from arachnoid cell rests as a part of migration. The sylvian fissure, pineal and intraventricular regions [45] are sites of location of those Meningiomas arising without any dural attachment.

Unlike other sites where meningothelial variant of Meningiomas were most common, fibrous meningioma occurs more commonly in intraparenchymal location without any dural attachment [45].

MULTIPLE MENINGIOMAS:

These are spatially separate independently arising Meningiomas. More commonly occurs in patients with NF2 mutation [11] . The mechanism that increases cell dissemination in multiple Meningiomas are correlated with it's enhanced NCAM expression as compared to it's solitary counterparts. Multiple Meningiomas also have down regulated expression of PR.

METASTASIS AND MENINGIOMA:

In majority of tumour types, presence of metastasis points to it's malignant behaviour. This does not stand good as far as Meningiomas are concerned. Metastasis is a very rare event accounting for about less than 1%. There has been an entity called as benign metastasizing Meningiomas where the cells have morphological pattern of grade I Meningiomas and have a indolent clinical behaviour. Thus in Meningiomas there are no straight forward relationship between metastasis, tumour histology and clinical outcome [42].

ROLE OF IMMUNOHISTOCHEMISTRY IN MENINGIOMAS:

Immunohistochemistry was first initiated in 1941 by Dr. Albert Coons. It is a process that uses specific antibody to detect the antigens present in the cells [46]. It is one of the best methods to analyse various antigens and receptor expression in tissues as it allows performing the test even in archived stored tissue samples and even with small quantity of tissue samples [47].

Following tissue processing the various steps involved in immunohistochemical staining are epitope / antigen retrieval, antigen and antibody reaction, followed by the detection or the visualization of the antigen antibody reaction.

The resulting antigen antibody interaction can be visualized by various methods [48] Some of these techniques utilize enzymes like peroxidases that gets conjugated with the antibody and catalyses to produce a colored reaction

product [49]. At times the antibody can be tagged to fluorophane such as rhodamine or fluorescein [50].

Immunohistochemical characteristics of Meningiomas are as follows:-

Meningiomas show positivity for EMA and vimentin. As against meningeal hemangiopericytomas, Meningiomas have only a focal weak positivity for CD99 and BCL-2 [51]. Meningiomas of secretory type shows focal expression of cytokeratins such as CK18, CK 19, CK 7, CK 8 and AE 1/3 but when there is diffuse and strong labeling of these antigens metastatic carcinomas are to be considered [52].

VEGF-A is involved in angiogenesis and vascular remodeling in meningiomas. VEGF-A expression were increased 2-fold in atypical and 10-fold in anaplastic meningiomas as compared to the benign ones. But some studies shows that increase in vessel number does not increase the histological grade proportionately[11].

Matrix metalloproteinase (MMPs) are proteolytic enzymes that causes degradation of extracellular matrix (ECM) components and aids in tissue remodeling. One among the MMPs, MMP-9, plays an important role in tumor invasion and angiogenesis. Matrix metalloproteinase expression in meningiomas has been found to be positively correlated with peritumoral odema, tumor invasiveness, malignancy and recurrence. [11] .

The estrogen (ER) and progesterone receptors (PR) are members of steroid receptor family with a nuclear localization identified by immunohistochemical staining. PR expression is said to be a favorable prognostic factor in various studies. Presence of ER and absence of PR expression in Meningiomas are linked with rapid tumour progression, higher rates of genetic mutations and tumor recurrence[53].

Kostron et al said that those atypical Meningiomas that lack expression of progesterone receptors had increased recurrence rates and a shorter disease free duration [54]. Arlete hilbig et al and Piquer et al demonstrated that tumours with increased necrosis and proliferation rate had lower levels of progesterone expression [47, 55].

Some studies have given contradictory results. For example while Jay et al showed the effect on hormonal influence on growth of the tumour, Adams et al suggested that there was no role for PR in the growth of Meningiomas [56,57].

Though majority of Meningiomas express progesterone receptors it's been a question of debate whether these receptors are functional. Many studies involving cell cultures of Meningiomas with the progesterone and anti-progesterone drug mifepristone have demonstrated that these receptors are functional. However the results of invitro studies are variable.

The ER expression in Meningiomas are very rare and it's expression is very scarce in type I Meningiomas but some of the higher grade (grade II and III) Meningiomas were found to have ER expression. Those few Meningiomas that exhibit ER positivity have not been positive for progesterone receptors thereby adding to their poor prognostic value [58]. Arlete hilbig et al(116 cases) and M Taghipour et al(51 cases) in their study states that none of their cases tested for ER expression came out to be positive but majority of the cases were found to be express PR [47, 59].

The rate of expression of Ki67 (MIB-1antiboby labelling) has been associated with prognosis of Meningiomas. Many studies have found a positive correlation between lower proliferation indices and benignity of Meningiomas [42]. Tumour with higher Ki67 values behave in a most aggressive manner. The extent of Ki67 and PR expression are inversely correlated in Meningiomas. Greater the Ki67, lesser the PR and more likely those tumours will recur[53] .

TREATMENT:

Even benign Meningiomas are very challenging to treat. Meningiomas should be treated when it becomes symptomatic, size exceeds greater than 3cm or expansion of tumour size. The various treatment modalities includes presurgical angiographic embolisation of tumour, followed by surgery and post surgical irradiation [60]. Radiotherapy plays a very important role in treatment of Atypical (grade I) and Anaplastic (grade II) Meningiomas [61].

In vitro studies have shown that proliferation of Meningiomas were inhibited by RU486 (mifepristone), a progesterone receptor antagonist suggesting it as a treatment modality. However, only marginal responses [62], were obtained from various small clinical trials. Some of the prospective studies are still under trial awaiting completion.

RECURRENCE FOLLOWING SURGERY:

Though majority of Meningiomas are benign, tumor recurrence following curative surgery is a major clinical problem, the rates of which vary in different series occurring between 10% to 15% and 25% to 37% of patients after a follow up period of 5 and 10 years respectively [13] .

The best accepted way to predict recurrence is the Simpson grading system(1957) which assesses the completeness of resection [63]. The best accepted way to predict recurrence is the Simpson grading system(1957)[63] which assesses the completeness of resection based on the major causes for recurrence of tumour such as nodules of tumour in the adjacent dura, invasion of venous sinuses, and bone infiltration by meningothelial cells[63].

According to Simpson the extent of resection can be classified as:

Grade I - complete resection of tumour.

Grade II - complete resection of tumour and coagulation of the dural attachment.

Grade III - complete resection of tumour without coagulation of the dural attachment or removal of hyperostotic bone or sinus infiltrated by tumour.

Grade IV - subtotal removal of tumour.

Grade V - decompression of tumour/biopsy.

As said by simpson the recurrence rates for various grades of tumour resection includes 9%,16%,29%,39% and 100% for grade 1, grade 2, grade 3, grade 4 and grade 5 tumour resection respectively[63].

Numerous other factors are responsible for tumour recurrence as highlighted by various studies includes neoplastic dural cell remnants attached around the craniotomy site, increased neovascularization, increase in number of mitotic figures on histopathological examination[13].

PROGNOSTIC FACTORS:

Various factors associated with increased recurrence in Meningiomas includes location of tumour (non skull base location) , extent of surgical resection of tumour, histology and grade according to WHO grading system, proliferation associated markers such as Ki67, PR receptor status negativity[13].

MATERIALS AND METHODS

This is a Retrospective & Prospective study done at the department of neuropathology, Institute of Pathology and Rajiv Gandhi government hospital, Madras Medical College for a period of 3 years from June 2013 – may 2016.

Out of the total 877 CNS tumour specimens received at the department of neuropathology, Meningiomas constituted of about 209 cases (23.83%). A total of 60% of cases were in follow up and the mean follow up period was 30 months. The cases were followed up for once in three months for first year and once in 6 months there after. Radiology work up of cases were done at the end of 1 year followup.

DATA COLLECTION:

This study included all the intracranial and intraspinal Meningiomas of the three WHO grades, Recurrent Meningiomas, multiple Meningiomas.

All other tumours of meningeal origin such as hemangiopericytoma, hemangioblastoma and solitary fibrous tumours were not included in the study.

All the clinical data and radiological findings of the meningioma cases were obtained from the patient files in the pathology registers. The hematoxylin and eosin stained and mounted slides were retrieved from the archives of pathology laboratory.

All the slides were reviewed and graded according to the histopathological WHO classification of Meningiomas (2007) guidelines without the knowledge of previous grading or patient outcome [29].

The tumour subtyping was done according to the dominant histological pattern (>50%) seen in the microscopic sections of the tumour [64].

The following histopathological parameters such as hypervascularity, hypercellularity, sheet like pattern , mitotic counts, small cell change, macronucleoli, brain infiltration, necrosis, vesiculous nucleoli, nuclear pleomorphism, psamomma bodies, fibrosis, inflammatory cell infiltration, xanthomatous change and bone infiltration were analyzed in this study.

The criteria used for analyzing most of the factors were based on a study done by Thomas Backer- Grondahl et al [65].

Hypervascularity was defined by presence of prominent blood vessels at 10X magnification in 2 or more low power fields [65] .

Hypercellularity was analyzed in a semiquantitative manner as present or absent. All the non tumour cell areas such as those with vascular components, lymphocytes, xanthomatous cells, microcystic areas were not included in the analysis.

Sheet like pattern was identified by lack of characteristic growth pattern of Meningiomas seen in more than half of the field area at 10X magnification [65] .

Mitotic figures were counted in microscopic fields of tumour with high mitotic activity. Average number of mitotic figures in ten non overlapping consecutive high power fields (40X) were obtained [65].

Small cell change was identified by presence of increased nuclear cytoplasmic ratio.

Nucleoli seen prominently at 10X magnification was considered as macronucleoli [65].

Brain infiltration is identified by presence of tongue like irregular protrusions of tumour cells in to the brain parenchyma without any intervening leptomeninges between the brain parenchyma and the tumour cells infiltrating them [65].

Following treatment of Meningiomas, the appearance of a new radiologically identifiable tumour lesion at the previous site of the tumour is set as a criteria for recurrence [1].

Paraffin blocks of 60 randomly selected cases of Meningiomas (containing cases from all the three WHO grades) were collected for immunohistochemical staining for progesterone receptors. The sections were stained with monoclonal rabbit antihuman PR purchased from path insitu.

The immunohistochemical staining procedure for PR is given in annexure III.

Sections from breast carcinoma stained for PR were taken as positive control. Negative controls samples were obtained by avoiding the staining with the primary antibody step during the staining procedure.

INTERPRETATION AND SCORING:

The slides are assessed for the presence and cellular localization of the PR immunohistochemical staining. PR characteristically shows nuclear receptor positivity. Non specific staining of the connective tissue and the cytoplasm is considered as negative. The immunoreactive score were done as like that for breast cancer and are confirmed with Meningioma tissue. The percentage of cells that took up the stain and intensity of nuclear staining were analyzed and the scores of these two are added up to get the final score. Method of scoring the immunohistochemical staining of PR is given in annexure IV.

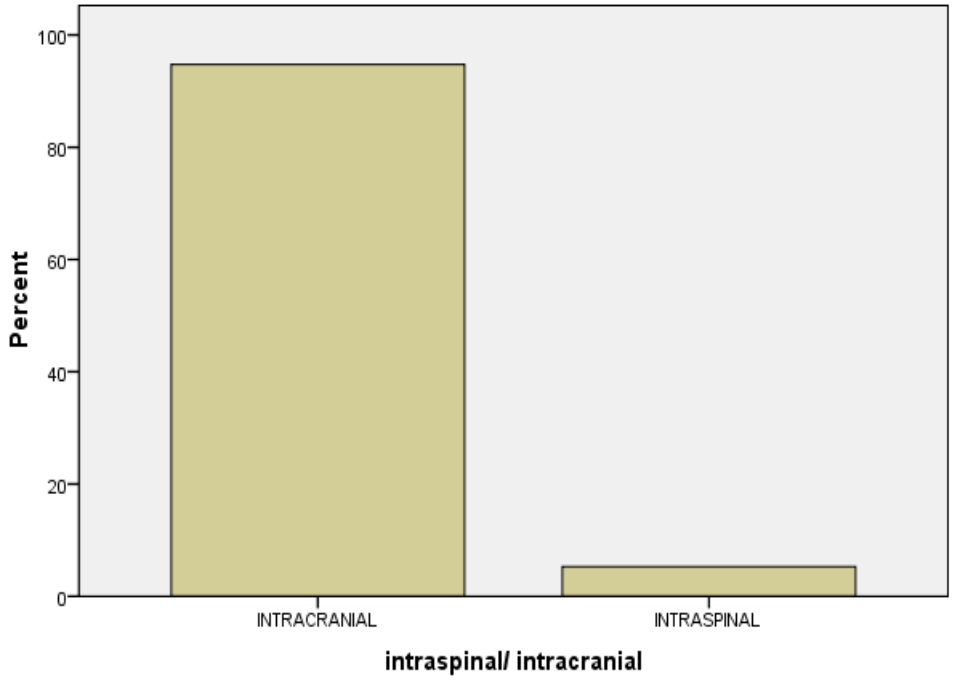
STATISTICAL ANALYSIS:

Statistical analysis was carried out using SPSS software version 17. Various tests used in the study were the chi square test and the T test. A significant association between various factors analyzed in the study was found with a level of significance 95% confidence interval and a P value of less than 0.05.

OBSERVATION AND RESULTS

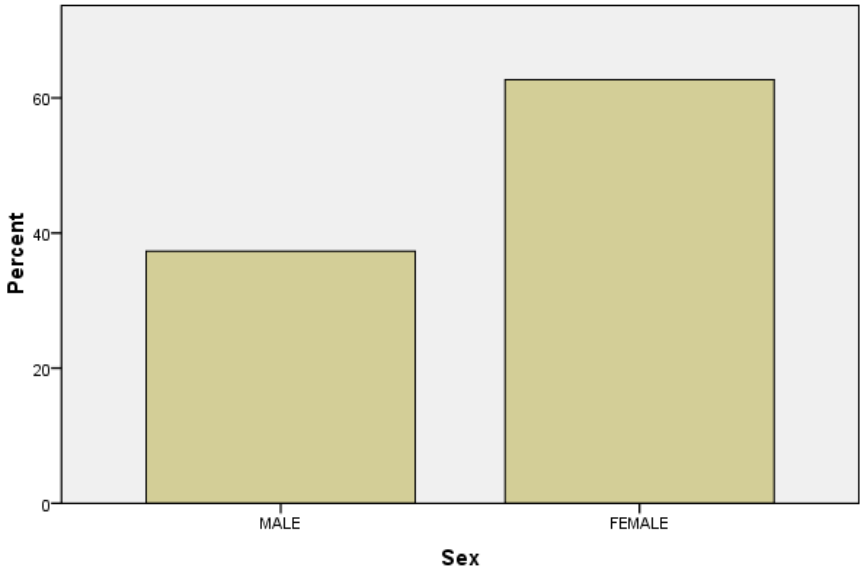
In this study about Meningiomas, 209 cases operated during a period of three years were included among which 198 (94.7%) and 11(5.3%) cases were intracranial and intraspinal Meningiomas respectively as given below in chart 1.

CHART 1:- INTRACRANIAL/ INTRASPINAL DISTRIBUTION OF MENINGIOMAS



The total number of male and female cases in the study were 78 (37.3%) and 131(62.7%) cases respectively and is shown below in chart 2.

CHART 2:- SEX DISTRIBUTION OF MENINGIOMAS



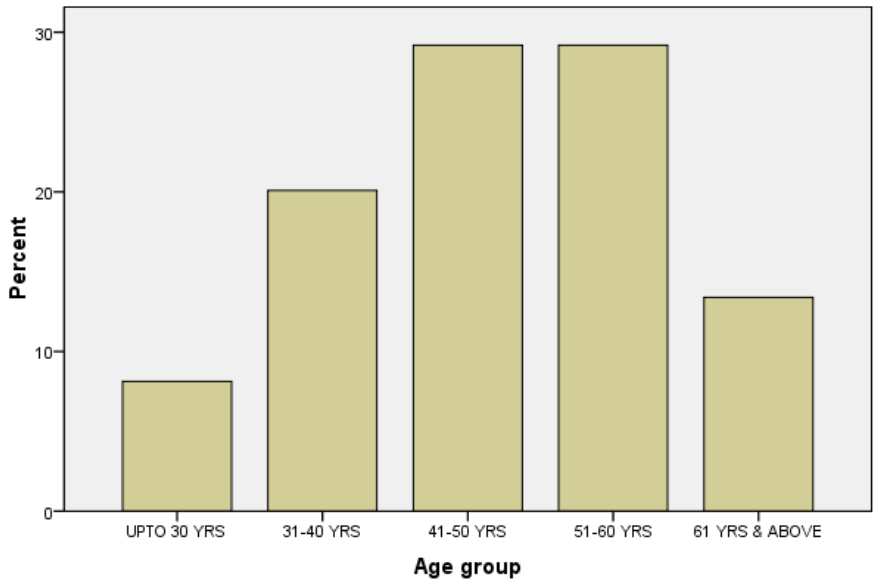
Among intracranial Meningiomas, male patients accounted for 77 cases and female patients accounted for about 121 cases with a male: female ratio of about 1: 1.6 . Among intraspinal Meningiomas, only one case belonged to male and female patients accounted for about 10 cases with a male: female ratio of about 1:10.

The mean age of occurrence of Meningiomas were found to be 48.12 and it did not vary significantly among male (49.24) and female (47.46). Maximum number cases were seen in fifth (29.2%) and sixth (29.2%) decades of life. Meningiomas were least prevalent in less than 30 years of age accounting for about 8.1 % of cases. The age distribution of Meningiomas are given below in table 1 and chart 3.

TABLE 1:- AGE DISTRIBUTION OF MENINGIOMAS

Age (in years)	Frequency	Percentage
UPTO 30	17	8.1
31-40	42	20.1
41-50	61	29.2
51-60	61	29.2
61 & ABOVE	28	13.4
Total	209	100

CHART 3:- AGE DISTRIBUTION OF MENINGIOMAS

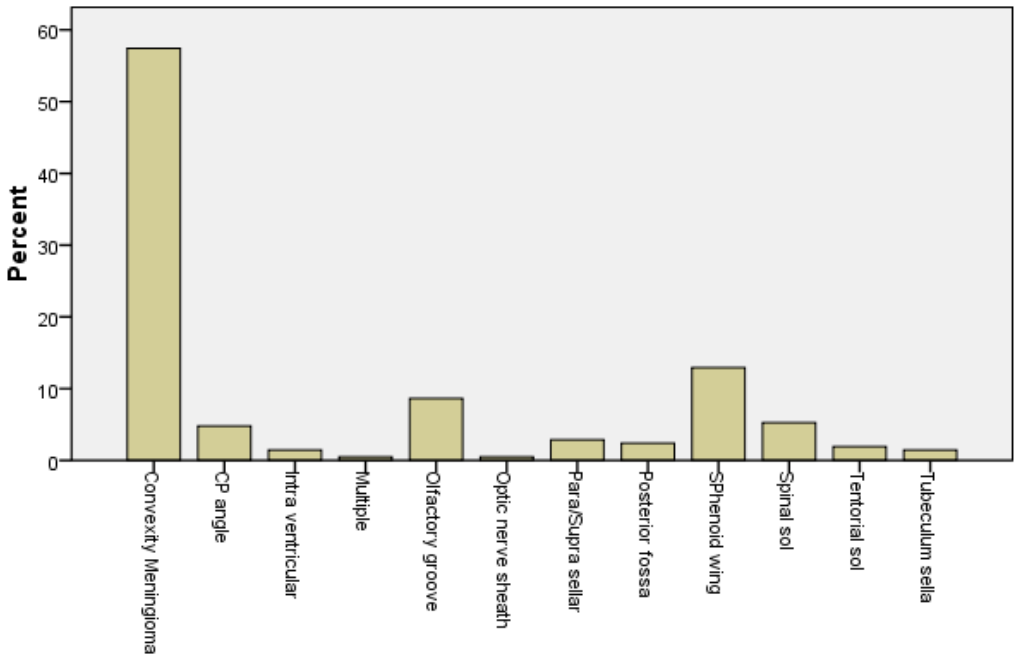


The frequency of occurrence of different types of Meningiomas in various sites is compared in table 2 and chart 4. The convexity Meningiomas (57.4%) that includes those on the convexity, falx and parasagittal regions together constitutes the most common site of occurrence of Meningiomas in this study.

TABLE 2:- SITE DISTRIBUTION OF MENINGIOMAS

SITE	Frequency	percentage
Convexity Meningioma	120	57.4
CP angle	10	4.8
Intra ventricular	3	1.4
Multiple meningioma	1	0.5
Olfactory groove	18	8.6
Optic nerve sheath	1	0.5
Para/Supra sellar	6	2.9
Posterior fossa	5	2.4
Sphenoid wing	27	12.9
Tentorial sol	4	1.9
Tuberculum sella	3	1.4
TOTAL	209	100

CHART 4:- SITE DISTRIBUTION OF MENINGIOMAS

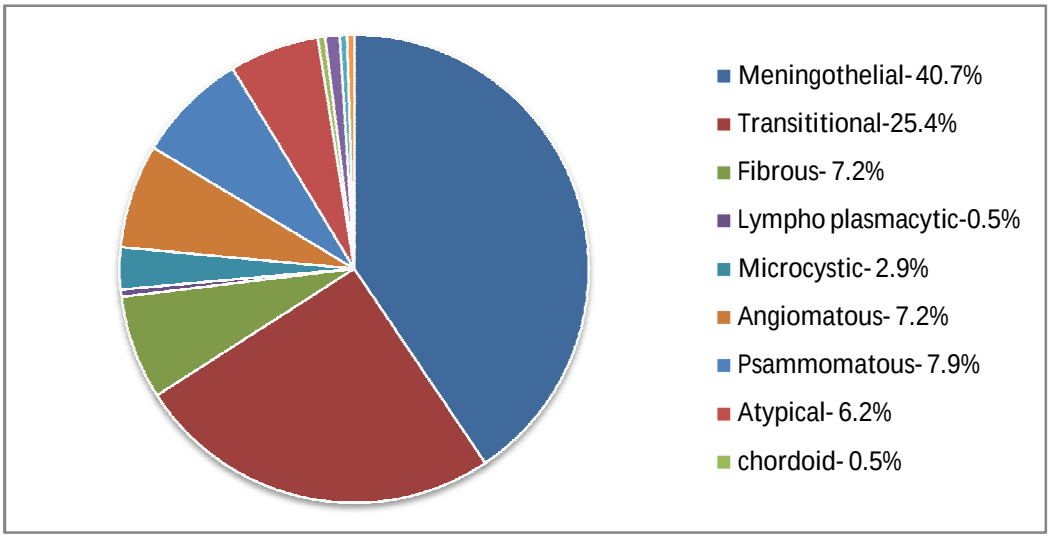


The various histopathological types of Meningiomas are given below in table 3 and chart 5. The most common types encountered in this study were meningothelial (40.7%) and transitional Meningiomas(25.4%).

TABLE 3:- FREQUENCY OF OCCURRENCE OF DIFFERENT HISTOPATHOLOGICAL TYPES OF MENINGIOMAS:

Grade	Hpe Types	Frequency	Percentage
GRADE I	Meningothelial Meningioma	85	40.7
	Transitional Meningioma	53	25.4
	Fibrous Meningioma	15	7.2
	Lympho plasmacyte rich Meningioma	1	0.5
	Microcystic Meningioma	6	2.9
	Angiomatous Meningioma	15	7.2
	Psammomatous Meningioma	16	7.7
GRADE II	Atypical Meningioma	13	6.2
	Chordoid Meningioma	1	0.5
	Clear cell Meningioma	2	1.0
GRADE III	Anaplastic Meningioma	1	0.5
	Papillary Meningioma	1	0.5
Total		209	100

CHART 5:- FREQUENCY OF OCCURRENCE OF DIFFERENT HISTOPATHOLOGICAL TYPES OF MENINGIOMAS

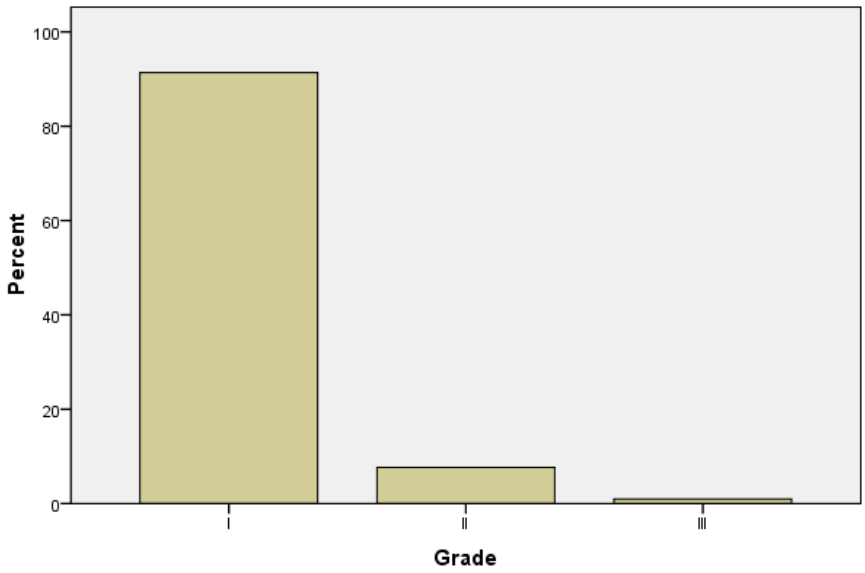


The number of cases in grade I, II & III were 191(91.4%), 16(7.6%) & 2(1%) respectively and is illustrated in table 4 and chart 6. Grade 1 or benign Meningiomas were found to be in higher numbers compared to grade II or III Meningiomas.

TABLE 4:- FREQUENCY OF OCCURRENCE OF VARIOUS GRADES OF MENINGIOMAS

Grade	frequency	percentage
I	191	91.4
II	16	7.7
III	2	1
Total	209	100

CHART 6:- FREQUENCY OF OCCURENCE OF VARIOUS GRADES OF MENINGIOMAS

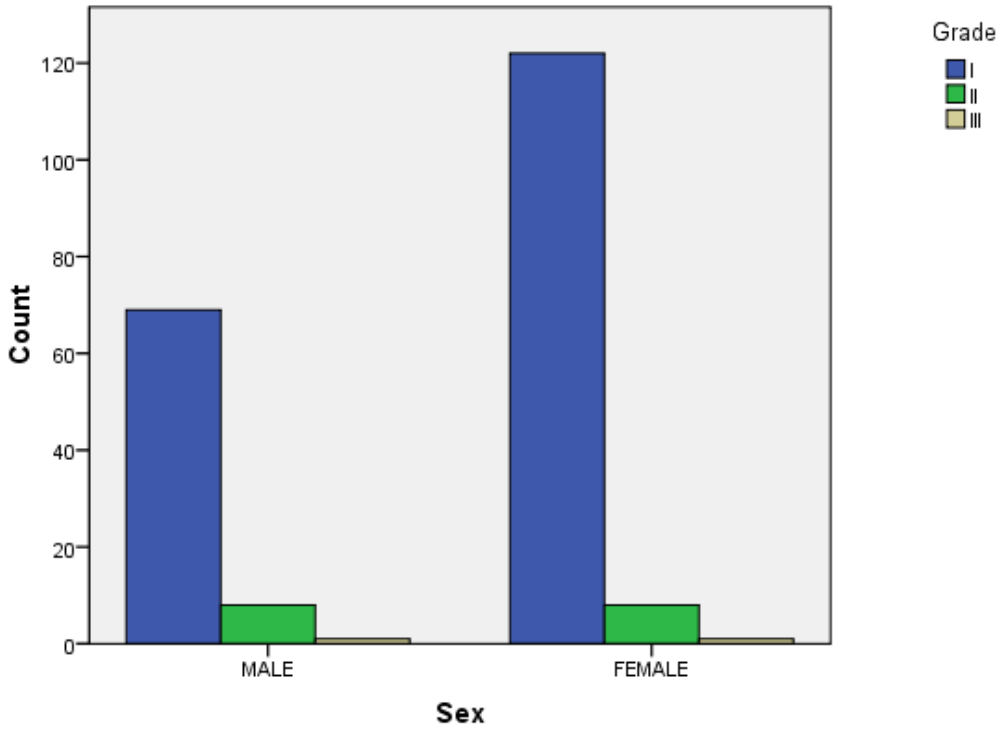


The male:female ratio for grade I, II and III Meningiomas were 1:1.76, 1:1 and 1:1 respectively. This showed that grade I Meningiomas were predominant in females and the male female ratio gets equalized as grade increases. However when subjected to statistical analysis the association between sex distribution among various grades of Meningiomas were not significant (P value= 0.508). Comparison of sex distribution among different grades of meningiomas is given below in table 5 and chart 7.

TABLE 5:- COMPARISON OF SEX DISTRIBUTION AMONG DIFFERENT GRADES OF MENINGIOMAS

	Grade I Meningiomas (number of cases & %)	Grade II Meningiomas (number of cases & %)	Grade III Meningiomas (number of cases & %)	TOTAL (number of cases & %)
MALE	69(36.1%)	8(50.0%)	1(50.0%)	78 (37.3%)
FEMALE	122 (63.9%)	8(50.0%)	1(50.0%)	131(62.7%)
TOTAL	191(100.0%)	16(100.0%)	2(100.0%)	209(100.0%)

CHART 7:- COMPARISON OF SEX DISTRIBUTION AMONG DIFFERENT GRADES OF MENINGIOMAS

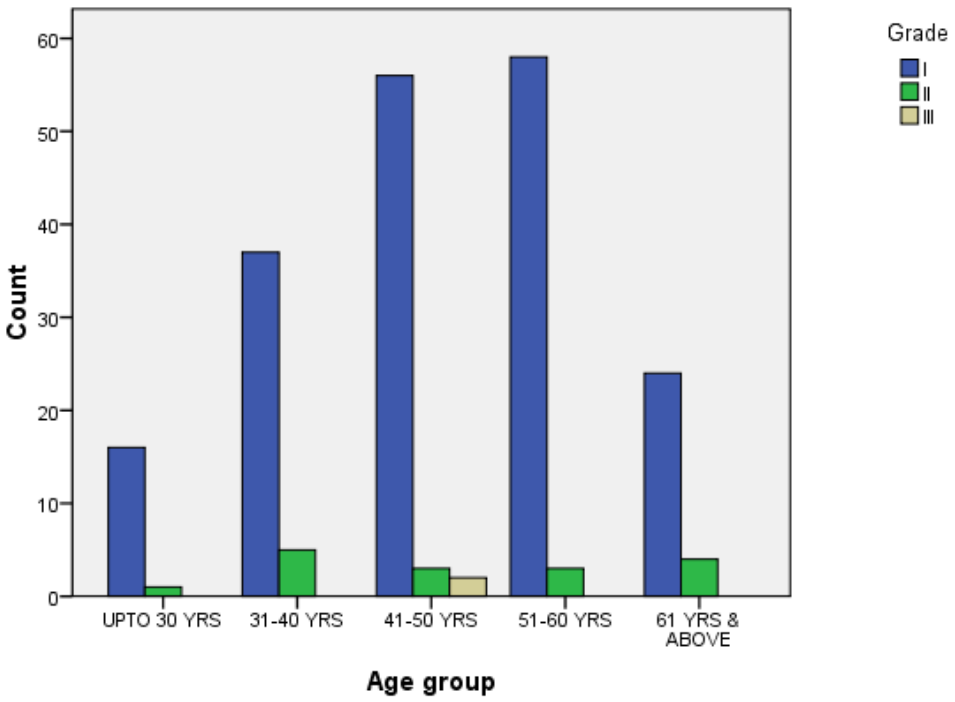


The mean age of occurrence of grade I, II and III Meningiomas were 48.07, 49.44 and 43 respectively. The age distribution among various grades of Meningiomas are given below in table 6 and chart 8. The association between the age of occurrence of Meningiomas and it's various grades were not significant (P value= 0.345).

TABLE 6:- COMPARISON OF AGE DISTRIBUTION AMONG DIFFERENT GRADES OF MENINGIOMAS

AGE IN YEARS	Grade I Meningiomas (number of cases & %)	Grade II Meningiomas (number of cases & %)	Grade III Meningiomas (number of cases & %)	TOTAL (number of cases & %)
UPTO 30	16(8.4%)	1(6.3%)	0(.0%)	17(8.1%)
31-40	37(19.4%)	5(31.3%)	0(.0%)	42(20.1%)
41-50	56(29.3%)	3(18.8%)	2(100.0%)	61(29.2%)
51-60	58(30.4%)	3(18.8%)	0(.0%)	61(29.2%)
61	24(12.6%)	4(25.0%)	0(.0%)	28(13.4%)
Total	191(100.0%)	16(100.0%)	2(100.0%)	209(100.0%)

TABLE 8: COMPARISON OF AGE DISTRIBUTION AMONG DIFFERENT GRADES OF MENINGIOMAS



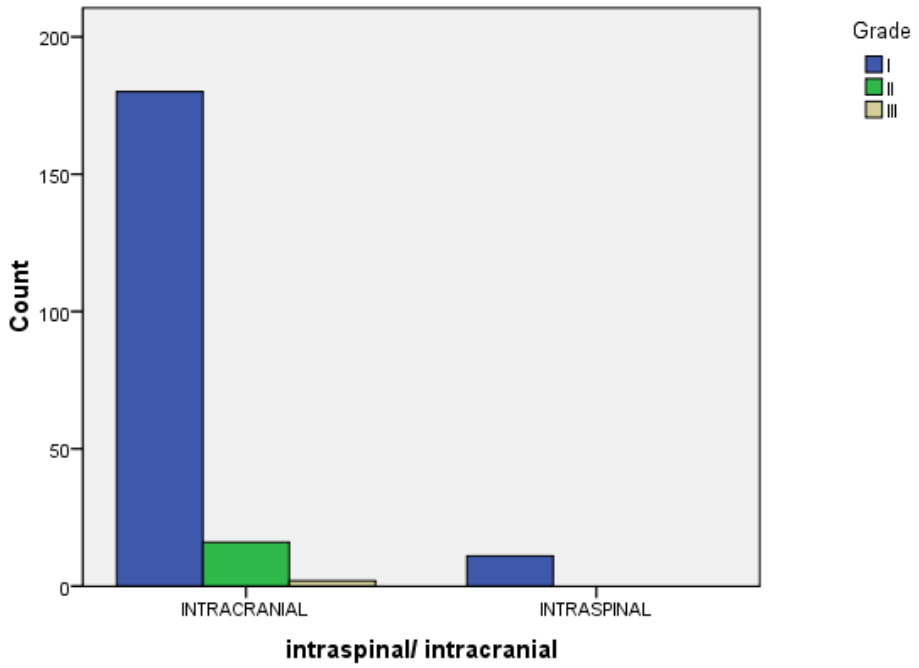
Among intracranial and intraspinal Meningiomas, all intraspinal Meningiomas were of grade I type and all grade II and III Meningiomas were intracranial in distribution. There was so significant association (with a P value

of 0.579) between different grades of Meningiomas and their distribution among intracranial and intraspinal location. The intracranial and intraspinal distribution of grade I, II and III Meningiomas are given below in table 7 and chart 9.

TABLE 7:- COMPARISON OF INTRACRANIAL AND INTRASPINAL LOCATION OF MENINGIOMAS AND THEIR DIFFERENT GRADES

	Grade I Meningiomas (number of cases & %)	Grade II Meningiomas (number of cases & %)	Grade III Meningiomas (number of cases & %)	TOTAL (number of cases & %)
INTRACRANIAL	180(86)	16(7.7)	2(1)	198(94.7)
INTRASPINAL	11 (5.3)	0 (0)	0 (0)	11 (5.3)
	191 (91.4)	16 (7.7)	2 (1)	209 (100)

CHART 9:- COMPARISON OF INTRACRANIAL AND INTRASPINAL LOCATION OF MENINGIOMAS AND THEIR DIFFERENT GRADES



There is also no association between the three grades of Meningiomas and their various intracranial location (statistically insignificant, P value= 0.995). The various intracranial location of Meningiomas with regard to different grades are given in table 8.

TABLE 8:- COMPARISON OF VARIOUS SITES OF LOCATION OF MENINGIOMAS AND THEIR DIFFERENT GRADES :

SITE	Grade I Meningiomas (number of cases & %)	Grade II Meningiomas (number of cases & %)	Grade III Meningiomas (number of cases & %)	TOTAL (number of cases & %)
Convexity Meningiomas	107 (54)	12 (6)	1 (0.5)	120 (60.6)
CP angle	9 (4.5)	1 (0.5)	0 (0)	10 (5)
Intra ventricular	3 (1.5)	0 (0)	0 (0)	3 (1.5)
Multiple Meningiomas	1 (0.5)	0 (0)	0 (0)	1 (0.5)
Olfactory groove	16 (8)	1 (0.5)	1 (0.5)	18 (9)
Optic nerve sheath	1 (0.5)	0 (0)	0 (0)	1 (0.5)
Para/Supra sellar	6 (3)	0 (0)	0 (0)	6 (3)
Posterior fossa	5 (2.5)	0 (0)	0 (0)	5 (2.5)
Sphenoid wing	25 (12.6)	2 (1)	0 (0)	27 (13.6)
Tentorial sol	4 (2)	0 (0)	0 (0)	4 (2)
Tuberculum sella	3 (1.5)	0 (0)	0 (0)	3 (1.5)
TOTAL	180 (90.9)	16 (8)	2 (1)	198 (100)

The mean size of Meningiomas were 4.4cm.The average maximum diameter of grade I, II and III Meningiomas were 3.4cm, 5.06cm, and 5cm respectively. High grade Meningiomas were slightly large in size when compared to the grade I Meningiomas.

The various histopathological features analyzed among all the three grades of Meningiomas in the study were detailed in table 9.

TABLE 9:- COMPARISON OF VARIOUS HISTOPATHOLOGICAL FEATURES IN DIFFERENT GRADES OF MENINGIOMAS AND THE STATISTICAL ASSOCIATION OF THESE FEATURES WITH BENIGN GRADE I MENINGIOMAS AND HIGH GRADE (GRADE II AND III) MENINGIOMAS

Histopathological features	Grade I meningioma number of cases & % to total grade I cases(191)	Grade II meningioma number of cases & % to total grade II cases(16)	Grade III meningioma number of cases & % to total grade III cases (2)	p value
Sheet like pattern	40 (20.8)	15 (93.8)	2 (100)	<0.0000001
Hypercellularity	23 (12)	16 (100)	2 (100)	<0.0000001
Small cell change	5 (2.6)	7 (43.8)	2 (100)	<0.0000001
Macronucleoli	0 (0)	3 (18.8)	1 (50)	<0.0000001
Necrosis	0 (0)	9 (56.3)	2 (100)	<0.0000001
Brain infiltration	0 (0)	10 (62.5)	2 (100)	<0.0000001
Nuclear pleomorphism	0 (0)	6 (37.5)	2 (100)	<0.0000001
Vesiculous nuclei	0 (0)	1 (0.5)	2(100)	<0.0000001
Hypervascularity	49 (25.7)	15 (93.8)	2 (100)	<0.0000001
Lymphocytic infiltration	10 (5.2)	2 (12.5)	0 (0)	0.4539
Foamy cell change	12 (6.3)	2 (12.5)	0 (0)	0.5853
Psamomma bodies	144 (75)	1 (0.5)	0 (0)	0.000001
Fibrosis	148 (77.1)	2(12.5)	0 (0)	0.000001

Features such as small cell change, hypercellularity ,sheet like pattern, nuclear pleomorphism, macronucleoli, vesiculous nuclei, necrosis and brain invasion were seen predominantly in higher grades (grade II and III) of Meningiomas thereby proving their association with aggressive behaviour of tumour and their association was statistically significant with a P value of <0.0000001. Though hypervascularity was seen in some of grade I

Meningiomas, their association with high grades of Meningiomas were statistically significant with a P value of <0.0000001.

The mean mitotic figures per 10 high power field were 0.9, 6, 22 in Meningiomas of grade I , II and III respectively. There by showing increased mitotic rates is associated with higher grades of the tumour.

Xanthomatous / foamy cell change of the tumour cells was seen in Meningiomas irrespective of their grade. Most of these cases were found to have hypervascularity with the foamy cells arranged around the blood vessels. Their presence did not affect the grades of tumours and their association was not statistically significant with a P value of 0.5853.

Lymphocytic infiltration in tumour was seen in Meningiomas irrespective of their grades. Hence their association was statistically insignificant with a P value of 0.4539 and were in no way found to play a role in the tumour severity.

Psamomma bodies were seen more commonly with grade I tumours and their presence was associated with increased fibrosis among the tumor cells. Most of the Meningiomas of intraspinal location were found to have increased number of psamomma bodies . Psamomma bodies and fibrosis were more commonly found in grade I rather than grade II and III tumours and was found to be statistically significant with a P value of 0.000001.

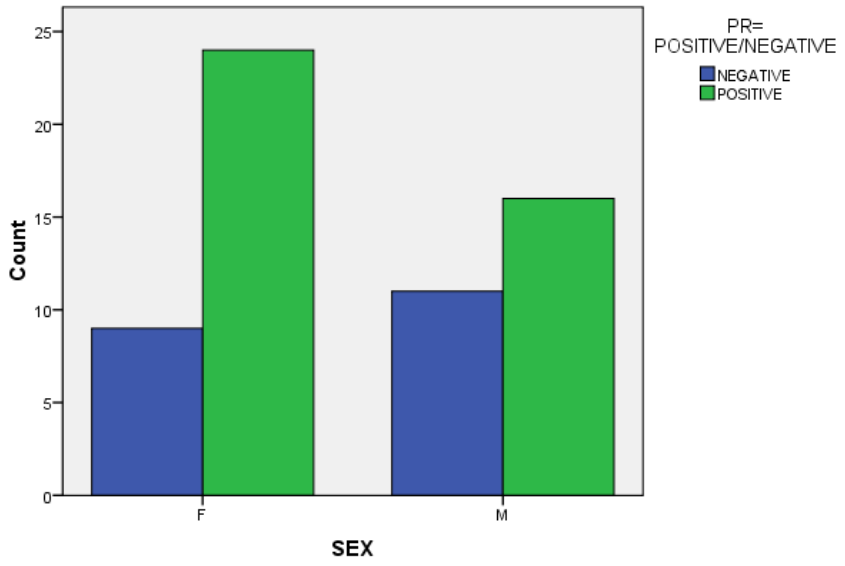
Of all these cases immunohistochemical study for progesterone receptor was done for 60 randomly selected cases of Meningiomas. The total percentage of positivity of Meningiomas for progesterone receptors was found to be

66.7%. The number of male and female patients selected for PR immunohistochemical study were 27 and 33 cases respectively and their PR receptor status is given in table 10 and chart 10. There was no difference in the degree of positivity of Meningiomas among male and female patients and were not statistically significant with a P value of 0.271.

TABLE 10:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG MALE AND FEMALE PATIENTS:

SEX	PR POSITIVE (number of cases & %)	PR NEGATIVE (number of cases & %)	TOTAL (number of cases & %)
MALE	16 (26.6)	11 (18.3)	27 (45)
FEMALE	24 (40)	9 (15)	33 (55)
TOTAL	40 (66.7)	20 (33.3)	60 (100)

CHART 10:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG MALE AND FEMALE PATIENTS



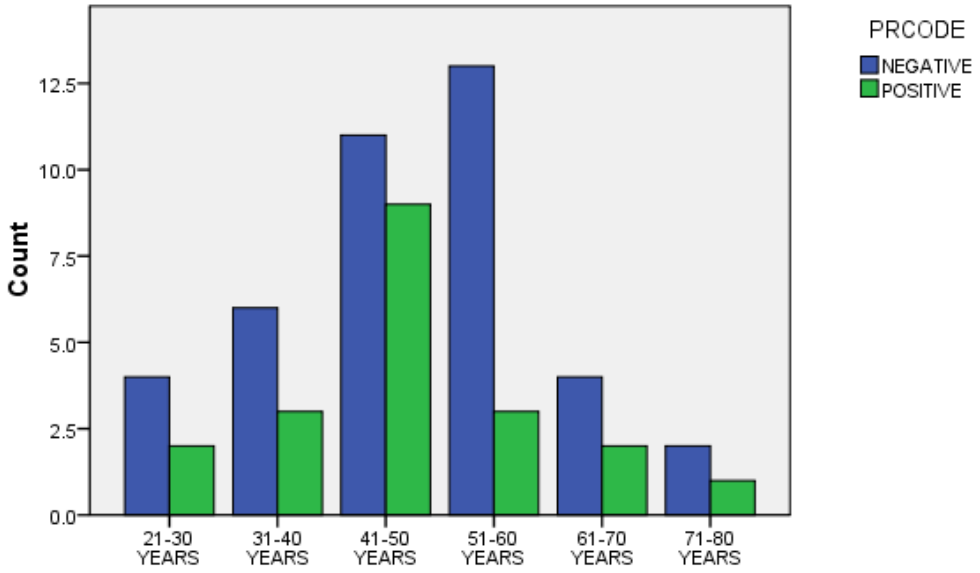
The various age at presentation were compared with the level of PR expression and is given below in table and chart 11. There was no difference in

the degree of positivity of Meningiomas among different age at presentation and were not statistically significant with a P value of 0.738.

TABLE 11:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG THE DIFFERENT AGE AT PRESENTATION

AGE	PR POSITIVE (number of cases & %)	PR NEGATIVE (number of cases & %)	TOTAL (number of cases & %)
21-30	4(6.7)	2 (3.3)	6 (10)
31-40	6 (10)	3(5)	9 (15)
41-50	11 (18.3)	9 (15)	20 (33.3)
51-60	13(21.7)	3 (5)	16 (26.7)
61- 70	4(6.7)	2 (3.3)	6 (10)
71 and above	2 (3.3)	1 (1.7)	3 (5)
Total	40 (66.7)	20 (33.3)	60 (100)

CHART 11:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG DIFFERENT AGE AT PRESENTATION



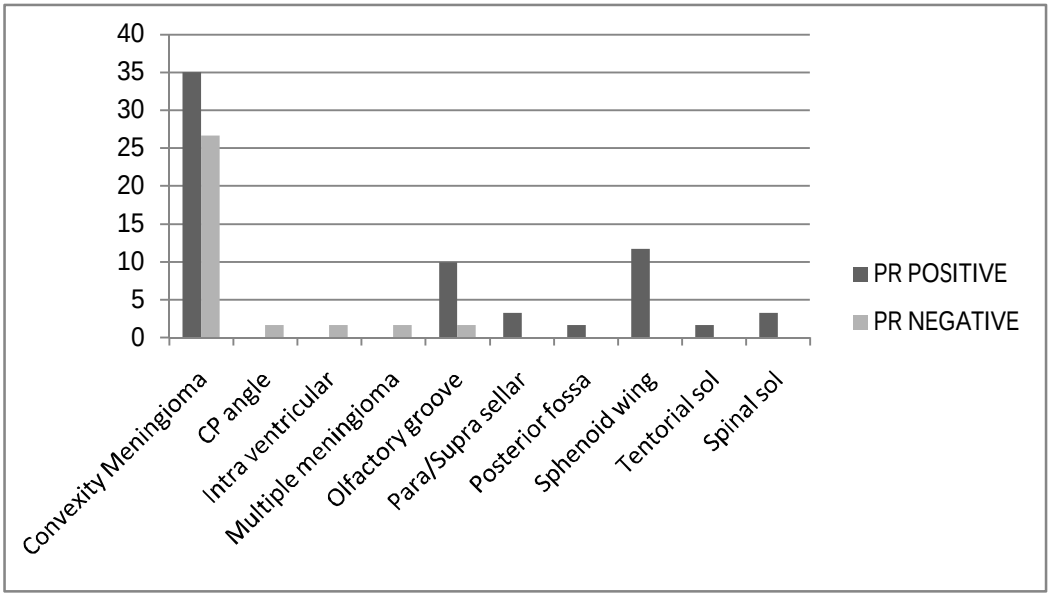
Of all the 60 cases, 38/58 intracranial Meningiomas and 2/2 of the intraspinal Meningiomas were positive for PR. The various site of occurrence of Meningiomas were compared with the level of PR expression and is given below in table and chart 12. There was no difference in the degree of positivity

of Meningiomas among different location of Meningiomas and were not statistically significant with a P value of 0.542.

TABLE 12:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG THE VARIOUS SITES OF OCCURRENCE OF MENINGIOMAS

SITE		PR POSITIVE (number of cases & %)	PR NEGATIVE (number of cases & %)	TOTAL (number of cases & %)
Intracranial	Convexity Meningiomas	21 (35)	16 (26.7)	37 (61.7)
	CP angle	0 (0)	1 (1.7)	1 (1.7)
	Intra ventricular	0 (0)	1 (1.7)	1 (1.7)
	Multiple Meningiomas	0 (0)	1 (1.7)	1 (1.7)
	Olfactory groove	6 (10)	1 (1.7)	7 (11.7)
	Para/Supra sellar	2 (3.3)	0 (0)	2 (3.3)
	Posterior fossa	1 (1.7)	0 (0)	1 (1.7)
	Sphenoid wing	7 (11.7)	0 (0)	7 (11.7)
	Tentorial sol	1 (1.7)	0 (0)	1 (1.7)
Intraspinal	Spinal sol	2 (3.3)	0 (0)	2 (3.3)
	TOTAL	40 (66.7)	20 (33.3)	60 (100)

CHART 12:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG THE VARIOUS SITES OF OCCURRENCE OF MENINGIOMAS

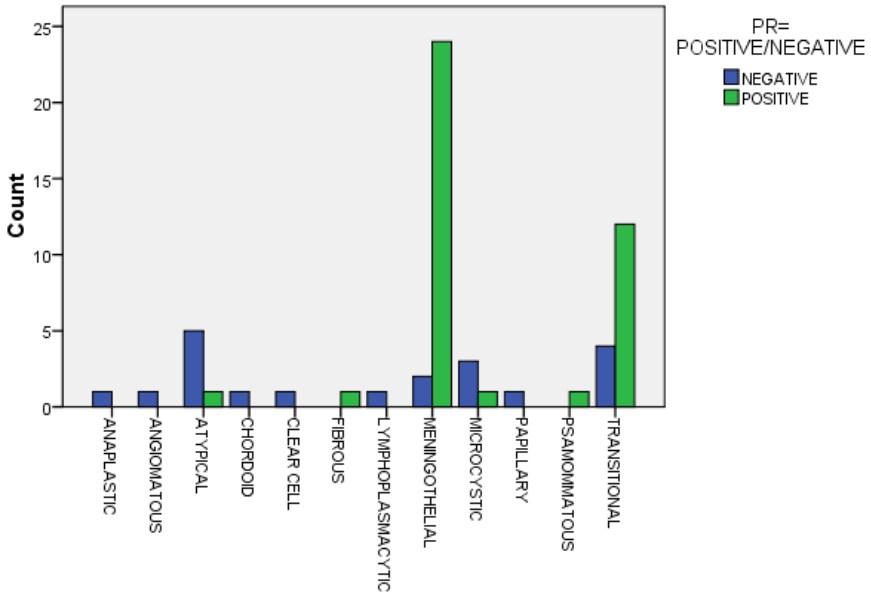


The PR expression in different histopathological types of Meningiomas are given below in table and chart 13. Among all types of Meningiomas, meningothelial variant (40% of total PR positive cases) showed the maximum expression of PR followed by the transitional type(20% of total PR positive cases). One case of multiple Meningioma (transitional type) in the cerebral convexity was encountered and it showed negativity for progesterone receptors.

TABLE 13:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG DIFFERENT HISTOPATHOLOGICAL TYPES OF MENINGIOMAS

GRADE	HPE TYPES	TOTAL NUMBER OF CASES	PR POSITIVE (number of cases & %)	PR NEGATIVE (number of cases & %)
GRADE I	Meningothelial Meningioma	26 (43.3)	24 (40)	2 (3.3)
	Transitional Meningioma	16 (26.7)	12 (20)	4 (6.7)
	Fibrous Meningioma	1 (1.7)	1 (1.7)	0 (0)
	Lympho plasmacyte rich Meningioma	1 (1.7)	0 (0)	1 (1.7)
	Microcystic Meningioma	4 (6.7)	1 (1.7)	3 (5)
	Angiomatous Meningioma	1 (1.7)	0 (0)	1 (1.7)
	Psammomatous Meningioma	1 (1.7)	1 (1.7)	0 (0)
GRADE II	Atypical Meningioma	6 (10)	1 (1.7)	5 (8.3)
	Chordoid Meningioma	1 (1.7)	0 (0)	1 (1.7)
	clear cell Meningioma	1 (1.7)	0 (0)	1 (1.7)
GRADE III	Anaplastic Meningioma	1 (1.7)	0 (0)	1 (1.7)
	Papillary Meningioma	1 (1.7)	0 (0)	1 (1.7)

CHART 13:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG DIFFERENT HISTOPATHOLOGICAL TYPES OF MENINGIOMAS

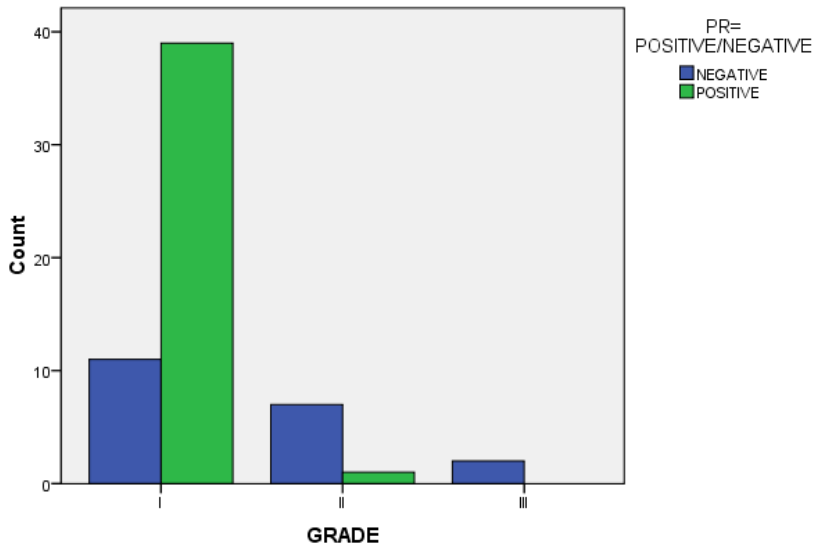


Among the 60 cases, 50, 8 and 2 cases belonged to grade I, II and III respectively and their progesterone receptor positivity status is given in table and chart 14.

TABLE 14:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG DIFFERENT GRADES OF MENINGIOMAS

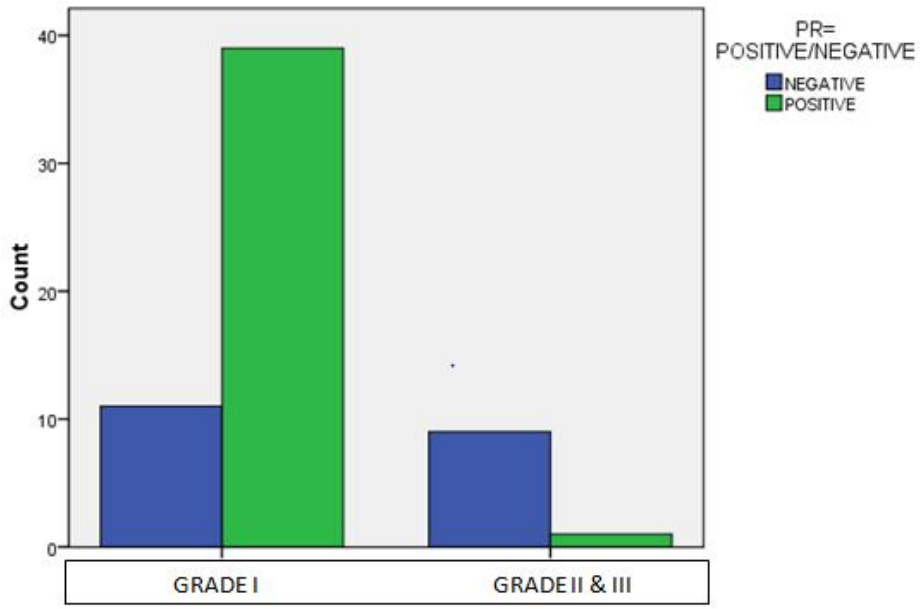
	Grade I Meningiomas (number of cases & %)	Grade II Meningiomas (number of cases & %)	Grade III Meningiomas (number of cases & %)	TOTAL (number of cases & %)
PR POSITIVE	39 (65)	1 (1.7)	0 (0)	40 (66.7)
PR NEGATIVE	11 (18.3)	7 (11.7)	2 (3.3)	20 (33.3)
TOTAL	50 (83.3)	8 (13.3)	2 (3.3)	60 (100.0%)

CHART 14:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG DIFFERENT GRADES OF MENINGIOMAS



Comparison of immunohistochemical expression of PR in grade I Meningiomas with high grade Meningiomas is shown below in table 15

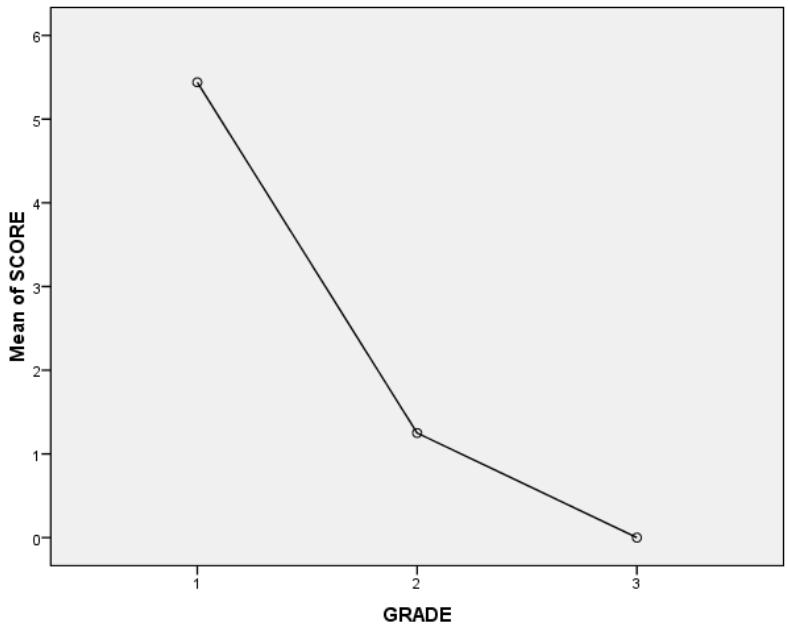
TABLE 15:-COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION OF GRADE I WITH HIGHER GRADE (GRADE II AND III) MENINGIOMAS



In comparison with grade I Meningiomas the immunohistochemical expression of PR in high grade (II and III) Meningiomas were found to be from weak to absent (as shown above in table 15), thereby showing a statistically significant (P value= 0.00) association between low rates of expression of PR and increased tumour aggressiveness.

The mean cumulative progesterone receptor positivity score (obtained by addition of the intensity score with the score for percentage of positive cells) also shows that the scores are high with grade I Meningiomas and decreases as one moves through grade II to grade III as shown below in chart 15.

CHART 15:- COMPARISON OF THE MEAN CUMULATIVE PROGESTERONE RECEPTOR POSITIVITY SCORE AMONG DIFFERENT GRADES OF MENINGIOMAS



The recurrence rate among Meningiomas in this study period of 3 years was 3.3% (7 cases). Of these 7 cases , 2(28.6%), 4(57%) and 1(14%) cases belonged to grade I,II and III respectively(given in chart 16). All these cases of recurrent Meningiomas showed negativity for progesterone receptors. The two cases of grade I Meningiomas that showed recurrence had evidence of brain infiltration. Thereby showing that loss of PR expression is associated with increased tumour aggressiveness and recurrence proving their association to be statistically significant (P value= 0.000).

CHART 16:- COMPARISON OF PROGESTERONE RECEPTOR EXPRESSION AMONG CASES OF RECURRENT MENINGIOMAS WITH RESPECT TO COMPARISON BETWEEN BENIGN (GRADE I) MENINGIOMAS AND HIGH GRADE (GRADE II AND III) MENINGIOMAS

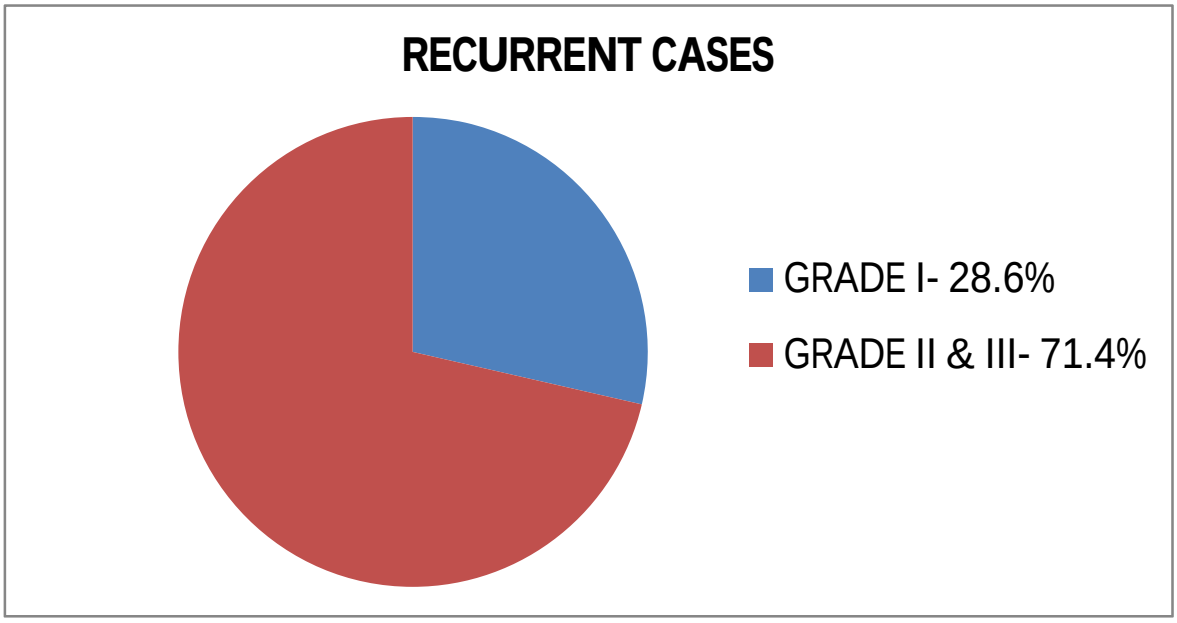
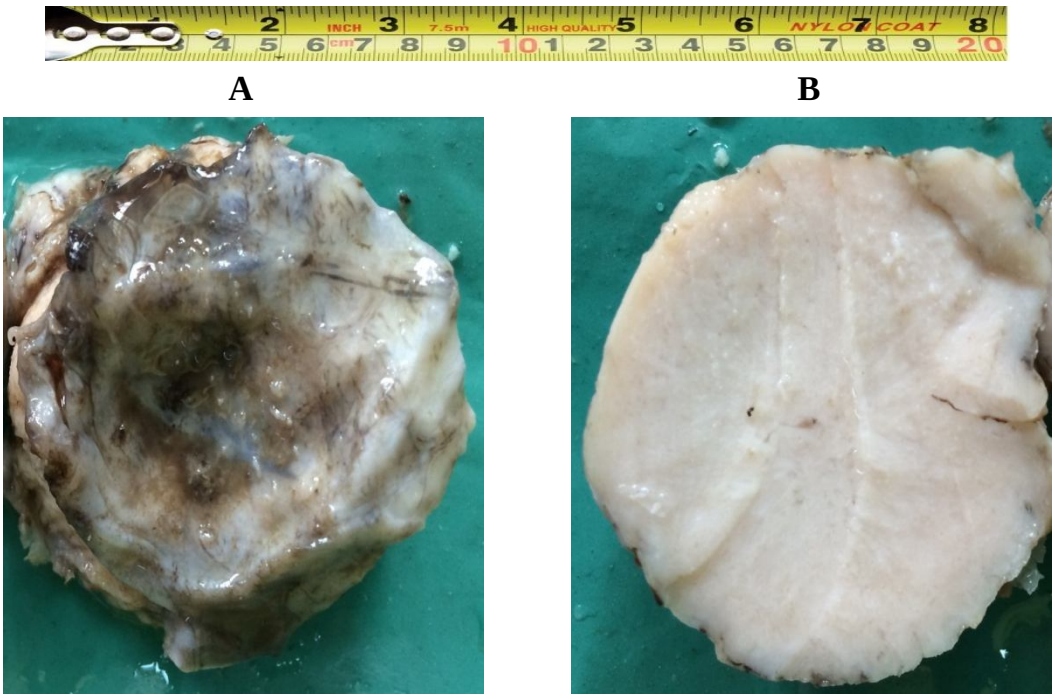
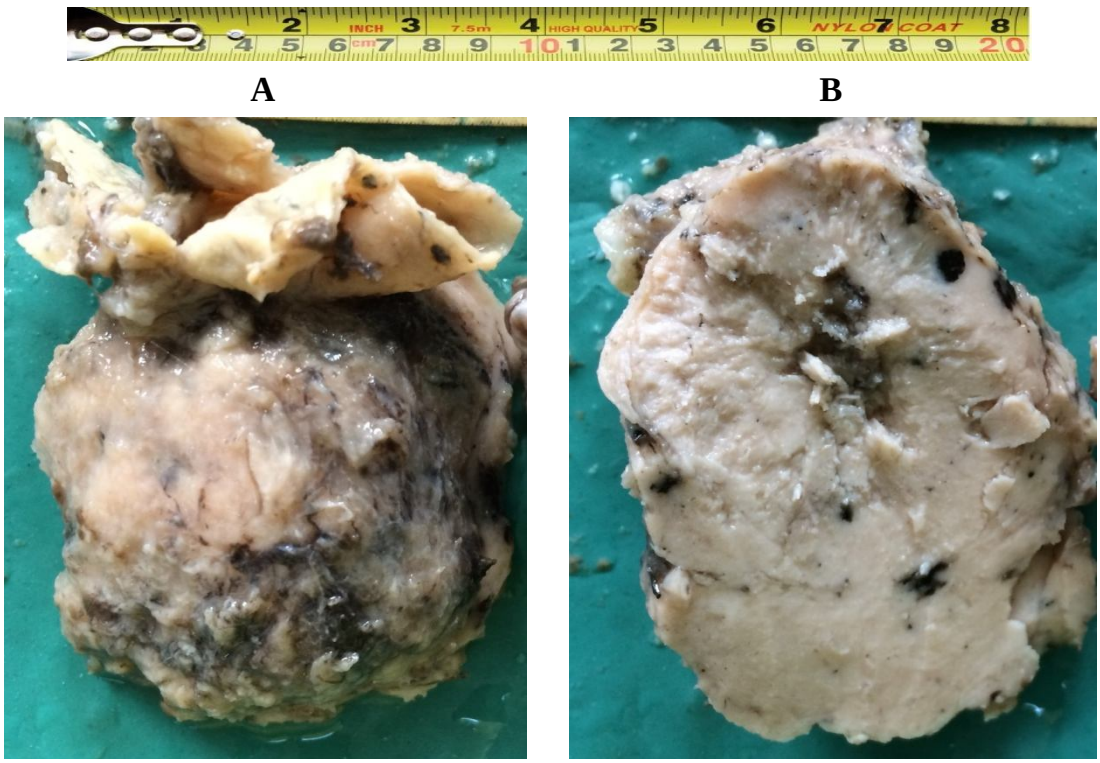


FIGURE 1 :- 178/15:– grade I Meningioma- (A) External surface showing dural attachment. (B) Cut surface showing homogenous solid and whorled appearance



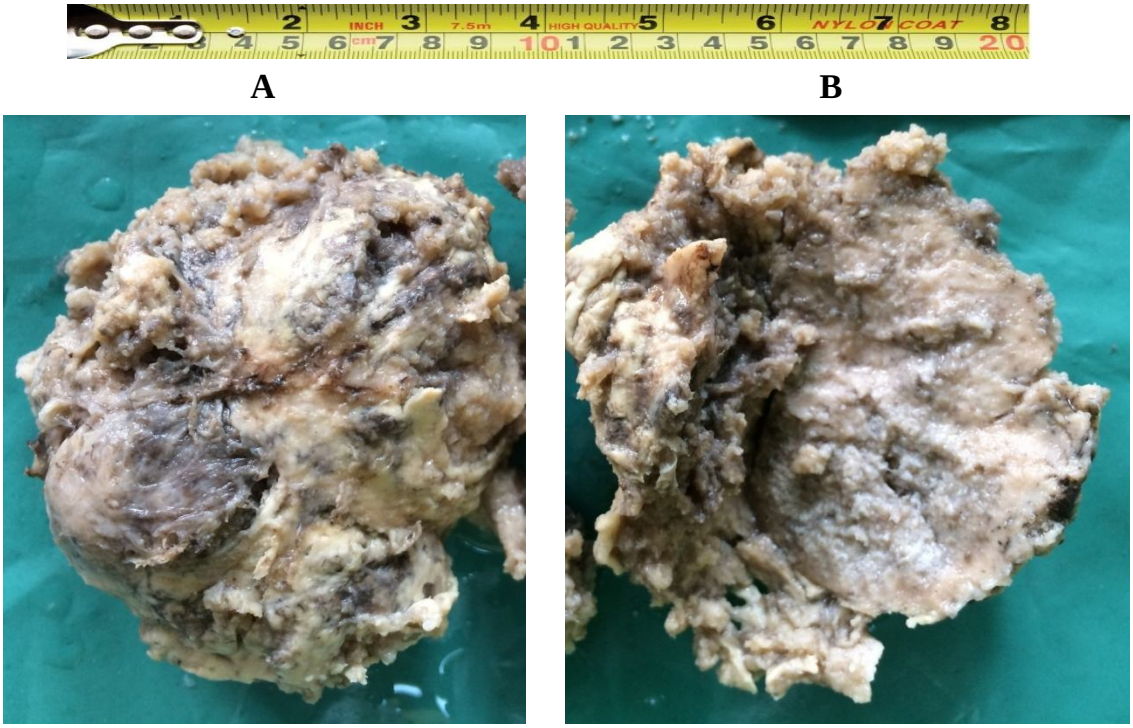
A **B**

FIGURE 2 :- 326/14:– Atypical (grade II) Meningioma- (A) External surface showing dural attachment. (B) Cut surface showing solid grey white mass with focal necrotic foci.



A **B**

FIGURE 3:- 215/15:– Papillary (grade III) Meningioma- (A) External surface. (B) Cut surface showing large solid, friable mass with papillary projections with necrotic and hemorrhagic areas.



A **B**

FIGURE 4:- HPE number 53/14:- Meningothelial Meningioma H&E(400X)

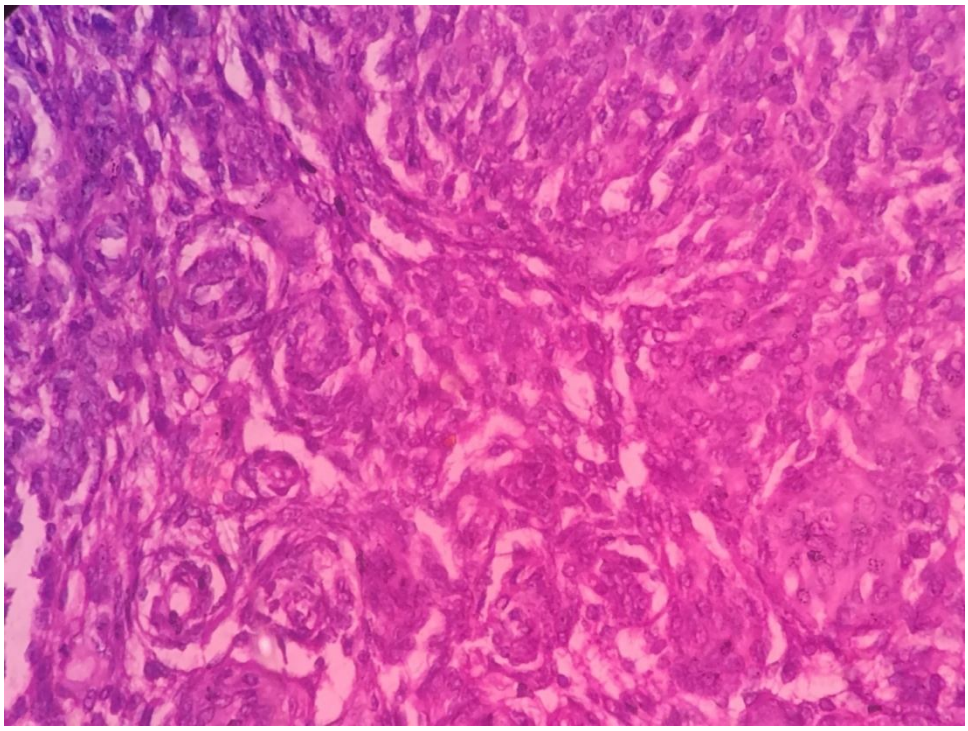


FIGURE 5:- HPE number 178/15:- PR strong positivity (score 8/8) in Meningothelial Meningioma (400X)

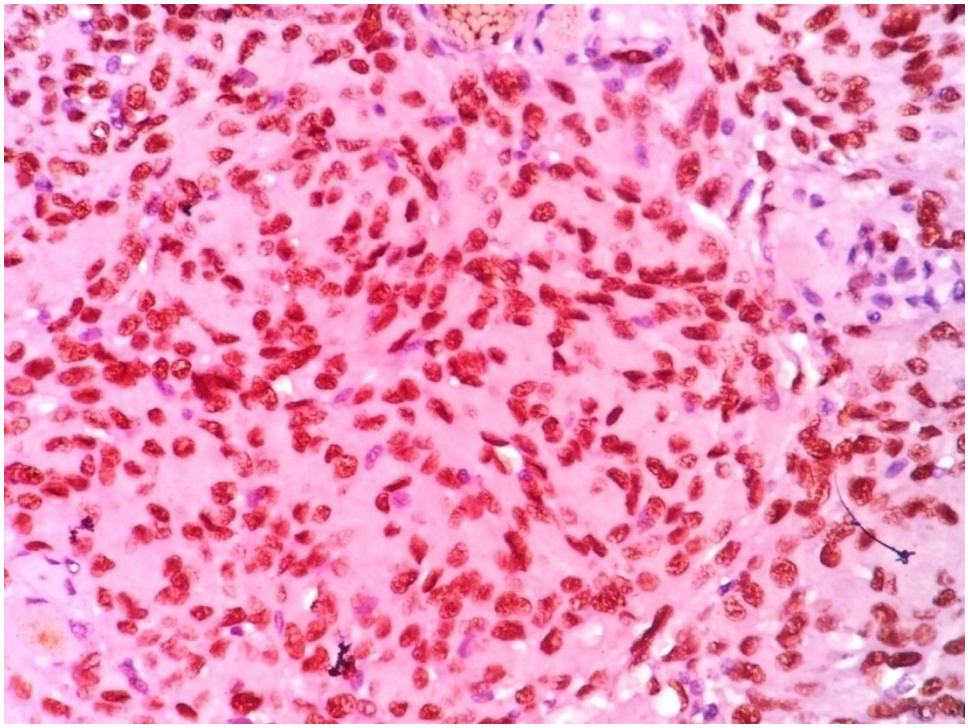


FIGURE 6:- HPE number 567/15:- PR moderate intensity of positivity (score 7/8) in Meningothelial Meningioma (400X)

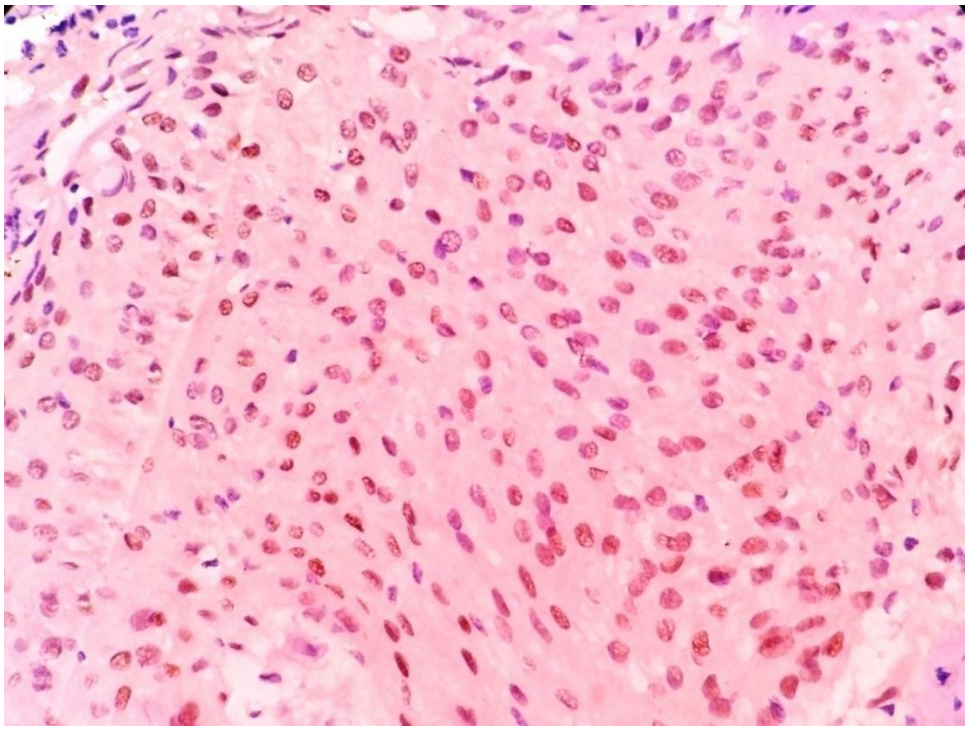


FIGURE 7:- HPE number 273/13:- PR weak intensity of positivity (score 3/8) in Meningothelial Meningioma (400X)

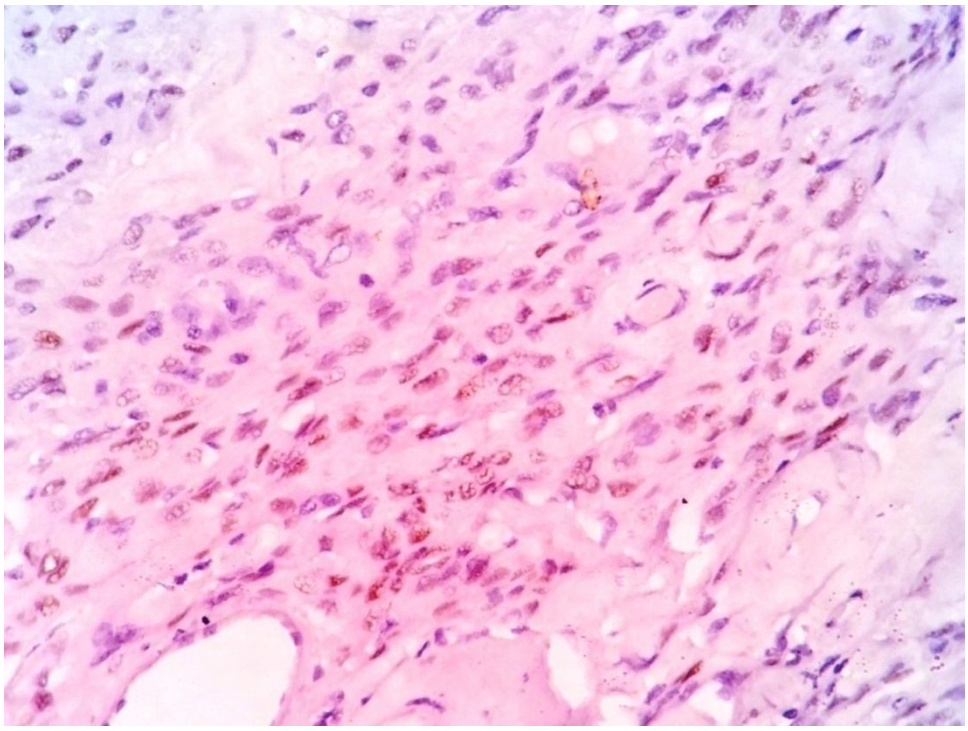


FIGURE 8:- HPE number 629/14:- Fibroblastic Meningioma H&E (100X)

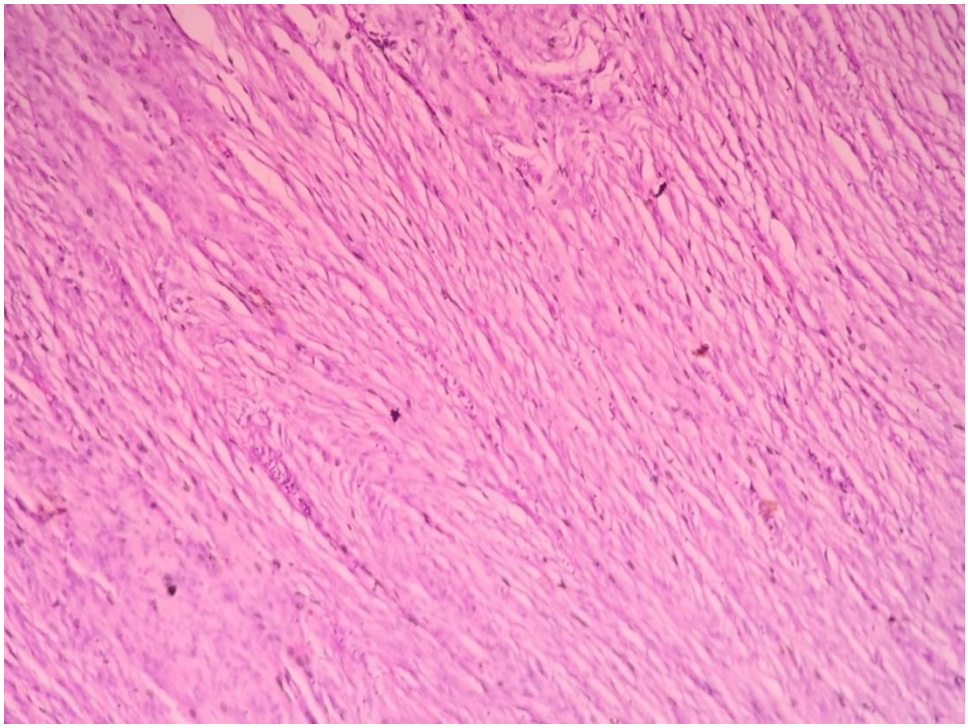


FIGURE 9:- HPE number 629/14:- moderate intensity of PR positivity (score 6/8) in Fibroblastic Meningioma (400X)

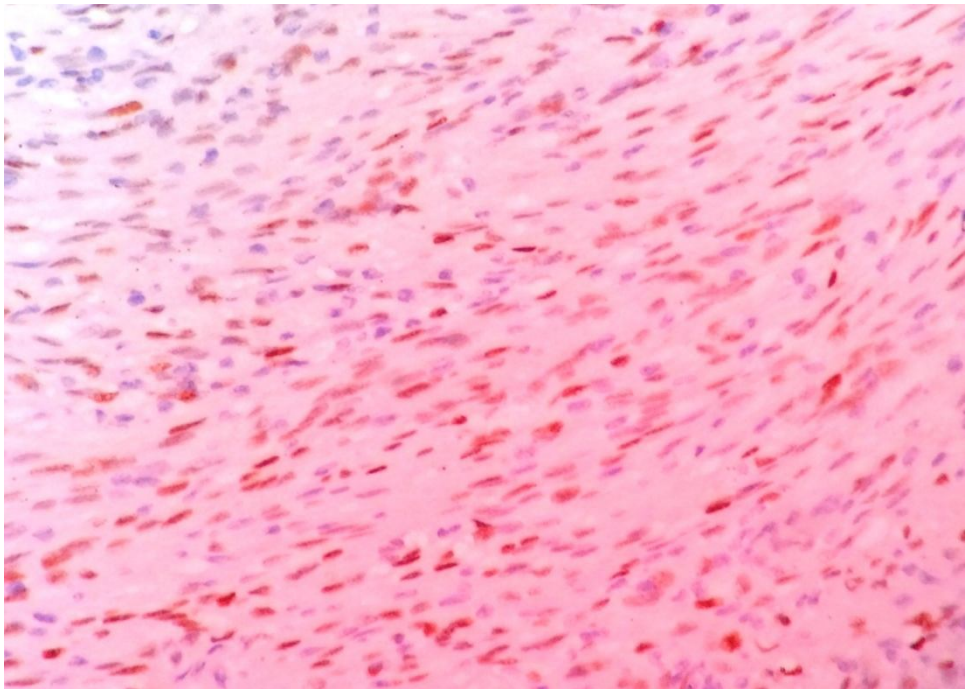


FIGURE 10:- HPE number 412/13:- Transitional Meningioma H&E (100X)

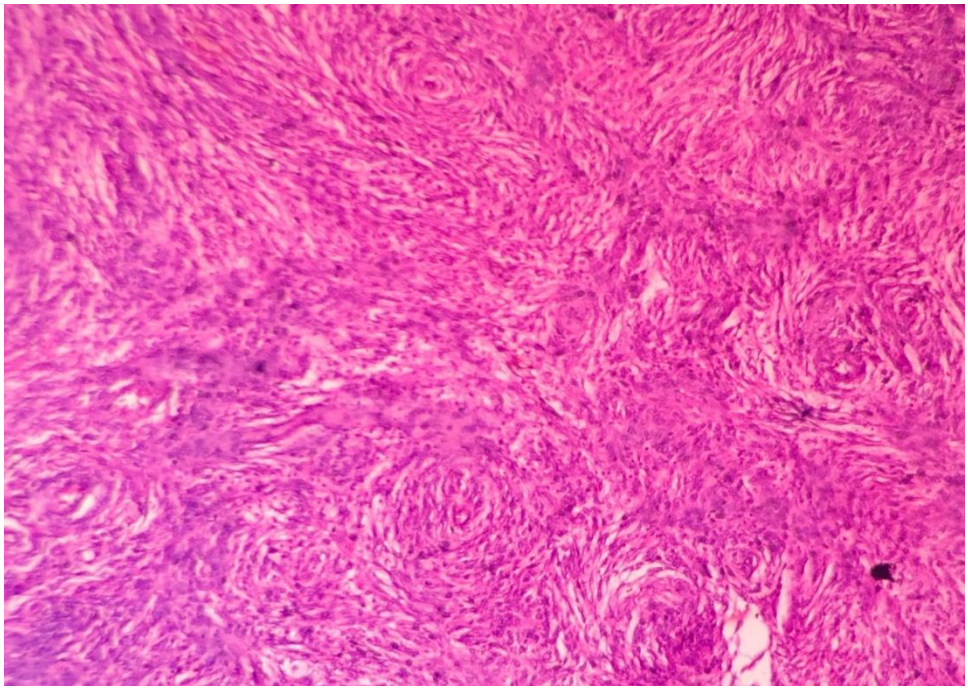


FIGURE 11:- HPE number 412/13: :- moderate intensity of PR positivity (score 8/8) in - Transitional Meningioma (100X)

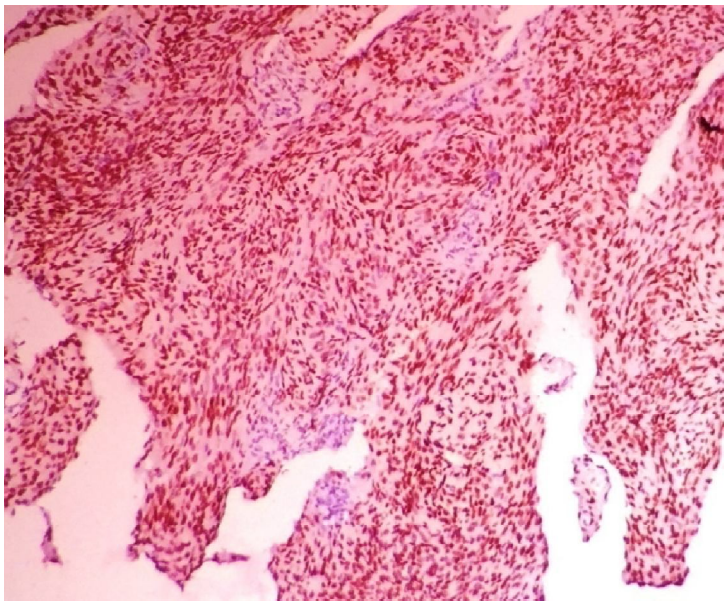


FIGURE 12:- HPE number 160/13:- Microcystic Meningioma H&E (400X)

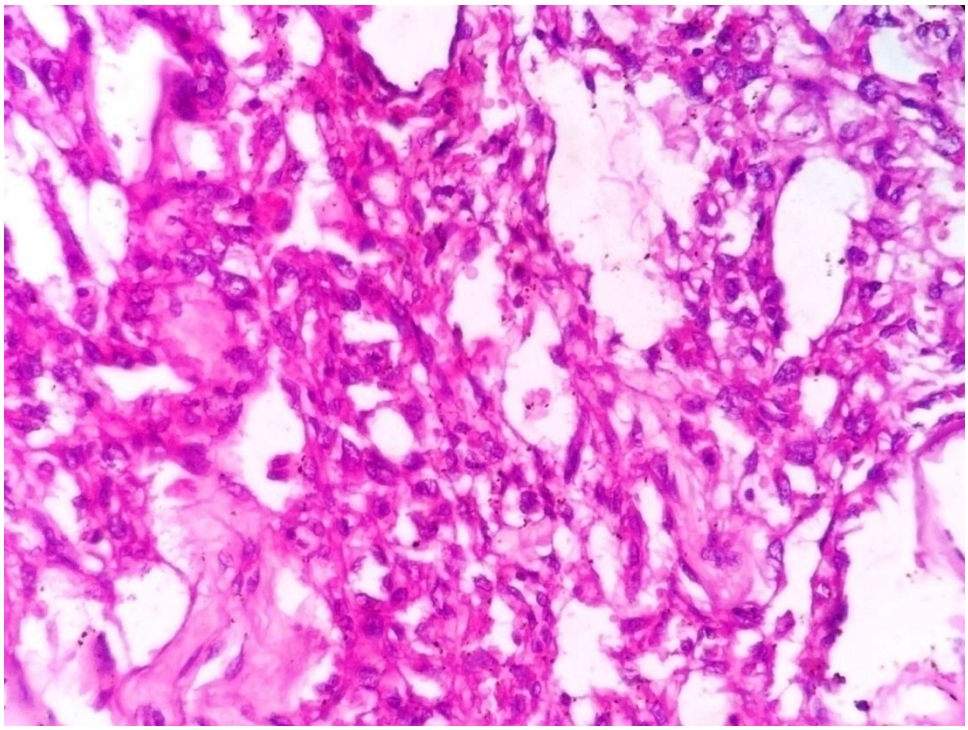


FIGURE 13:- HPE number 197/14: :- moderate intensity of PR positivity (score 4/8) in - Microcystic Meningioma (400X)

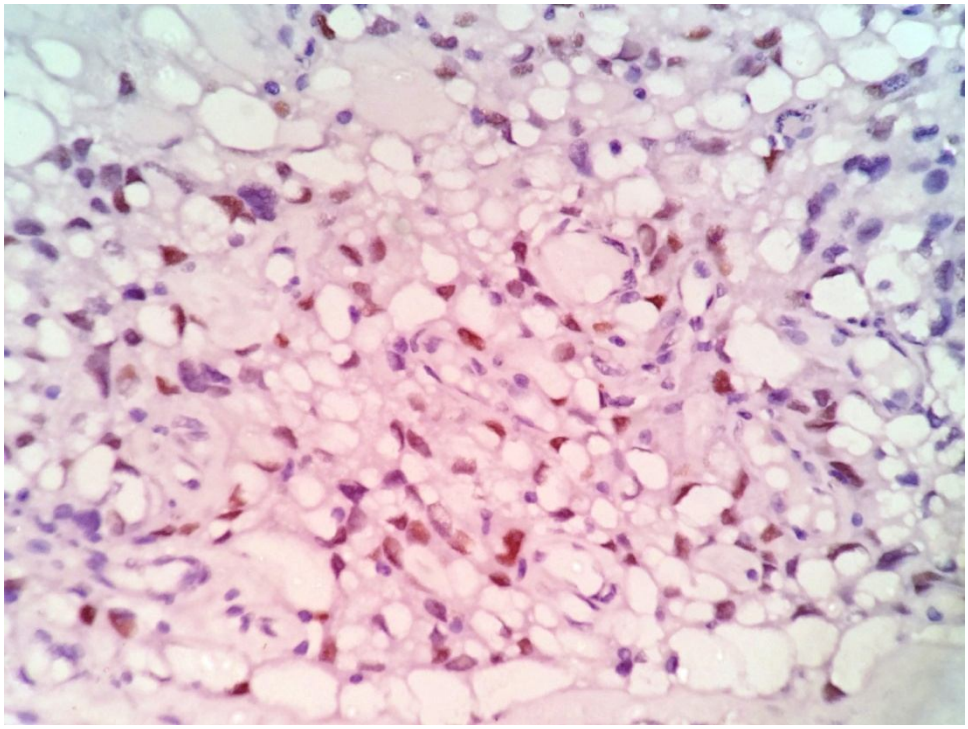


FIGURE 14:- HPE number 190/14:- Angiomatous Meningioma H&E (400X)

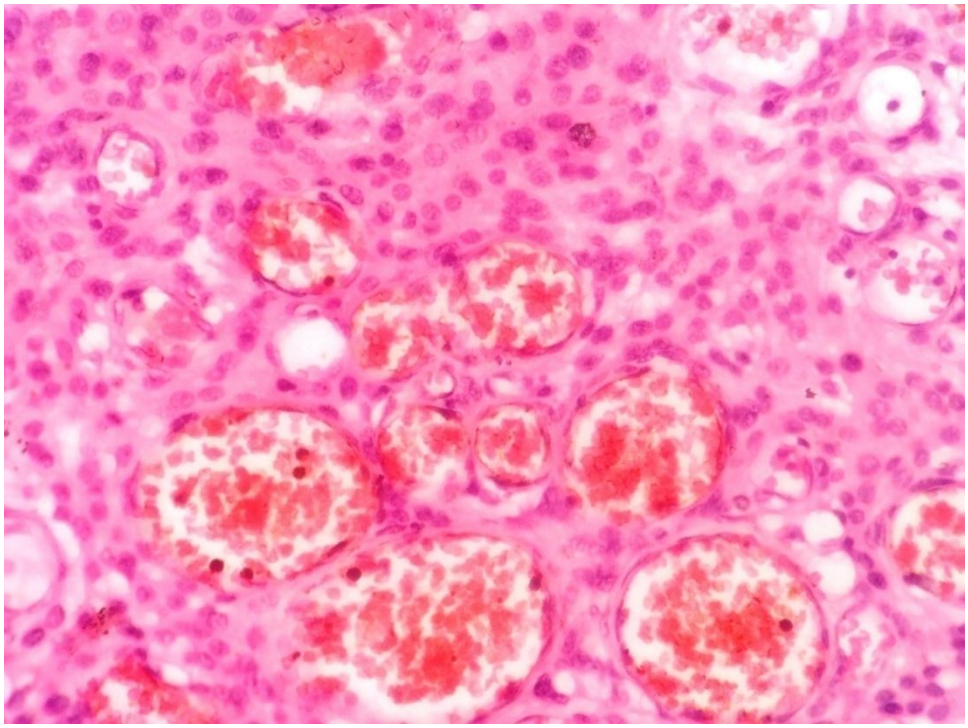


FIGURE 15:- HPE number 190/14: :- negative for PR (score 0) in Angiomatous Meningioma (400X)

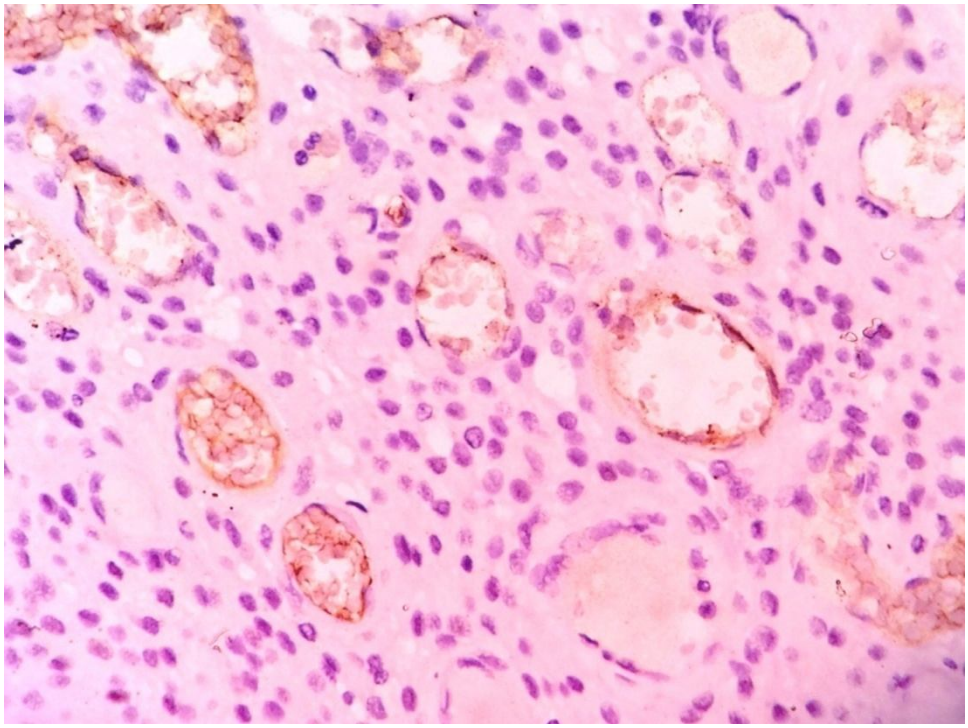


FIGURE 16:- HPE number 7/13:- Psamommatous Meningioma H&E (100X)

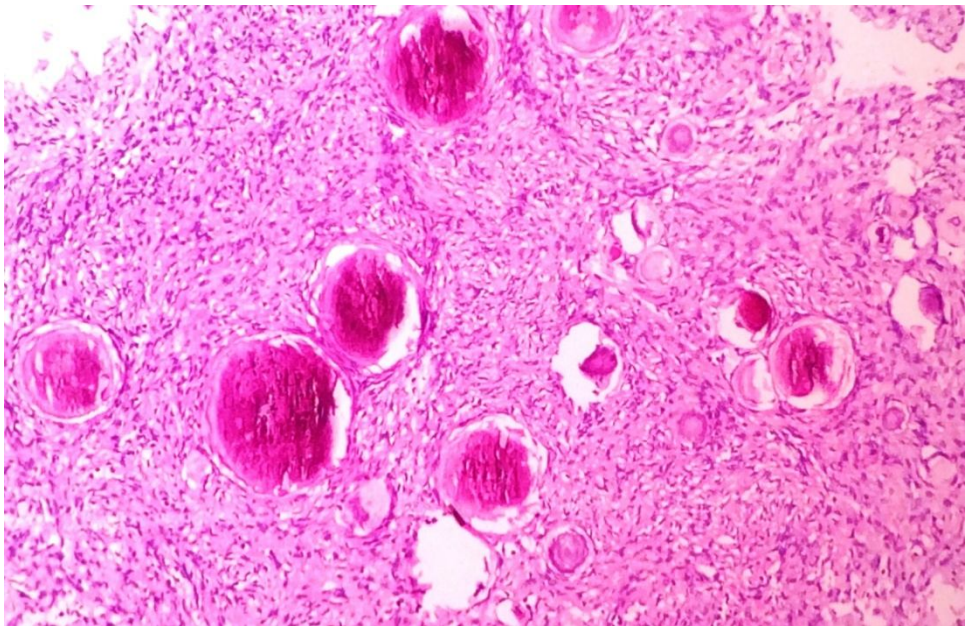


FIGURE 17:- HPE number 7/13: :- strong intensity of PR positivity (score 8/8) in – Psammomatous Meningioma (100X)

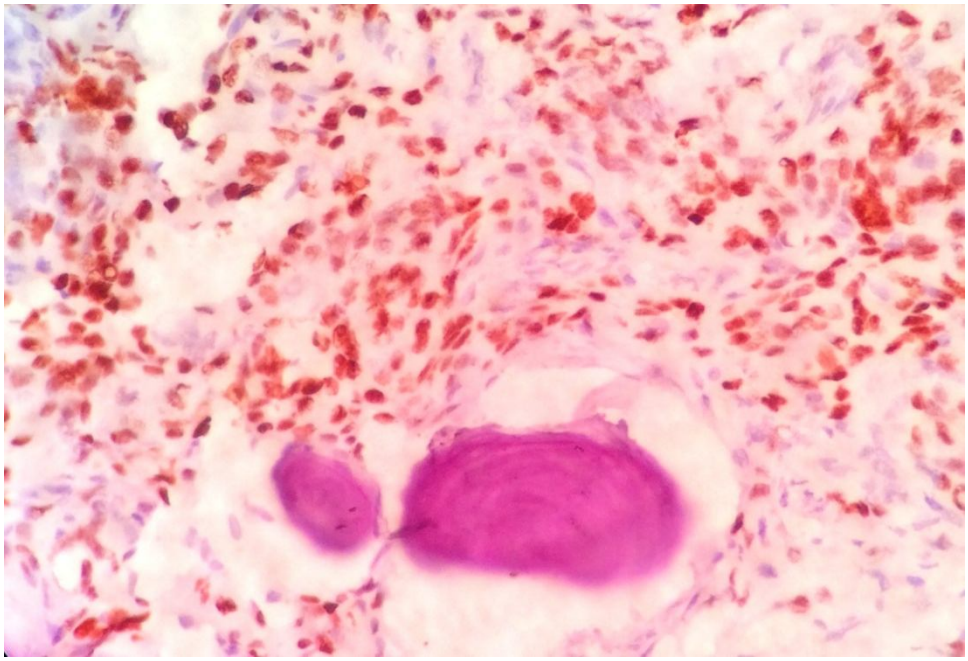


FIGURE 18:- HPE number 198/13:-Lymphoplasmacyte rich Meningioma H&E (400X)

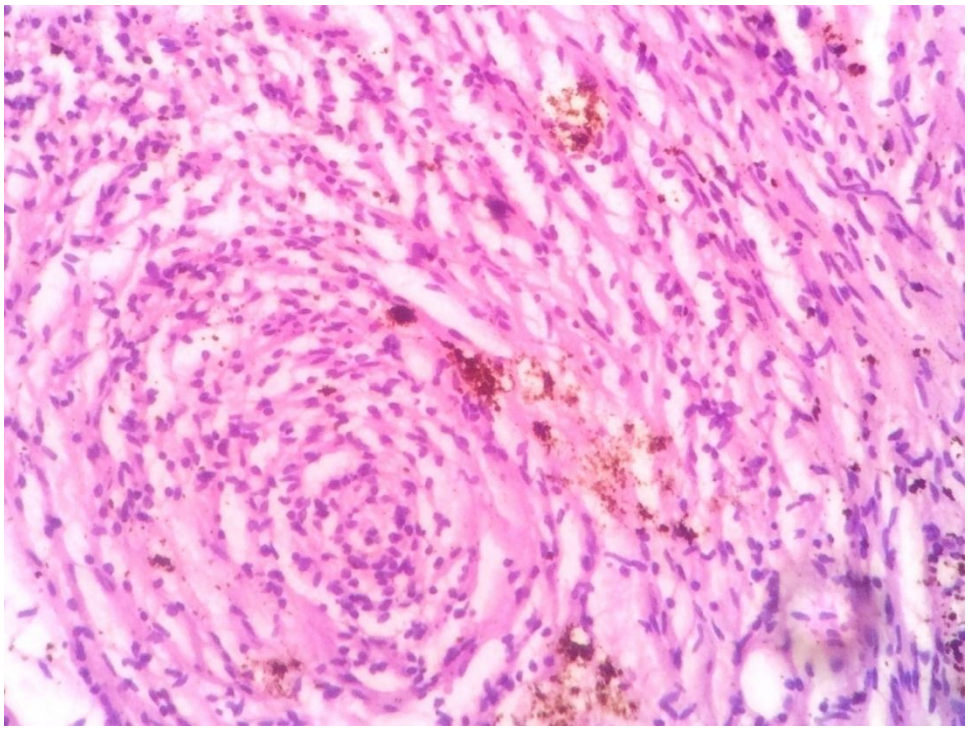


FIGURE 19:- HPE number 198/13: :- negative for PR (score 0) in – Lymphoplasmacyte rich Meningioma (100X)

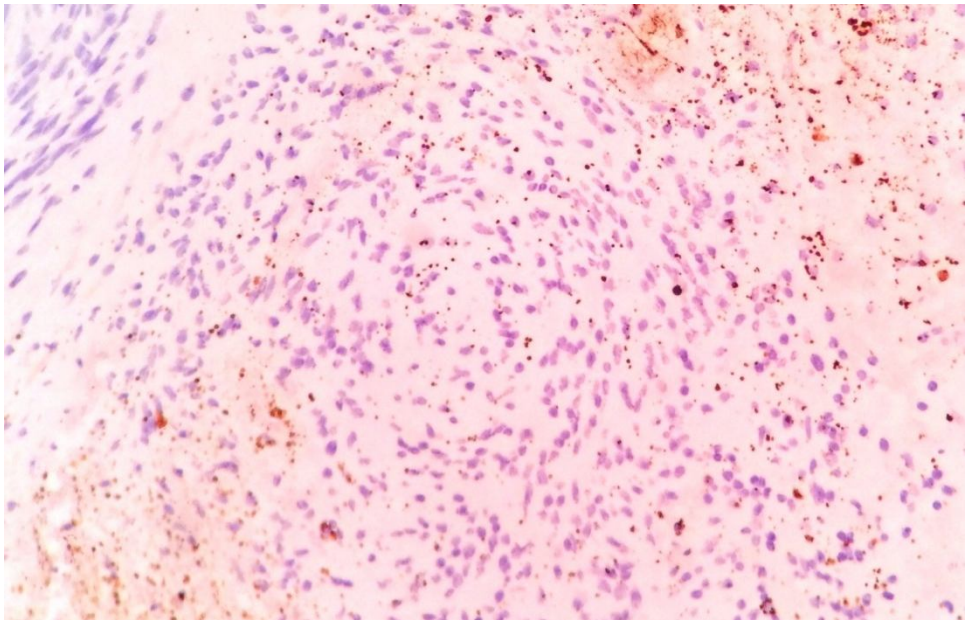


FIGURE 20:- HPE number 634/14:-Atypical Meningioma- showing sheet like pattern H&E (100X)

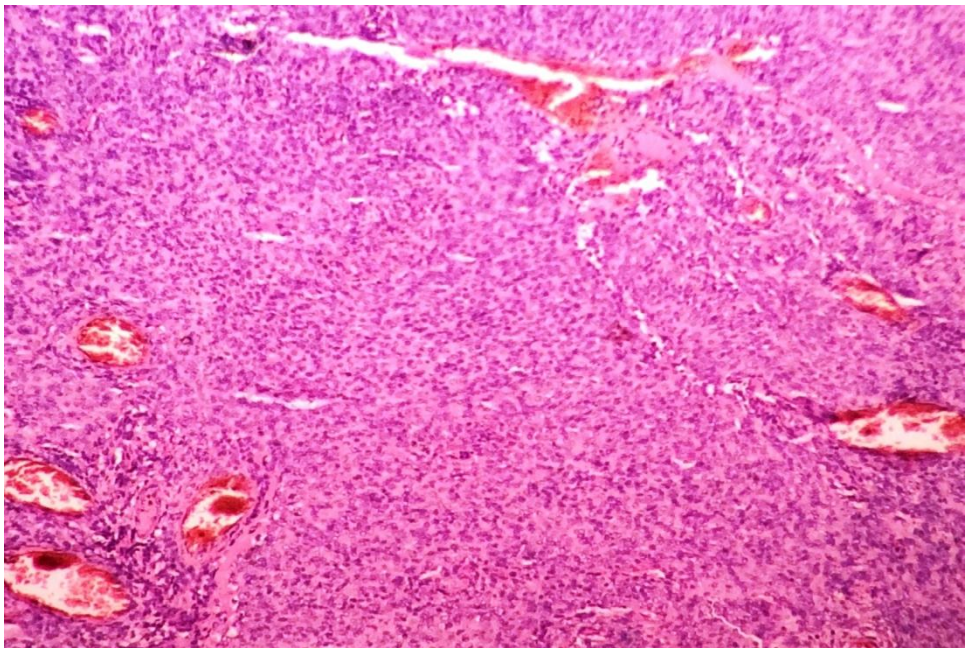


FIGURE 21:- HPE number 634/14:-Atypical Meningioma- showing necrosis H&E (400X)

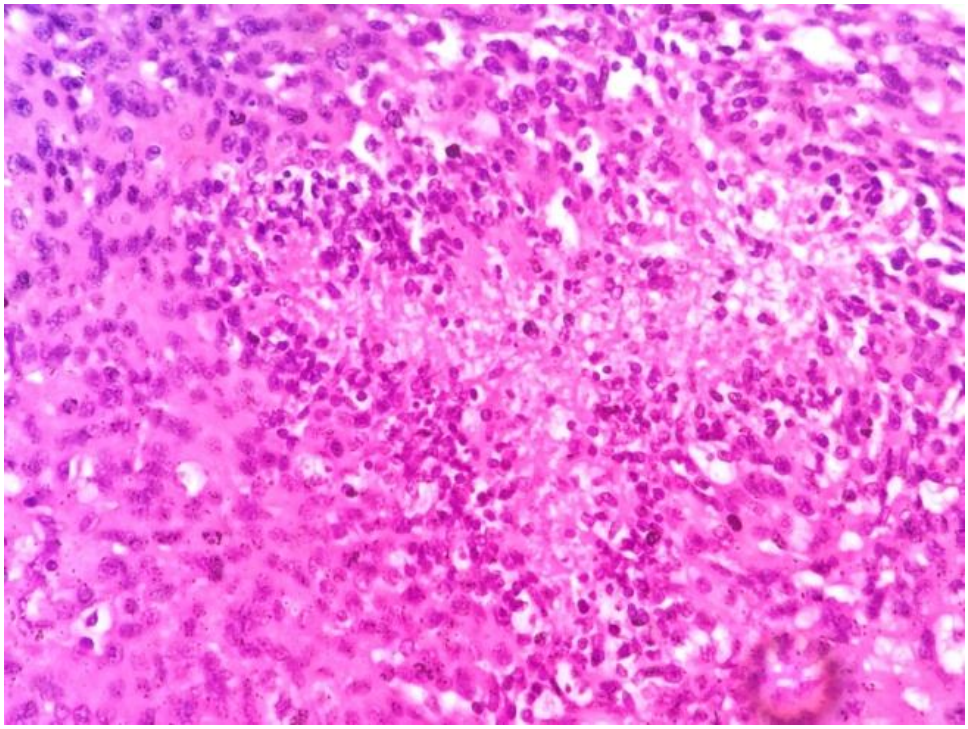


FIGURE 22:- HPE number 233/15: :- negative for PR (score 0) in – Atypical Meningioma (400X)

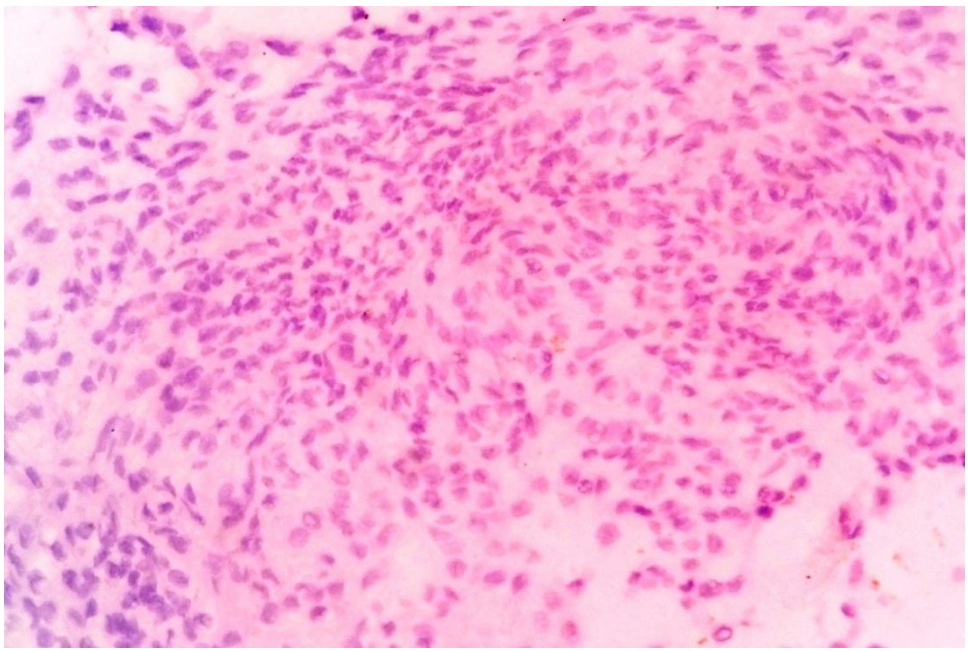


FIGURE 23:- HPE number 431/13:-Clear cell Meningioma H&E (400X)

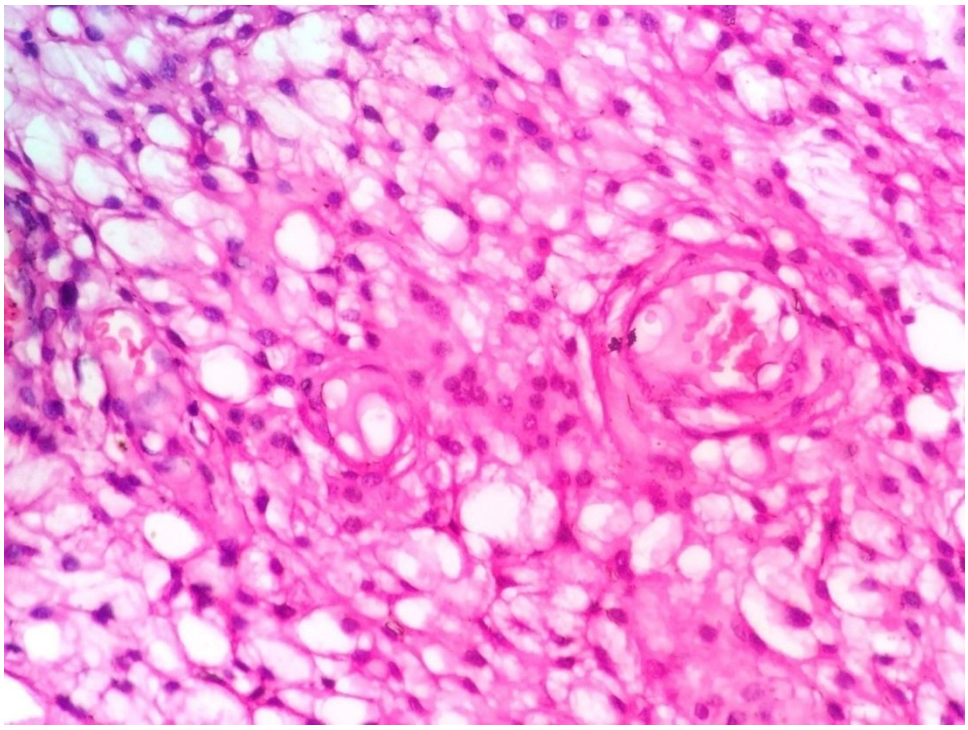


FIGURE 24:- HPE number 431/13: :- negative for PR (score 0) in Clear cell Meningioma (400X)

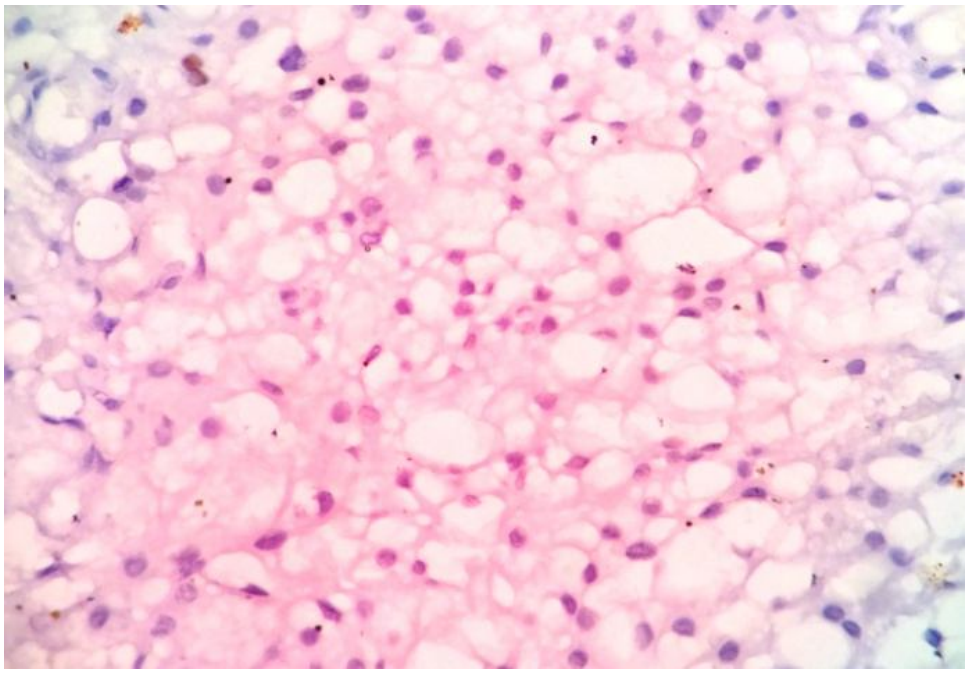


FIGURE 25:- HPE number 531/13:-Chordoid meningioma H&E (400X)

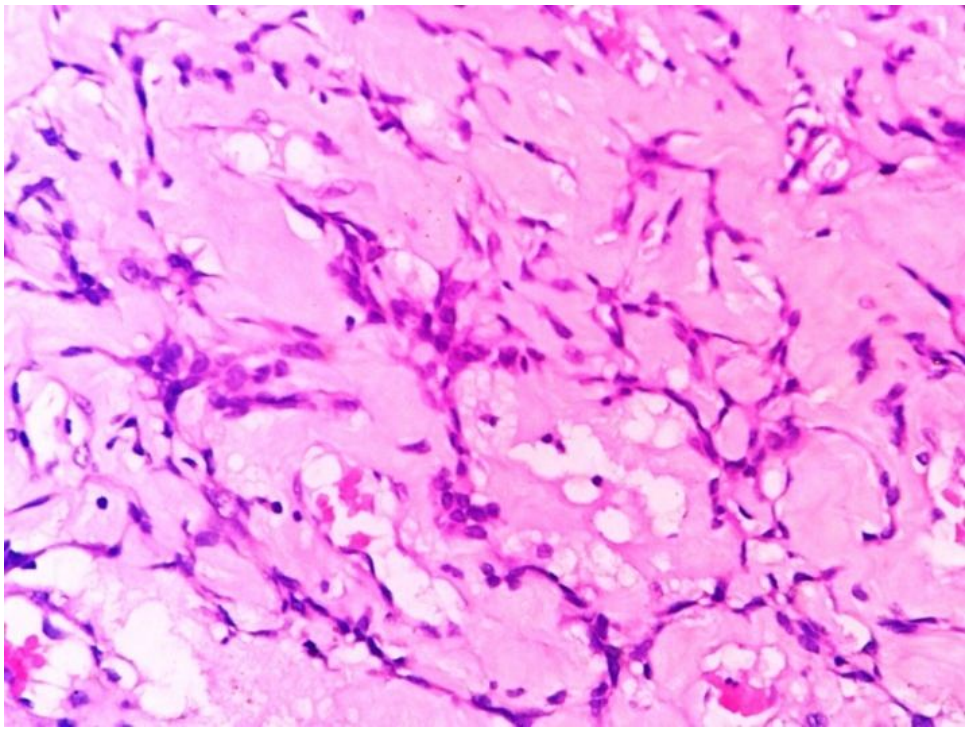


FIGURE 26:- HPE number 531/13: :- negative for PR (score 0) in – Chordoid Meningioma (400X)

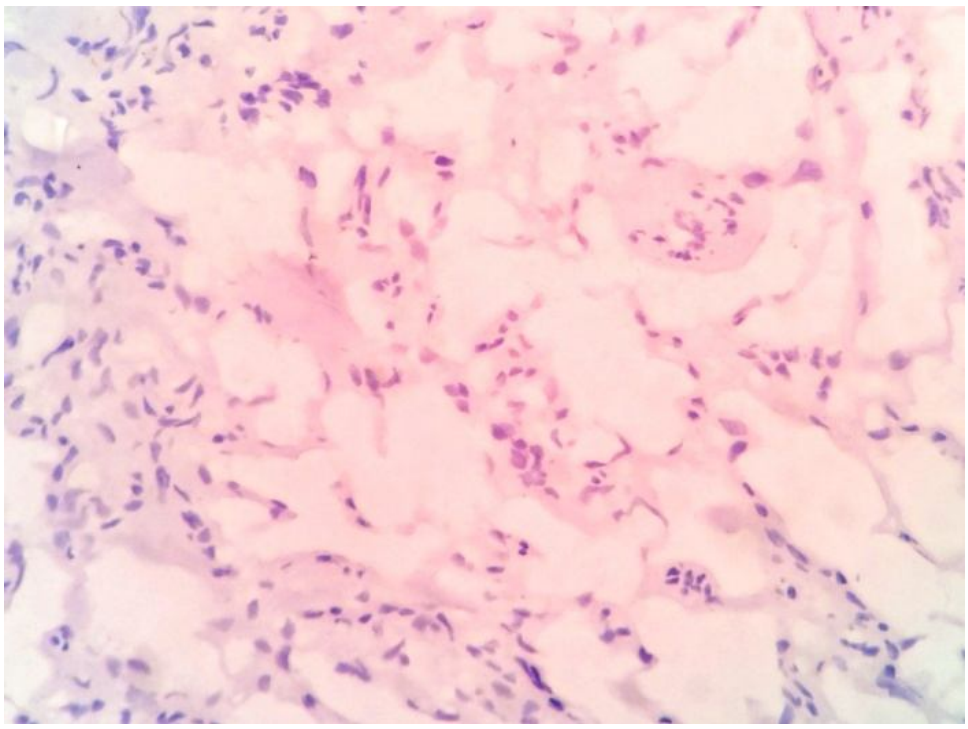


FIGURE 27:- HPE number 488/13:-Anaplastic Meningioma showing mitotic figures H&E (400X)

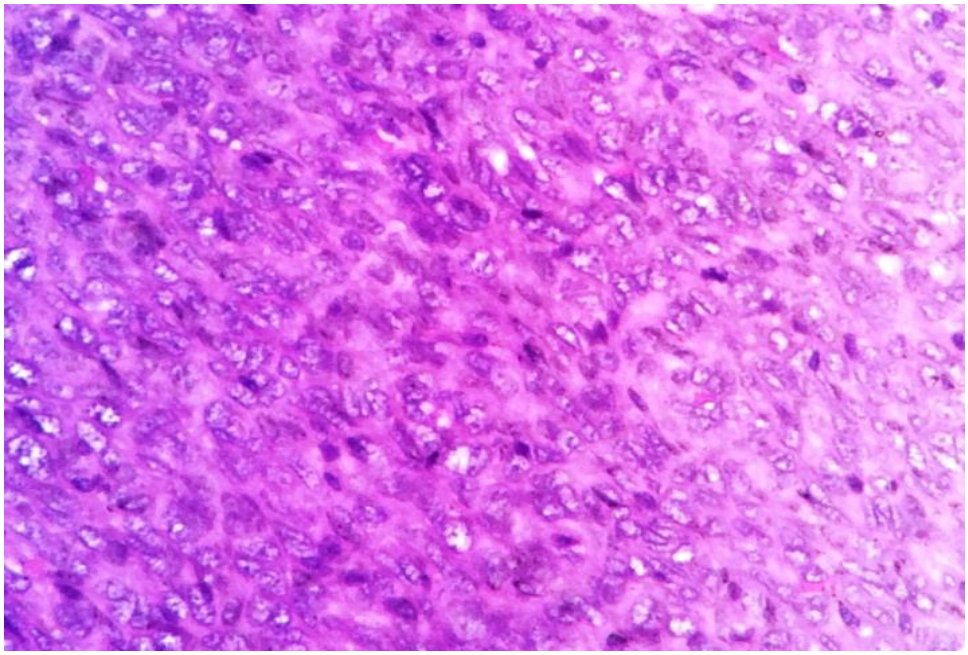


FIGURE 28:- HPE number 488/13:- negative for PR (score 0) in – Anaplastic Meningioma (400X)

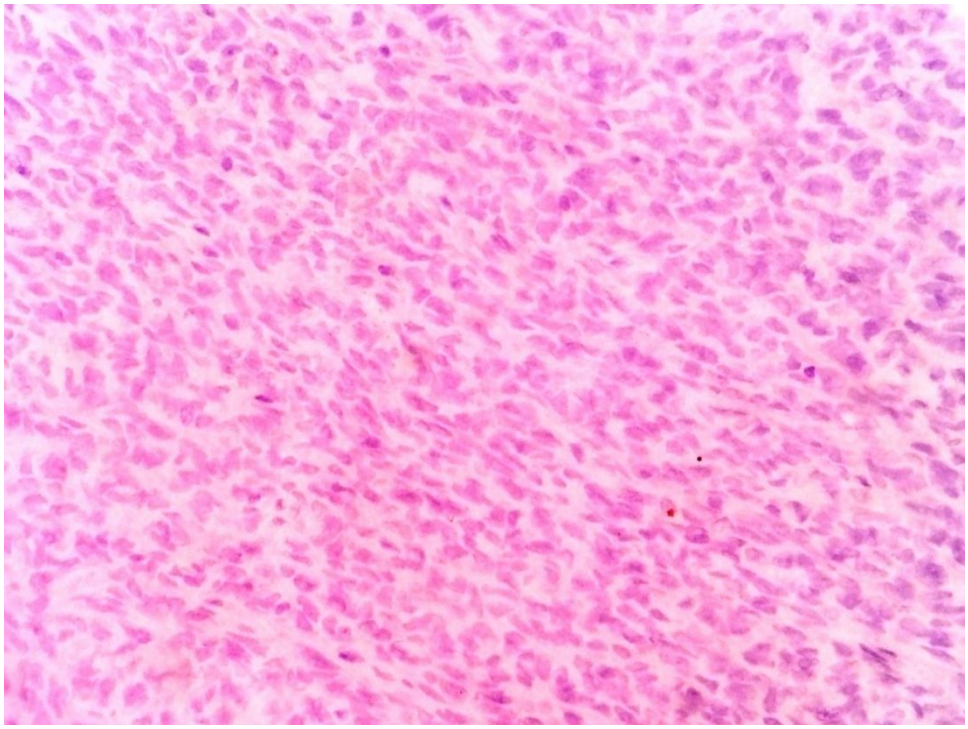


FIGURE 29:- HPE number 215/15:-Papillary Meningioma H&E (400X)

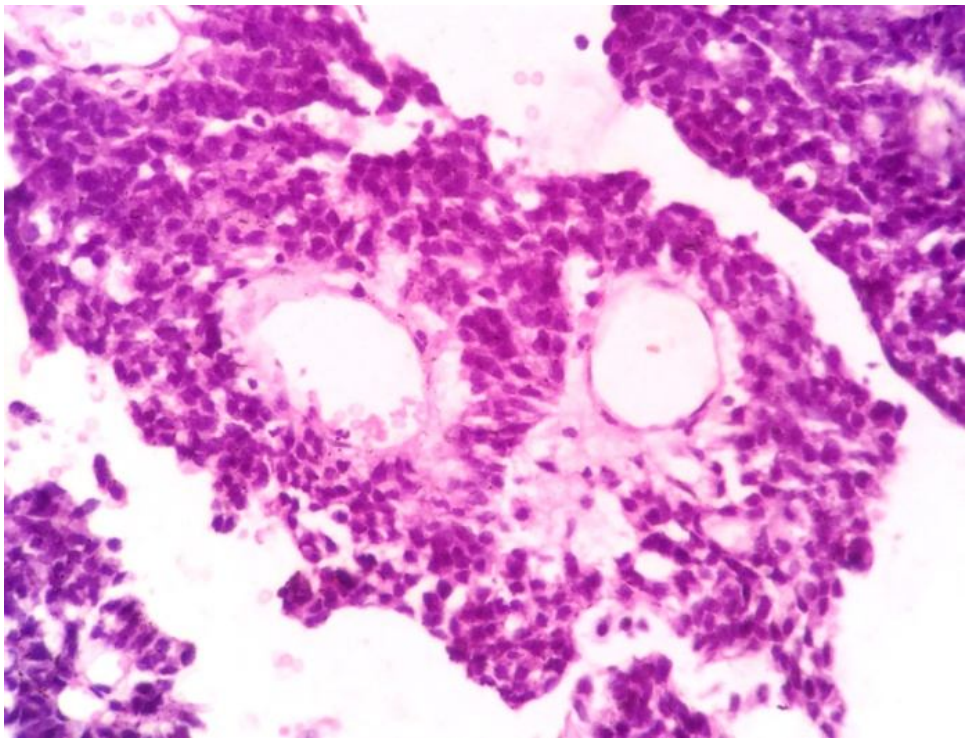
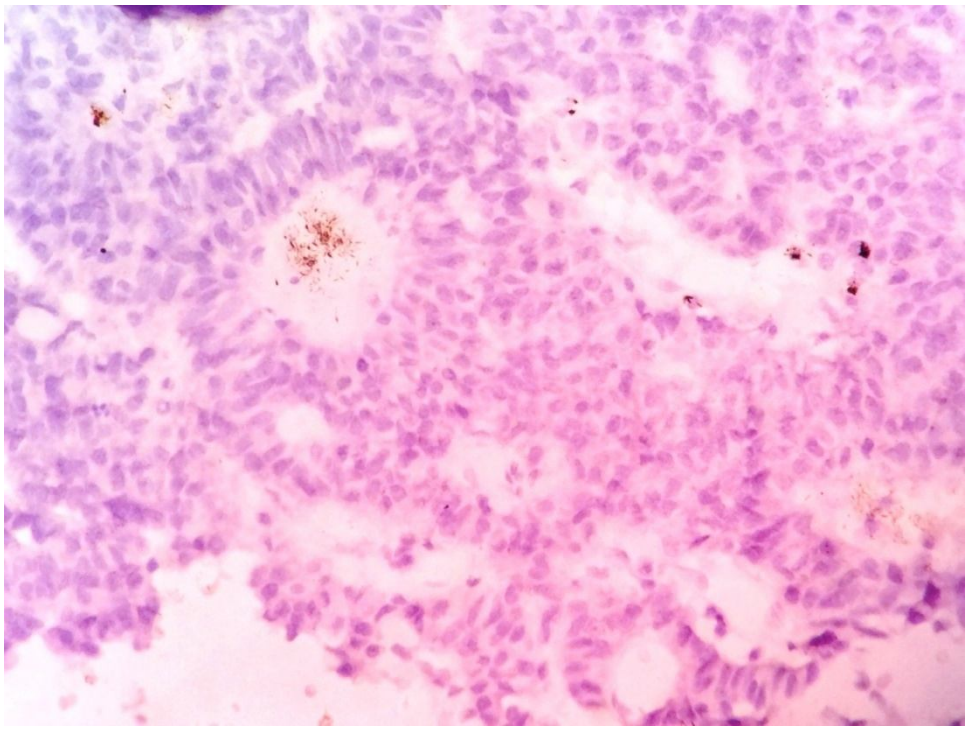


FIGURE 30:- HPE number 215/15: :- negative for PR (score 0) in – Papillary Meningioma (400X)



DISCUSSION

Meningiomas are the most common benign CNS neoplasms with a higher prevalence in women[1]. Though most of the tumours are benign and well circumscribed with a slow growth rate, many of them have been found to possess atypical and anaplastic features. Some of these turn out to be inoperable due to extensive invasion of brain and vessels or due to increased age at presentation with poor clinical condition to tolerate surgery.

The recurrence rate of benign, atypical and malignant Meningiomas were found to be 20,50 and 66% respectively at the end of 10 years[66].The major factors for recurrence includes young age at presentation, subtotal resection, increased proliferation rates, brain infiltration, higher histological grades and specific subtypes [65] .

Histomorphology of Meningiomas are so diverse that it required a revision in the WHO 2000 to WHO 2007 classification [65] . This study is undertaken not only to analyze the histopathological spectrum of Meningiomas and their grading but also to know about the association of different histopathological features with the behaviour of the tumours.

Clinical & epidemiological data reveal that Meningiomas are hormone sensitive tumours and they have been found to express hormonal receptors. Introduction of specific monoclonal antibodies to these steroid

hormone receptors have led to their identification [47] . This current study also throws light on the immunohistochemical expression of Progesterone receptor (PR) in various histopathological types and grades of Meningiomas & it's correlation with some of the clinical parameters.

The mean age at surgery among benign, atypical and malignant Meningiomas in the present study and other studies done by M taghipour et al, Thomas backer- grondahl et al, Arlete hilbig et al and Ramesh babu telungu et al are as follows:-

(i) The age of occurrence of benign meningiomas ranged from 45-58 years.

(ii) The age of occurrence of atypical meningiomas ranged from 44-59 years.

(iii) The age of occurrence of malignant meningiomas ranged from 43-50.6 years.

Comparison of age distribution of Meningiomas among various studies as given below in table 16.

TABLE 16:- COMPARISON OF AGE DISTRIBUTION OF MENINGIOMAS BETWEEN THE PRESENT STUDY AND OTHER STUDIES

	AGE IN YEARS		
	BENIGN	ATYPICAL	MALIGNANT
Present study	48	49	43
M taghipour et al [59]	47	49	58
Thomas Backer-Grondahl et al [65]	58	59	61
Arlete hilbig et al [47]	48	44	44
Ramesh babu telungu et al [67]	45	44.2	50.6

As in other studies, there was a greater prevalence of Meningiomas among female patients in this study also, that explains the hormonal dependant growth of these tumours [59, 65] .

Comparison of sex distribution of Meningiomas among various studies as given below in table 17.

The prevalence of meningiomas among male and female patients in the present and the other studies ranged from 25 to 37.3% and 62.7 to 75% respectively. The male:female ratio in various studies ranged from 1:1.6 to 1:3.

TABLE 17:- COMPARISON OF SEX DISTRIBUTION OF MENINGIOMAS BETWEEN THE PRESENT STUDY AND OTHER STUDIES

	MALE	FEMALE	MALE : FEMALE RATIO
Present study	37.3%	62.7%	1 :1.6
Arlete hilbig et al [47]	32.1%	67.9%	1:2.5
Thomas Backer-Grondahl et al [65]	25%	75%	1 : 3
Nasrin shayanfar et al [53]	32%	68%	1:2.5
Ramesh babu telungu et al [67]	34.82%	65.18%	1:1.9

Convexity Meningiomas were the ones that were most commonly encountered in various studies as like this study of interest. Few studies states about the predilection of atypical meninigiomas for non skull base locations as encountered in this study [68,69].

Comparison of site distribution of Meningiomas among various studies as given below in table 18.

TABLE 18:-COMPARISON OF LOCATION OF MENINGIOMAS BETWEEN THE PRESENT STUDY AND OTHER STUDIES

SITE	Present study (%)	Thomas Backer-Grondahl et al [65] (%)
Falcine and Convexity Meningiomas	60.6	59
Posterior fossa & Tentorial sol	7.5	10.8
Intra ventricular	1.5	0.7
Basal	30.4	29.5

According to Nasrin shayanfar et al and Thomas Backer-Grondahl et al the first 3 most common types of ,Meningiomas were meningothelial, transitional and fibrous types and this correlates well with this study also. The distribution of various types of Meningiomas in this study parallels the finding in other studies also such as done by Thomas backer at al, Willis J et al and Uzum N et al[10,70].

Comparison of the frequency of occurrence of the different histopathological types of Meningiomas among various studies as given below in table 19.

The minor differences in the proportion of cases in each type of Meningiomas between the current study and study done by Ramesh babu telungu et al may be due to subjective error in the grading of the tumour.

TABLE 19:- FREQUENCY OF OCCURRENCE OF DIFFERENT HISTOPATHOLOGICAL TYPES OF MENINGIOMAS BETWEEN THE PRESENT STUDY AND A STUDY BY RAMESH BABU TELUNGU ET AL:-

VARIOUS TYPES OF MENINGIOMAS	Present study (%)	Ramesh babu telungu et al [67] (%)
Meningothelial Meningioma	40.7	23.6
Transitional Meningioma	25.4	17.85
Fibrous Meningioma	7.2	12.5
Lympho plasmacyte- rich Meningioma	0.5	-
Microcystic Meningioma	2.9	2.67
Angiomatous Meningioma	7.2	4.91
Psammomatous Meningioma	7.7	14.28
Secretory Meningioma	-	0.44
Atypical Meningioma	6.2	1.33
Clear cell Meningioma	0.5	1.33
Chordoid Meningioma	0.5	-
Anaplastic Meningioma	0.5	0.52
Papillary Meningioma	0.5	2.23

The grade I or benign Meningiomas were most frequently encountered in all the studies. Except for a slight degree of variation in the proportion of cases among various grades, this study goes well with most other studies done by Thomas backer- grondahl et al, Arlete hilbig et al, Nasrin shayanfar et al, Norden et al and Ramesh babu telungu et al with regard to the three grades of Meningiomas.

Comparison of the frequency of occurrence of the different grades of Meningiomas among various studies as given below in table 20.

TABLE 20:- FREQUENCY OF OCCURRENCE OF VARIOUS GRADES OF MENINGIOMAS IN THE PRESENT STUDY AND OTHER STUDIES

	GRADE I	GRADE II	GRADE III
Present study	91.4%	7.7%	1%
Thomas Backer-Grondahl et al [65]	68.9%	30.1%	1%
Arlete hilbig et al [47]	75.2%	19.9%	5.68%
Nasrin shayanfar et al [53]	80.7%	12.8%	6.4%
Norden AD et al [71]	90%	5-7%	1-3%
Ramesh babu telungu et al [67]	86%	10.7%	3.1%

Some studies suggested that the prevalence of atypical and malignant Meningiomas were high among males [59,65,72] .But the current study did not correlate with these findings and there was a higher female prevalence among benign meninigiomas where as the prevalence was equal among male and female cases among high grade Meningiomas in this study.

The comparison of prevalence of sex among various grades of Meningiomas between various studies are given below in table 21.

TABLE 21:- FREQUENCY OF OCCURENCE OF VARIOUS GRADES OF MENINGIOMAS AMONG MALES AND IN THE PRESENT STUDY AND A STUDY DONE BY RAMESH BABU TELUNGU ET AL

Sex		GRADE I	GRADE II	GRADE III
Male	Present study	36.1%	50.0%	50.0%
	Ramesh babu telungu et al [67]	34.7%	35.2%	28.6%
Female	Present study	63.9%	50.0%	50.0%
	Ramesh babu telungu et al [67]	65.28%	62.5%	71.43%

DETAILED ANALYSIS OF VARIOUS HISTOPATHOLOGICAL FEATURES DEALT IN THIS STUDY

As assessed in this study, the mutual correlation between high grade Meningiomas and the histological features such as small cell change, sheet like pattern, high mitotic counts, necrosis, prominent nucleoli and hypercellularity has also been positively correlated by Thomas backer et al in 2012 in their study on histopathological spectrum of meningiomas.

These five histopathological features that were used assess the aggressive behaviour of Meningiomas are together called as "soft criteria" [65]. Presence of these features along with increased mitotic activity in the tumour cells points to aggressive nature of the tumour and they should be labelled as high grade Meningiomas. Presence of atleast one of the above features in an otherwise benign Meningiomas should prompt the labelling of these tumours as "benign meningioma with atypical features" [65] and the other associated features for a high grade tumour must also be carefully searched for.

The various confounding factors faced during analysis of these soft criteria deserves a special mention.

The small cell change was also difficult to access in certain foci of tumour that had inflammatory cell infiltrate, apoptotic changes and in those cells found in close proximity to necrosis.

The normal syncytial pattern of growth of Meningiomas, hypervascularity and inflammatory infiltrates in some Meningiomas simulated a sheet like architecture or hypercellularity of the tumour.

Regarding necrosis in Meningiomas, they can either be small or large. Most of the large areas of necrosis arising out of radiation therapy or preoperative embolisation were not included in the study. Only those spontaneously occurring micronecrosis arising out of tumour undernourishment or tumor cell hypoxia were accounted.

As said by perry et al, those nucleoli visible at 10x magnification shall be called as macronucleoli was so useful in assessing this feature in the tumours included in this study[73]. Nuclear pleomorphism in tumour cells was seen not as a sign of anaplasia but as a simple degenerative phenomenon[73] by some investigators. But the findings in this particular study correlated the association between nuclear pleomorphism and increased grades of tumour.

In a study by Thomas Backer-Grondahl et al [65] , presence of vesiculous tumour nuclei was positively correlated with grade II meningioma. This study also finds a similar association between vesiculous nuclei and higher grades of Meningiomas.

In this present study hypervascularity was seen more commonly with atypical and anaplastic variants of Meningiomas but they were also demonstrated in good number of cases of grade I Meningiomas such as angiomatous, microcystic and a few cases of meningothelial Meningiomas. Though hypervascularity indicates aggressive behaviour of tumour as said in some studies[65] and also in the current study, their association with some benign Meningiomas prevents from considering it as a full-fledged criteria for aggressive behaviour of the tumour.

Mitotic counts are one of the most important criterion to assess the grading pattern in Meningiomas. There are various techniques of assessing the mitotic counts and the most common and simplest method being evaluation for mitotic figures in a normal hematoxylin and eosin stained sections. But this method produces inconsistent results due to interobserver variability and mistaking of pyknotic cells for mitotic figures. Therefore to ward over this problem, some of the methods that produces more consistent results have been brought in to play such as immunohistochemical staining for Ki67 (MIB-1 labelling) and PHH 3 (phospohistone H3)[74] . This study also finds that increasing grades of Meningiomas had increased mitotic activity in their tumour cells.

The presence of psamomma bodies indicates an increased occurrence of fibrosis in the tumour. The increased fibrosis and collagen deposition seen in Meningiomas have been linked to the production of certain growth factors such as VEGF and EGF by the meningothelial cells[75] . These findings are seen in all Meningiomas irrespective of whether they are benign or high grade meninigiomas as said in few studies [65] . But in this current study of interest both the psamomma bodies and fibrosis with collagen deposition were predominantly seen among benign Meningiomas and their effect on prognosis of the tumour is unknown.

Xanthomatous or foamy cell change in the meningotheliomatous cells were seen predominantly in tumours cells that surrounds the bloodvessels. This may be due to the fluid leaking out of blood vessels being uptaken by the surrounding tumour cells producing a foamy nature of the cytoplasm.

Inflammatory cells such as lymphocytes and plasma cells are seen in meningiomas represents an immune response towards the tumour cells regardless of its type or grade. Both the foamy cell change and inflammatory cell infiltration was seen in almost all grades of meningioma in this study and hence had no diagnostic or prognostic significance.

Though many of the above histopathological features helps the pathologist to gauge and grade the nature of the tumour, some subjective errors occurs in assessing these features and not all areas in the tumour have similar features. Therefore in combination with the histopathological features, immunohistochemical evaluation for PR and Ki67 expression helps us decide better about the behaviour of the tumour.

Immunohistochemical expression of PR and ER was described in many studies. In all these studies related to Meningiomas the ER expression was found to be undetectable to very low and majority of these cases were found to be immunoreactive for PR[76] . Thus unlike other hormone sensitive tumours such as that of breast and endometrium where the expression of PR and ER are interrelated to each other, the expression of PR in Meningiomas are independent of ER.

Various authors have come up with different results based on their studies and hence the effect of hormones on the tumorigenesis or growth of Meningiomas remains unclear. The results of some of the invitro hormone receptor studies had turned out to be contradictory.

In their study in 2000, fewings et al concluded that the rates of recurrence are least with benign Meningiomas which had increased PR positivity. Fewings et al also suggested that the production of thrombospondin-1, an inhibitor of angiogenesis is enhanced by progesterone. But some other studies such as done by roser et al said in contradiction that progesterone plays a role in angiogenesis, thereby making it very difficult to draw conclusion from these datas [72].

Some studies stated that absence of PR expression is correlated with rate of progression to higher grades and aggressive behaviour of Meningiomas[77].

M Taghipour et al. said that the reason why those Meningiomas that lack progesterone receptor expression behave in an aggressive manner has not yet been known clearly. This could possibly be explained by the presence of increased angiogenesis, cell turn over and increased mitotic rates in those tumours having low or absent PR expression.[59]

The finding in this study that there is no association between the magnitude of PR expression levels and age or site of the meningiomas goes well with other studies such as those done by Arlete hilbig et al and M Taghipour et al [47, 59].

The magnitude of PR expression among various studies done by M Taghipour et al, Nasrin shayanfar et al, Roser et al [1, 53, 59] and the current study ranges from 53% to 68.6% as given below in table 22.

TABLE 22:- PERCENTAGE OF PR POSITIVITY IN VARIOUS STUDIES

VARIOUS STUDIES	% OF POSITIVITY FOR PR
Present study	66.7%
Roser et al	53.5%
Arlete hilbig et al	53%
M Taghipour et al.,	68.6%

In the study done by M Taghipour at al., all the five cases of intraspinal Meningiomas included in their study showed strong positivity for progesterone receptors [59] . In this study also, the 2 / 2 cases of intraspinal Meningiomas showed strong PR expression.

As seen in this study of interest, females had a slight higher proportion of PR positive cases when compared to males goes well with other studies also[53,59] .

PR expression in males and females among various grades in the current study varied slightly with the results from other studies done by Nasrin shayanfar et al and Roser et al [1,53] as given below in table 23 and 24.

The progesterone receptor expression in Meningiomas with regard to the sex and the various grades of Meningiomas in the current study compared with a similar study done by Nasrin shayanfar et al showed slight variation in the PR expression owing to some regional differences in the incidence of various grades of Meningiomas..

TABLE 23:- COMPARISON OF PR IMMUNOHISTOCHEMICAL TESTING BETWEEN CURRENT STUDY AND A SIMILAR STUDY DONE BY NASRIN SHAYANFAR et al

	PRESENT STUDY	NASRIN SHAYANFAR et al., [53]
Total Number of Cases Tested For PR IHC	60	78
PR Positivity in Males	59.25%	68%
PR Positivity in Females	72.7%	89%
PR Positivity in Grade I Meningiomas	39/50 (78%)	61/63(96%)
PR Positivity in Grade II Meningiomas	1/8 (12.5%)	2/10(20%)
PR Positivity in Grade III Meningiomas	0/2(0%)	0/5(0%)

The prevalence of various grades of meningiomas among males and females in a study done by Roser et al did not correlate well with this study.

The difference in the size of the study population and regional variation in the incidence of cases might have led to this variation in results between the present study and the study done by roser et al.

The percentage of positivity of PR in both the studies in grade I Meningiomas ranged from 69.5 to 60.7% and 56.5 to 85% in males and females respectively.

The percentage of positivity of PR in both the studies in grade II Meningiomas ranged from 0 to 46.4% and 20 to 44.4% in males and females respectively.

The percentage of positivity of PR in both the studies in grade III Meningiomas ranged from 0% and 0 to 33.3% in males and females respectively.

Comparison of PR immunohistochemical testing between current study and a similar study done by roser et al is given below in table 24.

TABLE 24:- COMPARISON OF PR IMMUNOHISTOCHEMICAL TESTING BETWEEN CURRENT STUDY AND A SIMILAR STUDY DONE BY ROSER et al

	PRESENT STUDY PR positivity Number of cases(%)	Roser et al [1]
GRADE I		
Male	16/23 (69.5 %)	96/158 (60.7%)
Female	23/27 (85 %)	212/ 375 (56.5%)
GRADE II		
Male	0/3 (0)	13/28 (46.4 %)
Female	1/5 (20%)	8/18 (44.4 %)
GRADE III		
Male	0/1 (0)	0/6 (0)
Female	0/1 (0)	1/3 (33.3%)

According to Nasrin shayanfar et al, M Taghipour at al and Roser et al[1,53,59] , Meningothelial Meningiomas had higher expression of progesterone receptors among the various types of Meningiomas. This study also showed similar results.

Aleksandra et al in 2006 said that among all types of grade I Meningiomas in their study meningothelial Meningiomas had increased expression and fibrous type of Meningiomas had the weakest expression of PR. This might be because the line of the differentiation of cells in fibrous Meningiomas are more towards a mesenchyme rather than epithelial like cells[78].

Comparison of progesterone receptor expression among various histopathological types of meningiomas in the present study are compared with a similar study done by Roser et al are given below in table 25.

The percentage of positivity of PR in various histopathological types in present study varied slightly from the study done by Roser et al due to difference in the incidence of various histopathological types and also variation in size of the study samples in both the studies. The percentage of positivity of PR in various histopathological types in both the studies ranged from 64.6-92%, 50 to 73%, 31 to 100%, 25 to 60%, 0 to 66%, 60-100%,0 to 45% and 0% in Meningothelial, Transitional, Fibrous, Microcystic, Angiomatous, Psamommatous, Clear cell and Anaplastic Meningiomas respectively.

TABLE 25 :- COMPARISON OF PR EXPRESSION AMONG VARIOUS HISTOPATHOLOGICAL TYPES OF MENINGIOMA

	PERCENTAGE OF PR POSITIVITY	
VARIOUS TYPES OF MENINGIOMA	PRESENT STUDY Number of cases(%)	ROSER et al Number of cases(%)
Meningothelial Meningioma	24/26 (92)	205/376(64.6)
Transititional Meningioma	12/16 (73)	27/54(50)
Fibrous Meningioma	1/1 (100)	24/77(31.1)
Lymphoplasmacyte rich Meningioma	0 (0)	-
Microcystic Meningioma	1/ 4(25)	3/5(60)
Angiomatous Meningioma	0(0)	4/6(66)
Psammomatous Meningioma	1/1(100)	6/10(60)
Atypical Meningioma	1/6 (16.6)	-
Chordoid Meningioma	0 (0)	
Clear cell Meningioma	0 (0)	3/7(45)
Papillary Meningioma	0 (0)	-
Anaplastic Meningioma	0 (0)	0 (0)

The recurrence rates for benign (grade I), atypical (grade II) and malignant (grade III) Meningiomas ranged from 7 -25%, 29-52%, and 50-94% respectively in various studies[79,80,81,82]. The percentage of recurrence among various grades of Meningiomas in this study correlated with other studies also as given below in table 25.

TABLE 26:- COMPARISON OF RATES OF RECURRENCE AMONG VARIOUS GRADES OF MENINGIOMAS

% of recurrence	GRADE I	GRADE II	GRADE III
Present study	28.6%	42.9%	28.6%
Various studies	7-25%	29-52%	50-94%

It is very difficult to predict the behaviour of Meningiomas as even some benign or grade I Meningiomas tend to recur. Hence for those cases with a radiological suspicion of high grade Meningiomas or those Meningiomas exhibiting atypical features in histopathology a immunohistochemical study of PR can be done. Those Meningiomas found to have weak to absent progesterone receptor expression can be given adjuvant radiotherapy post surgically and should be kept under a strict follow up.

For some unknown reasons Meningiomas were found to recur inspite of best therapeutic efforts . Due to the factors such as aging, presence of other medical problems or too large tumours and tumours located at unfavorable sites a

successful surgical removal is not possible. These patients can be tried with alternative medical therapy.

Since majority of the Meningiomas have been found to express progesterone receptors, medical treatment of Meningiomas with anti-progesterone therapy has been described in many studies. Previously anti-progesterone therapy which was used to treat breast cancer patients has now been found to be useful in treating Meningiomas.

Mifepristone, a progesterone antagonist was tried in inoperable cases of Meningiomas in two studies. In one study done by Grunberg at al in 1991, out of the 13 patients who were given mifepristone therapy, 5 patients showed reduction in tumour, 3 showed improvement without reduction in tumour and 3 showed enlargement of tumour regardless of the therapy. Two of the three cases that failed to respond were malignant Meningiomas[83].

In the other study done by lamberts et al in 1992, with a study group of 10 patients of inoperable cases of Meningiomas 4 cases failed to respond to mifepristone therapy. Progesterone receptor study was not done in any of the above cases. May be the absence of progesterone receptors led to the failed response to the treatment with mifepristone in some cases[84].

Preoperative administration of medroxy progesterone in patients with positive PR had a better clinical outcome compared to those without PR expression as showed by walter et al in 2005[85].

Matsuda et al had shown both invivo and invitro effect of antiprogesterone agents on Meningiomas irrespective of the progesterone receptor expression status of these tumour. This suggested an existence of other pathways that mediate the anti tumourous effects of these drugs[86].

SUMMARY

- Meningiomas constituted about 23.83% of the total CNS tumours during the study period.
- Intracranial Meningiomas (94.7%) were more common than intraspinal (5.3%) Meningiomas.
- Meningiomas were more prevalent among females (62.7%) with a male: female ratio of about 1: 1.6 and 1:10 for intracranial and intraspinal Meningiomas respectively.
- Maximum number cases were encountered in fifth (29.2%) and sixth (29.2%) decades of life with the mean age of 48.12.
- The convexity Meningiomas (57.4%) formed the most common site of occurence of these tumours.
- The most common histopathological types encountered in this study were meningothelial(40.7%) and transitional Meningiomas(25.4%).
- Majority of the cases belonged to grade I (91.4%) with grade II & III accounting for about 7.6% and 1% of cases respectively. There was no predilection for various grades of Meningiomas for particular age, sex or site.
- Histopathological features such as small cell change, hypercellularity, sheet like pattern, nuclear pleomorphism, macronucleoli, high mitotic rates, necrosis and brain invasion were seen predominantly in higher grade Meningiomas (Grade II and III). Presence of psamomma bodies,

fibrosis, xanthomatous change, hypervascularity and inflammatory cell infiltrate did not affect the grade or behaviour of the tumour.

- Immunohistochemical expression of PR was seen in 66.7% of cases with a slightly higher positivity rate among female patients.
- There was no statistically significant association between the PR expression and the age or location of the tumour.
- Meningothelial variant showed the maximum rates of expression of PR followed by the transitional type .
- The greater the mean cumulative progesterone receptor positivity score the lower the grade of the tumour and the better it's behaviour.
- In comparison with grade I Meningiomas the immunohistochemical expression of PR in high grade (II and III) Meningiomas were found to be from weak to absent .
- The association between the loss of PR expression and the high grade of the tumour, increased rates of recurrence of the tumours were significant statistically.

CONCLUSION

After an extensive workup on the histomorphological series of Meningiomas and their immunohistochemical expression of progesterone receptors, the following conclusion have been arrived at. Majority of the Meningiomas are benign and features such as small cell change, sheet like pattern, increased mitotic activity, hypercellularity, necrosis, vesiculous nuclei, macronucleoli and certain histopathological subtypes such as chordoid, clear cell, rhabdoid and papillary Meningiomas by themselves indicate aggressive nature of the tumour.

Though many of the above features helps us predict the nature of the tumour, an immunohistochemical analysis of Meningiomas for progesterone receptors helped to predict the behaviour of tumour in a better way.

Most of the Meningiomas that expressed progesterone receptors have had increased cure rates with reduced chances of recurrence and those that did not express PR showed higher grades of tumour. Hence the expression of progesterone receptors even in small numbers of Meningiomas tumour cells have been considered as a useful prognostic tool in correlation with other histopathological features such as histological grade of the tumour, presence or absence of brain invasion and mitotic rates in assessing the behaviour of the tumour. Targeted therapy with progesterone receptor antagonists may be considered in the treatment of Meningiomas and it requires a more detailed research and investigation.

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ANNEXURE I

PROFORMA

Name:

Age/sex:

HPE number :

IP number :

Clinical history :

Risk factors, if any :

Clinical diagnosis :

History of recurrence:

Imaging CT/MRI: Site: Side:

Surgery:

GROSS : Size of tumour-

MICROSCOPY

Histological type :

Histological grade : Grade I /grade II/ grade III

Mitoses-

Brain invasion, necrosis, hypercellularity, small cell change, macronucleoli, sheet like pattern- present/absent

IMMUNOHISTOCHEMISTRY

PR- positive/ negative

PR score (% of tumour nuclei showing reaction + intensity of positivity)

ANNEXURE II

WHO GRADING OF MENINGIOMAS

(Reference:- WHO classification of tumours of the central nervous system, 2007, 4th edition, volume 1, 164-172)

GRADE I MENINGIOMAS

Meningothelial Meningioma

Fibrous (fibroblastic) Meningioma

Transitional Meningioma

Microcystic Meningioma

Psamommatous Meningioma

Angiomatous Meningioma

Secretory Meningioma

Metaplastic Meningioma

Lymphoplasmacyte rich Meningioma

GRADE II MENINGIOMAS

Atypical Meningioma

Clear cell Meningioma

Chordoid Meningioma

GRADE III MENINGIOMAS

Anaplastic Meningioma

Rhabdoid Meningioma

Papillary Meningioma

ANNEXURE III:- WHO CRITERIA FOR GRADING OF MENINGIOMAS

(Reference:- WHO classification of tumours of the central nervous system, 2007, 4th edition, volume 1, 164-172)

GRADE I MENINGIOMAS

Mitosis <4/10 high power field (HPF)

GRADE II MENINGIOMAS

a) Mitosis 4 - 19/10 HPF or

b) 3 or more of the following five features: 1. Increased cellularity 2. Uninterrupted pattern less or sheet-like growth 3. Small cells with a high nuclear/cytoplasmic ratio 4. Prominent nucleoli 5. Foci of 'spontaneous' or 'geographic' necrosis

GRADE III MENINGIOMAS

a) Mitosis ≥20/10 HPF or

b) Exhibiting loss of differentiated features resulting in carcinoma, melanoma or sarcoma like appearance.

ANNEXURE IV:- THE IMMUNOHISTOCHEMICAL STAINING PROCEDURE FOR PR

1. Formalin fixed paraffin embedded blocks were used to get sections of 4 microns thickness. These sections are coaded in gelatin chrom alum pretreated slides.
2. These glass slides must be incubated overnight at 58 degree celcius.
3. Deparaffinisation is done using two changes of xylene one each for 15 minutes.
4. Dehydration of tissues are done with two changes of absolute alcohol each lasting for 5 minutes.
5. The sections are then placed in two changes of distilled water each for 5 minutes.
6. Process of antigen retrieval:- Preheat the freshly prepared TRIS antigen retrieval buffer for 4 minutes at 800 watts in microwave oven. This s followed by heating the sections in TRIS buffer for 20 minutes as follows:- (i) 800 watts for 5 minutes (ii) 640 watts for 10 minutes and (iii) 480 watts for 5 minutes.
7. Cool the slides to room temperature.
8. Wash the slides in running tap water for 5 minutes and distilled water for 5 minutes.
9. Now wash the slides in phosphate buffer for 5 minutes.
10. Treat the slides with hydrogen peroxide for 5 minutes.
11. Wash the slides in old and new phosphate buffer for 2 and 5 minutes respectively.

12. The primary antibody is now added and is made to react for a period of 30 minutes.
13. Wash the slides with phosphate buffer and treat the slides with poly excel target binder for 12 minutes
14. Wash the slides with phosphate buffer and add horse radish peroxidase and allow it react for 12 minutes.
15. Wash the slides with phosphate buffer and then add DAB chromogen (prepared by adding 1ml of DAB buffer and 1 drop of DAB chromogen)
16. The sections are counter stained with hematoxylin 30 seconds, washed for 5 minutes in running tap water, air dried, cleared in xylene and mounted.

ANNEXURE V:- INTERPRETATION AND SCORING OF IMMUNOHISTOCHEMICAL STAINING OF PR:-

(i)INTENSITY OF STAINING:-

INTENSITY OF STAINING:-	SCORE
Negative	0
Weak	1
Moderate	2
Strong	3

(ii)PERCENTAGE OF CELLS POSITIVE FOR PR:-

PERCENTAGE OF CELLS POSITIVE FOR PR:-	SCORE
0 %	0
< 1%	1
1-10%	2
11-33%	3
34-66%	4
67-100%	5

(iii)FINAL SCORE:-

The percentage of cells that took up the stain and intensity of nuclear staining were analyzed and the scores of these two are added up to get the final score. Score of less than or equal to 2 is considered as negative. Score of more than 2 is considered positive with the maximum score being 8.

MASTER CHART I - CLINICOPATHOLOGICAL PARAMETERS OF MENINGIOMAS

SI NO	Biopsy No.	Age	Sex	intraspinal/ intracranial	site of meningioma/ radiology	Recurrent cases	size of tumour (maximum diameter)	Histopathological diagnosis	Grade
1	07/13	50	F	intraspinal	Spinal sol		2cm	Psamom menin	I
2	24/13	45	F	intracranial	convex menin		5.5cm	Atyp menin	II
3	25/13	65	M	intracranial	convex menin		3cm	Angio menin	I
4	45/13	55	F	intracranial	convex menin		5cm	Angio menin	I
5	65/13	35	M	intracranial	convex menin		3cm	Mening menin	I
6	77/13	52	F	intracranial	convex menin		4cm	Fibrous menin	I
7	87/13	52	F	intracranial	convex menin		5cm	Mening menin	I
8	91/13	65	M	intracranial	convex menin		5cm	Trans menin	I
9	97/13	40	F	intracranial	convex menin		5cm	Trans menin	I
10	99/13	68	F	intracranial	tuberc sel			Psamom menin	I
11	112/13	68	F	intracranial	convex menin		3cm	Atyp menin	II
12	125/13	60	F	intracranial	convex menin		1.5cm	Mening menin	I
13	129/13	45	F	intracranial	convex menin		1 cm	Trans menin	I
14	131/13	58	F	intracranial	convex menin		2cm	Mening menin	I
15	136/13	45	M	intracranial	convex menin		1.5cm	Microcys menin	I
16	142/13	45	F	intracranial	tento sol		5cm	Mening menin	I
17	155/13	50	F	intraspinal	Spinal sol	Recurrent	1 cm	Psamom menin	I
18	158/13	47	F	intracranial	sphe wing		1 cm	Angio menin	I
19	160/13	46	M	intracranial	convex menin		3cm	Microcys menin	I
20	166/13	48	F	intracranial	convex menin		4cm	Trans menin	I
21	531/13	47	M	intracranial	convex menin	Recurrent	5cm	chord menin	II
22	193/13	45	F	intracranial	CP angle		5cm	Mening menin	I
23	198/13	22	F	intracranial	convex menin		6cm	LP menin	I
24	201/13	65	F	intracranial	convex menin		2cm	Trans menin	I
25	204/13	74	M	intracranial	post fossa		4cm	Trans menin	I
26	208/13	74	M	intracranial	convex menin		5cm	Atyp menin	II
27	211/13	69	M	intracranial	olfac groov		2cm	Trans menin	i
28	213/13	70	M	intracranial	convex menin		3cm	Trans menin	I
29	216/13	60	F	intracranial	tuberc sel		2cm	Mening menin	I
30	223/13	73	F	intracranial	convex menin		3cm	Trans menin	I
31	229/13	20	M	intracranial	convex menin		2cm	Mening menin	I
32	231/13	75	F	intracranial	convex menin		4cm	Fibrous menin	i
33	236/13	35	M	intracranial	convex menin		5cm	Microcys menin	I
34	244/13	27	M	intracranial	sphe wing		4cm	Trans menin	i
35	259/13	54	F	intracranial	convex menin		3cm	Trans menin	I
36	280/13	45	F	intracranial	convex menin		1 cm	Trans menin	I
37	307/13	60	M	intracranial	convex menin		3cm	Fibrous menin	I
38	308/13	54	M	intracranial	convex menin		3cm	Trans menin	I
39	330/13	45	F	intracranial	post fossa		5cm	Fibrous menin	I
40	336/13	52	F	intracranial	convex menin		4cm	Mening menin	I
41	348/13	52	F	intracranial	olfac groov		4cm	Mening menin	I
42	350/13	63	F	intracranial	convex menin		1 cm	Trans menin	I
43	383/13	58	F	intraspinal	Spinal sol		3cm	Mening menin	I
44	387/13	49	F	intracranial	convex menin		3cm	Fibrous menin	I
45	388/13	55	F	intracranial	convex menin		5cm	Mening menin	I
46	409/13	32	F	intracranial	convex menin		1 cm	Trans menin	I
47	412/13	55	M	intracranial	para/sup sel		1.5cm	Trans menin	I
48	431/13	32	M	intracranial	convex menin	Recurrent	6cm	clear cell meni	II
49	458/13	41	F	intracranial	olfac groov		4cm	Trans menin	I
50	462/13	50	M	intracranial	convex menin		5cm	Trans menin	I
51	469/13	37	M	intracranial	olfac groov		5cm	Atyp menin	II
52	481/13	41	M	intracranial	convex menin		2cm	Trans menin	I
53	488/13	41	F	intracranial	convex menin	Recurrent	7.5cm	Anapl menin	III
54	500/13	40	F	intracranial	para/sup sel		2cm	Mening menin	I
55	503/13	47	F	intracranial	convex menin		4.5cm	Atyp menin	II
56	505/13	50	F	intracranial	sphe wing		2cm	Trans menin	I
57	507/13	59	M	intracranial	convex menin		1 cm	Mening menin	I
58	509/13	55	M	intracranial	convex menin		4cm	Trans menin	I
59	522/13	34	M	intracranial	convex menin		4.5cm	Atyp menin	II
60	523/13	69	M	intracranial	sphe wing		2cm	Mening menin	I
61	533/13	36	F	intracranial	convex menin		4.5cm	clear cell meni	II

62	550/13	42	M	intracranial	sphe wing		1 cm	Mening menin	I
63	585/13	41	F	intracranial	convex menin		2cm	Fibrous menin	I
64	592/13	29	M	intracranial	sphe wing		5cm	Trans menin	I
65	595/13	37	F	intracranial	olfac groov		5cm	Mening menin	I
66	05/14	25	M	intracranial	sphe wing		5cm	Trans menin	I
67	14/14	52	F	intracranial	convex menin		2cm	Mening menin	I
68	18/14	40	F	intracranial	convex menin		3cm	Fibrous menin	I
69	21/14	53	M	intracranial	para/sup sel		3cm	Trans menin	I
70	23/14	40	M	intracranial	CP angle		3cm	Mening menin	I
71	37/14	37	F	intracranial	olfac groov			Microcys menin	I
72	48/14	54	M	intracranial	sphe wing		2cm	Trans menin	I
73	53/14	40	F	intracranial	olfac groov		3cm	Mening menin	I
74	58/14	53	M	intracranial	convex menin		1 cm	Mening menin	I
75	67/14	38	F	intracranial	tento sol			Trans menin	I
76	68/14	29	F	intracranial	sphe wing		2cm	Angio menin	I
77	90/14	52	F	intracranial	sphe wing		2cm	Angio menin	I
78	94/14	29	F	intracranial	olfac groov		1 cm	Trans menin	I
79	172/14	54	M	intracranial	sphe wing		4cm	Mening menin	I
80	181/14	60	F	intracranial	para/sup sel		1 cm	Trans menin	I
81	184/14	56	M	intracranial	convex menin		3cm	Psamom menin	I
82	187/14	40	F	intracranial	convex menin		3cm	Mening menin	I
83	190/14	40	M	intracranial	convex menin		2cm	Angio menin	I
84	197/14	45	M	intracranial	convex menin		4cm	Microcys menin	I
85	201/14	61	F	intracranial	convex menin			Fibrous menin	I
86	202/14	37	M	intracranial	intra ventr		4cm	Mening menin	I
87	204/14	56	M	intracranial	para/sup sel		1 cm	Psamom menin	I
88	215/14	62	M	intracranial	convex menin		5cm	Angio menin	I
89	228/14	23	F	intracranial	olfac groov		2cm	Mening menin	I
90	234/14	55	M	intracranial	convex menin		2cm	Mening menin	I
91	243/14	47	M	intracranial	olfac groov		3cm	Trans menin	I
92	248/14	55	F	intracranial	convex menin		4cm	Trans menin	I
93	249/14	45	F	intracranial	tuberc sel		1 cm	Mening menin	I
94	252/14	40	F	intraspinal	Spinal sol		1.5cm	Fibrous menin	I
95	255/14	53	F	intracranial	convex menin		4cm	Trans menin	I
96	275/14	40	M	intracranial	convex menin		4cm	Atyp menin	II
97	277/14	28	F	intracranial	convex menin	Recurrent	1 cm	Trans menin	I
98	278/14	45	F	intracranial	CP angle		1 cm	Angio menin	I
99	294/14	40	F	intracranial	convex menin		3.5cm	Trans menin	I
100	296/14	36	F	intracranial	convex menin		3cm	Mening menin	I
101	303/14	55	F	intracranial	convex menin		5cm	Psamom menin	I
102	316/14	52	F	intracranial	sphe wing		2cm	Psamom menin	I
103	322/14	30	F	intracranial	intra ventr		1 cm	Angio menin	I
104	326/14	48	F	intracranial	intra ventr		5.5cm	Atyp menin	II
105	328/14	52	M	intracranial	CP angle		5cm	Trans menin	I
106	353/14	30	F	intracranial	sphe wing		4cm	Trans menin	I
107	354/14	43	F	intracranial	convex menin		3cm	Psamom menin	I
108	361/14	28	M	intracranial	convex menin			Mening menin	I
109	376/14	60	F	intracranial	convex menin		4cm	Angio menin	I
110	380/14	60	F	intracranial	sphe wing		5cm	Trans menin	I
111	386/14	35	F	intracranial	convex menin		2.5 cm	Mening menin	I
112	388/14	45	F	intracranial	convex menin		4cm	Mening menin	I
113	400/14	47	F	intraspinal	Spinal sol		1 cm	Mening menin	I
114	402/14	55	F	intracranial	convex menin		1 cm	Trans menin	I
115	407/14	35	F	intracranial	convex menin			Microcys menin	I
116	411/14	60	M	intracranial	convex menin		2cm	Mening menin	I
117	414/14	60	F	intraspinal	Spinal sol		1 cm	Trans menin	I
118	461/14	45	F	intracranial	para/sup sel		2cm	Fibrous menin	I
119	481/14	45	M	intracranial	convex menin		1 cm	Angio menin	I
120	490/14	45	F	intracranial	convex menin		2.5 cm	Trans menin	I
121	495/14	45	F	intracranial	convex menin		4cm	Psamom menin	I
122	496/14	40	M	intracranial	tento sol		0.5cm	Trans menin	I
123	500/14	55	M	intracranial	convex menin		1.5cm	Fibrous menin	I
124	501/14	55	M	intracranial	convex menin		5cm	Psamom menin	I
125	517/14	55	M	intracranial	convex menin		4cm	Angio menin	I
126	521/14	60	F	intracranial	convex menin		4cm	Mening menin	I
127	522/14	52	M	intracranial	sphe wing		3cm	Mening menin	I
128	524/14	65	M	intracranial	convex menin		2cm	Trans menin	I
129	554/14	34	F	intracranial	convex menin		3cm	Angio menin	I
130	566/14	65	M	intracranial	convex menin		2cm	Angio menin	I

131	573/14	50	F	intraspinal	Spinal sol		1 cm	Mening menin	I
132	585/14	34	F	intracranial	sphe wing		2cm	Mening menin	I
133	595/14	33	F	intracranial	convex menin		5cm	Mening menin	I
134	605/14	51	M	intracranial	convex menin		1 cm	Mening menin	I
135	615/14	70	M	intracranial	convex menin		3.8cm	Atyp menin	II
136	616/14	50	F	intracranial	convex menin			Mening menin	I
137	617/14	47	F	intracranial	convex menin		4cm	Mening menin	I
138	622/14	35	F	intracranial	convex menin		2cm	Mening menin	I
139	629/14	48	F	intracranial	convex menin		2cm	Fibrous menin	I
140	634/14	51	F	intracranial	convex menin		6cm	Atyp menin	II
141	637/14	32	M	intracranial	sphe wing		2cm	Mening menin	I
142	93/15	74	M	intracranial	sphe wing	Recurrent	5.3cm	Atyp menin	II
143	97/15	45	M	intracranial	convex menin		3cm	Mening menin	I
144	101/15	63	F	intracranial	sphe wing		2cm	Mening menin	I
145	103/15	26	M	intracranial	convex menin		3cm	Angio menin	I
146	140/15	61	F	intracranial	sphe wing		3cm	Mening menin	I
147	141/15	59	F	intracranial	convex menin		3cm	Mening menin	I
148	145/15	55	F	intracranial	convex menin		5cm	Trans menin	I
149	150/15	48	F	intracranial	convex menin		5cm	Trans menin	I
150	157/15	63	F	intracranial	olfac groov		3cm	Mening menin	I
151	161/15	50	M	intracranial	convex menin		5cm	Trans menin	I
152	163/15	48	F	intraspinal	Spinal sol		1 cm	Psamom menin	I
153	172/15	48	M	intracranial	convex menin		6cm	Mening menin	I
154	178/15	60	F	intracranial	sphe wing		4cm	Trans menin	I
155	187/15	45	F	intracranial	multi menin		4cm	Trans menin	I
156	193/15	40	M	intracranial	olfac groov		2cm	Mening menin	I
157	203/15	54	F	intracranial	CP angle		2cm	Trans menin	I
158	215/15	45	M	intracranial	olfac groov	Recurrent	2.5cm	Papi menin	III
159	222/15	65	M	intracranial	convex menin		5cm	Mening menin	I
160	225/15	65	F	intracranial	convex menin		1 cm	Mening menin	I
161	230/15	32	M	intracranial	convex menin		5cm	Trans menin	I
162	233/15	28	F	intracranial	CP angle		8.5cm	Atyp menin	II
163	234/15	45	F	intracranial	convex menin			Mening menin	I
164	235/15	48	M	intracranial	convex menin		3cm	Mening menin	I
165	239/15	53	F	intracranial	convex menin		2.5 cm	Trans menin	I
166	244/15	50	F	intraspinal	Spinal sol		1 cm	Psamom menin	I
167	245/15	61	F	intracranial	convex menin		4cm	Atyp menin	II
168	263/15	40	F	intracranial	convex menin		5cm	Mening menin	I
169	268/15	73	F	intracranial	olfac groov		5cm	Mening menin	I
170	270/15	60	F	intracranial	CP angle		2cm	Mening menin	I
171	278/15	64	F	intracranial	CP angle		5cm	Trans menin	I
172	289/15	50	F	intracranial	convex menin		2cm	Mening menin	I
173	312/15	45	F	intracranial	convex menin		3cm	Mening menin	I
174	319/15	60	F	intracranial	convex menin		3cm	Mening menin	I
175	328//15	35	F	intracranial	convex menin		5cm	Mening menin	I
176	329/15	57	F	intracranial	post fossa		5cm	Mening menin	I
177	331/15	52	M	intracranial	convex menin		5cm	Mening menin	I
178	335/15	37	F	intracranial	CP angle		1 cm	Mening menin	I
179	352/15	59	M	intracranial	convex menin		3cm	Mening menin	I
180	364/15	45	F	intracranial	convex menin		3cm	Mening menin	I
181	365/15	70	F	intracranial	convex menin		3cm	Mening menin	I
182	371/15	35	F	intracranial	olfac groov		3cm	Mening menin	I
183	372/15	41	M	intracranial	sphe wing		2cm	Psamom menin	I
184	391/15	33	F	intraspinal	Spinal sol		1.5cm	Psamom menin	I
185	403/15	53	M	intracranial	convex menin		0.5cm	Mening menin	I
186	404/15	62	M	intraspinal	Spinal sol		1 cm	Psamom menin	I
187	415/15	54	M	intracranial	olfac groov		4cm	Mening menin	I
188	428/15	30	F	intracranial	sphe wing		1 cm	Mening menin	I
189	441/15	47	F	intracranial	sphe wing		5cm	Mening menin	I
190	450/15	28	M	intracranial	convex menin		1 cm	Mening menin	I
191	453/15	45	F	intracranial	para/sup sel		0.5cm	Fibrous menin	I
192	458/15	33	F	intracranial	convex menin		3cm	Mening menin	I
193	483/15	60	M	intracranial	sphe wing			Fibrous menin	I
194	489/15	55	F	intracranial	CP angle		1 cm	Mening menin	I
195	508/15	46	F	intracranial	convex menin		2cm	Mening menin	I
196	511/15	48	F	intracranial	convex menin		4cm	Mening menin	I
197	525/15	50	M	intracranial	tento sol		1.5cm	Psamom menin	I
198	543/15	48	F	intracranial	olfac groov		2cm	Mening menin	I
199	545/15	48	F	intracranial	post fossa		1.5cm	Fibrous menin	I

200	548/15	65	M	intracranial	convex menin		2cm	Mening menin	I
201	557/15	58	M	intracranial	convex menin		2.5 cm	Mening menin	I
202	558/15	24	M	intracranial	convex menin		2.5 cm	Mening menin	I
203	567/15	58	F	intracranial	olfac groov		3cm	Mening menin	I
204	570/15	48	F	intracranial	convex menin		1.5cm	Mening menin	I
205	572/15	56	F	intracranial	sphe wing		2cm	Mening menin	I
206	576/15	58	M	intracranial	convex menin		7cm	Mening menin	I
207	44/16	52	F	intracranial	convex menin		3cm	Trans menin	I
208	32/16	48	F	intracranial	post fossa		4cm	Trans menin	I
209	20/16	57	F	intracranial	sphe wing		1 cm	Trans menin	I

MASTER CHART - II - PR EXPRESSION IN MENINGIOMAS

SI NO	BIOOSY NO	AGE	SEX	SITE	HISTOPATHOLOGICAL DIAGNOSIS	GRADE	% OF CELLS POSITIVE	INTENSITY	SCORE	PR= POSITIVE/NEGATIVE
1	53/14	40	F	olfac groov	Mening menin	I	100	STRONG	8	(+)
2	521/14	60	F	convex menin	Mening menin	I	0	NEGATIVE	0	(-)
3	125/13	60	F	convex menin	Mening menin	I	25	WEAK	4	(+)
4	142/13	45	F	tento sol	Mening menin	I	90	MODERATE	8	(+)
5	371/15	35	F	olfac groov	Mening menin	I	90	MODERATE	8	(+)
6	178/15	60	F	sphe sol	Mening menin	I	95	STRONG	8	(+)
7	592/13	29	F	sphe sol	Mening menin	I	35	MODERATE	6	(+)
8	65/13	35	M	convex menin	Mening menin	I	80	STRONG	7	(+)
9	222/15	65	M	convex menin	Mening menin	I	60	MODERATE	6	(+)
10	353/14	30	F	sphe sol	Mening menin	I	80	MODERATE	8	(+)
11	14/14	52	F	convex menin	Mening menin	I	100	MODERATE	7	(+)
12	567/15	58	F	convex menin	Mening menin	I	80	MODERATE	7	(+)
13	331/15	52	M	convex menin	Mening menin	I	60	STRONG	6	(+)
14	184/14	56	M	convex menin	Mening menin	I	0	NEGATIVE	0	(-)
15	172/14	54	M	sphe sol	Mening menin	I	50	MODERATE	6	(+)
16	622/14	35	F	spinal sol	Mening menin	I	10	WEAK	3	(+)
17	24/13	45	F	convex menin	atyp menin	II	1	WEAK	2	(-)
18	233/15	28	F	cp angle	atyp menin	II	0	NEGATIVE	0	(-)
19	548/15	65	M	convex menin	Mening menin	I	65	MODERATE	6	(+)
20	216/13	45	F	para/ sup sel	Mening menin	I	50	MODERATE	6	(+)
21	543/15	48	F	olfac groov	Mening menin	I	60	STRONG	7	(+)
22	229/13	20	M	convex menin	Mening menin	I	25	WEAK	4	(+)
23	411/14	60	M	convex menin	Mening menin	I	65	STRONG	7	(+)
24	273/13	42	M	convex menin	Mening menin	I	30	WEAK	3	(+)
25	235/15	48	M	convex menin	Mening menin	I	70	STRONG	8	(+)
26	268/15	73	F	olfac groov	Mening menin	I	70	STRONG	8	(+)
27	522/14	52	M	sphe sol	Mening menin	I	60	MODERATE	7	(+)
28	131/13	58	F	convex menin	Mening menin	I	70	STRONG	8	(+)
29	190/14	40	M	convex menin	angio menin	I	0	NEGATIVE	0	(-)
30	197/14	45	M	convex menin	Microcys menin	I	50	WEAK	4	(+)
31	136/13	45	M	convex menin	Microcys menin	I	0	NEGATIVE	0	(-)
32	160/13	46	M	convex menin	Microcys menin	I	0	NEGATIVE	0	(-)
33	236/13	35	M	convex menin	Microcys menin	I	0	NEGATIVE	0	(-)
34	629/14	48	F	convex menin	fibrous menin	I	40	MODERATE	6	(+)
35	198/13	22	F	convex menin	LP menin	I	0	NEGATIVE	0	(-)
36	7/13	50	F	spinal sol	psamom menin	I	100	STRONG	8	(+)
37	223/13	73	F	convex menin	Trans menin	I	80	MODERATE	7	(+)
38	412/13	55	M	para/ sup sel	Trans menin	I	95	STRONG	8	(+)
39	462/13	50	M	convex menin	Trans menin	I	0	NEGATIVE	0	(-)
40	469/13	37	F	olfac groov	Trans menin	I	80	STRONG	8	(+)
41	409/13	32	F	convex menin	Trans menin	I	10	WEAK	3	(+)
42	576/15	58	M	convex menin	Trans menin	I	0	NEGATIVE	0	(-)
43	187/15	45	F	Multi menin	Trans menin	I	0	NEGATIVE	0	(-)
44	524/14	65	M	convex menin	Trans menin	I	40	WEAK	5	(+)
45	228/14	23	F	olfac groov	Trans menin	I	60	MODERATE	6	(+)
46	44/16	52	F	convex menin	Trans menin	I	70	STRONG	8	(+)
47	32/16	48	F	post fossa	Trans menin	I	30	MODERATE	5	(+)
48	20/16	57	F	sphe sol	Trans menin	I	60	STRONG	7	(+)
49	161/15	50	M	convex menin	Trans menin	I	90	STRONG	8	(+)
50	364/15	45	F	convex menin	Trans menin	I	40	WEAK	5	(+)
51	140/15	61	F	sphe sol	Trans menin	I	80	MODERATE	7	(+)
52	91/13	65	M	convex menin	Trans menin	I	0	NEGATIVE	0	(-)
53	208/13	74	M	convex menin	atyp menin	II	0	NEGATIVE	0	(-)
54	326/14	48	F	intra vent	atyp menin	II	0	NEGATIVE	0	(-)
55	431/13	32	M	convex menin	clear cell menin	II	0	NEGATIVE	0	(-)
56	488/13	41	F	convex menin	anapl menin	III	0	NEGATIVE	0	(-)
57	215/15	45	M	olfac groov	Papi menin	III	0	NEGATIVE	0	(-)
58	531/13	47	M	convex menin	chord menin	II	0	NEGATIVE	0	(-)
59	634/14	51	F	convex menin	atyp menin	II	60	MODERATE	6	(+)
60	615/14	70	M	convex menin	atyp menin	II	0	NEGATIVE	0	(-)

KEY TO MASTER CHART

SEX:-

M	-	Male
F	-	Female

SITE/RADIOLOGY:-

Convex menin	-	convexity meningioma
Intra ventr	-	intraventricular meningioma
Multi menin	-	multiple meningioma
Olfac groov	-	olfactory groove
Optic nr sh	-	optic nerve sheath
Para/sup sel	-	para/supra sellar
Post fossa	-	posterior fossa
Sphe wing	-	sphenoid wing
Tento sol	-	tentorial sol
Tuberc sel	-	tuberculum sella

HISTOPATHOLOGICAL DIAGNOSIS:-

Mening menin	-	Meningothelial Meningioma
Fibrous menin	-	Fibrous Meningioma
Trans menin	-	Transitional Meningioma
Psamom menin	-	Psammomatous Meningioma
Microcys menin	-	Microcystic Meningioma
Angio menin	-	Angiomatous Meningioma
LP menin	-	Lymphoplasmacyte rich Meningioma

Atyp menin	-	Atypical Meningioma
clear cell meni	-	Clear cell Meningioma
chord menin	-	Chordoid Meningioma
Papi menin	-	Papillary Meningioma
Anapl menin	-	Anaplastic Meningioma

PR EXPRESSION:-

(+)- positive

(-)- negative

INFORMATION SHEET

- We are conducting a study on Meningioma, a CNS Neoplasm among patients attending Government General Hospital, Chennai and for that your specimen may be valuable to us.
- The purpose of this study is to do certain special tests in cases of meningioma.
- We are selecting certain cases and if your specimen is found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator

Signature of participant

Date:

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு : **மூளை மற்றும் தண்டுவடம் சுற்றி ஏற்படும் Meningioma எனும் கட்டியில் Progesterone Receptor (PR) எனும் சிறப்பு குறியீடு இட்டு செய்யும் ஆய்வு.**

ஆய்வாளர் : மரு. செண்பகம் **J.M.**
நோய்குறியியல் துறை,
சென்னை மருத்துவக் கல்லூரி,
சென்னை - 600003.

தங்களது மூளை மற்றும் தண்டுவடம் சுற்றி ஏற்படும் Meningioma எனும் கட்டி (அறுவை சிகிச்சை செய்யப்பட்ட கட்டி) இங்கு பெற்றுக் கொள்ளப்பட்டது.

இராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் நோயாளிகளிடம் இருக்கும் மூளை மற்றும் தண்டுவடம் சுற்றி ஏற்படும் Meningioma எனும் கட்டிகளைப் பற்றிய ஒரு ஆராய்ச்சி இங்கு நடைபெற்று வருகின்றது.

இந்த மூளை மற்றும் தண்டுவடம் சுற்றி ஏற்படும் Meningioma எனும் கட்டியில் Progesterone Receptor (PR) எனும் குறியீடு காண்பித்தால் டார்கெட் தெரபி Antiprogesterone Therapy – Mifepristone எனும் மருந்தின் மூலம் நோயின் வீரியத்தை கட்டுப்படுத்தலாம். இவையே எனது ஆய்வின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய திசுக்களை எடுத்து சில சிறப்புப் பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்குள்ளாகாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆய்வை பற்றிய சந்தேகங்களுக்கு தொடர்பு கொள்ள வேண்டியவர் : மரு. செண்பகம் J.M, செல் : 9942699014

பங்கேற்பாளர் கையொப்பம்..... இடம் :..... தேதி :.....

பங்கேற்பாளர் பெயர் மற்றும் விலாசம் .....

ஆராய்ச்சியாளர் கையொப்பம்..... இடம் :..... தேதி :.....

INFORMED CONSENT FORM

Title of the study : **"A STUDY OF PROGESTERONE RECEPTOR (PR) EXPRESSION IN MENINGIOMA, AND ITS CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS"**

Name of the Participant:
Name of the Principal (Co-Investigator) :
Name of the Institution : Madras Medical College
Name and address of the sponsor / agency (ies) (if any) :

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in **"A STUDY OF PROGESTERONE RECEPTOR (PR) EXPRESSION IN MENINGIOMA, AND ITS CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS".**

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study in which the resected tumors will be subjected to immunohistochemistry and histopathological examination.
4. I have been explained about my rights and responsibilities by the investigator. I have the right to withdraw from the study at any time.
5. I have informed the investigator of all the treatments I am taking or have taken in the past _____ months including any native (alternative) treatment.
6. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
7. I have understand that my identity will be kept confidential if my data are publicly presented
8. I have had my questions answered to my satisfaction.
9. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:
Name and signature / thumb impression of the participant (or legal representative if participant incompetent)
Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு : **மூளை மற்றும் தண்டுவடம் சுற்றி ஏற்படும் Meningioma எனும் கட்டியில் Progesterone Receptor (PR) எனும் சிறப்பு குறியீடு இட்டு செய்யும் ஆய்வு.**

சென்னை மருத்துவக் கல்லூரி நோய்குறியியல் துறையில் பயிலும் முதுகலை மருத்துவர் செண்பகம் J.M, அவர்கள் மேற்கொள்ளும் இந்த ஆய்வில் பங்குகொள்ள ..... ஆகிய நான் முழு மனதுடன் சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் மூளை மற்றும் தண்டுவடம் சுற்றி ஏற்படும் Meningioma எனும் கட்டிகள் குறித்த இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

எனக்கு அறுவை சிகிச்சை செய்யப்பட்டு நோய்க்குறியியல் துறையில் சதைப் பரிசோதனைக்கு பயன்பட்ட மெழுகுக்கட்டிகளை வைத்து ஆராய்ச்சி மற்றும் சிறப்புப் பரிசோதனை செய்யது கொள்ள சம்மதம் தெரிவிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம்..... இடம் :..... தேதி :.....

பங்கேற்பாளர் பெயர் மற்றும் விலாசம் .....

ஆராய்ச்சியாளர் கையொப்பம்..... இடம் :..... தேதி :.....