Ocular Oncology

AIOS CME Series (No 35)
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Foreword

Ocular Oncology, as a subspecialty of ophthalmology has evolved immensely over the years. Encompassing eyelid, surface and intraocular tumours – ocular oncology specialists treat a variety of cases. This issue is dedicated to intraocular tumours and covers a wide variety of conditions: retinoblastoma, melanomas and metastatic lesions among others.

Over the years, surgical techniques and other adjuvant measures like external beam radiation, focal treatment and chemotherapy have vastly increased the survival rate and vision preservation rates in patients with intraocular tumours. In the recent years, anti-VEGF agents have also been used to treat malignant conditions such as choroidal metastases. All recent updates in the management of intraocular tumours have been included in this treatise.

The authors have done an admirable job by contributing relevant articles that highlight the clinical conditions and discuss the management of intraocular tumours in detail. I also wish to congratulate the editor for having curated this exhaustive compilation. I am sure that the members of the All India Ophthalmological Society will find this issue useful.

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“Never believe that a few caring people can’t change the world. For, indeed, that’s all who ever have” – Margaret Mead

Ocular oncology is the one of the fastest growing sub-specialities in Ophthalmology today. With advanced diagnostic and treatment modalities, we have been able to salvage more lives and vision in the past decade than ever before. And today I feel proud to say, that India has been one of the pioneers in the research and management of these diseases.

On the other side, lies a stark contrast, where adequate diagnosis and treatment remains out of bounds for the millions of people living beyond the reach of super-speciality care. To add to this, even when a family is able to reach a comprehensive ophthalmologist, timely diagnosis and referral remains suboptimal. So despite the numbers, are we really doing enough?

This CME series is a humble attempt to put together a comprehensive review and update of the most important tumors of the eye, which we hope will help the comprehensive ophthalmologist about the nuances of this field. Differential diagnosis of these diseases from the more benign ocular disorders is crucial, and timely referral to a tertiary centre remains the key.

Another most important factor remains the awareness of the families regarding malignancies of the eye, because it is ultimately the parents who are most important caregivers and determinants of timely treatment of the child.

The authors of respective chapters in this CME series are all stalwarts in the field of ocular oncology, and they have done an excellent job of giving a comprehensive update of such a huge subject. Moreover, we have the included the recent advances in the diagnosis and treatment of all the diseases, which will help our fellow ophthalmologists keep themselves updated with the latest trends.

We wish to thank Dr P Mahesh Shanmugam, the Editor of this CME series, for all the hard work for compiling this CME series.

Dr. Partha Biswas
Chairman-ARC, AIOS
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1. INTRODUCTION

Ocular Surface Squamous Neoplasia (OSSN) is a clinical term that covers the entire spectrum of neoplastic changes of the squamous epithelium of the cornea and conjunctiva. This name was first proposed by Lee and Hirst as an umbrella term to describe squamous epithelial lesions of the ocular surface. These range from mild dysplasia to intraepithelial neoplasia (i.e. carcinoma in situ) and frank squamous cell carcinoma. UV-associated mutations in tumour suppressor genes such as p53 have been demonstrated in OSSN, and hereditary deficiency of DNA repair such as in xeroderma pigmentosum increases the risk of OSSN formation. There are many risk factors that have been attributed to OSSN including ultraviolet radiation, smoking, genetics, ocular surface injury, exposure to chemicals (petroleum products, beryllium, trifluridine, arsenic) and vitamin A deficiency. While human papilloma virus (HPV) especially subtypes 16 and 18 known to be carcinogenic in cervical and head and neck squamous cell carcinomas, definitive data regarding the role of HPV in the pathogenesis of OSSN is still lacking. However, immunosuppressive states like HIV are known to be a risk factor for developing OSSN.

2. HIV AND OSSN

While there has been a decline in the incidence of HIV in recent years, there has been an increase in the incidence of OSSN in the population with HIV. It has been established that HIV not only increases the risk of OSSN but also influences the severity of disease and its prognosis. Studies from India have shown that HIV positivity was noticed in 38%-41% of patients with OSSN, of which 70% were unaware of their status prior to screening. In 26% of patients, OSSN was the first
and only evident manifestation of HIV.\textsuperscript{[3,4]} A systematic review and meta-analysis of 12 studies showed that HIV infection augmented the risk of OSSN, with an overall relative risk estimate of 8.06 (95% CI 5.29–12.3).\textsuperscript{[5]} Any patient under the age of 50 years who presents with OSSN, should be screened for HIV. OSSN occurring in HIV patients tend to be more aggressive and invasive; often times requiring enucleation or even exenteration.\textsuperscript{[6]}

\section*{3. CLINICAL PRESENTATION}

Typically, OSSN presents as a mass lesion in the interpalpebral area of the perilimbal conjunctiva. However, it can also extend across the limbus to involve the cornea. On occasions, OSSN can show isolated corneal involvement as well. Atypical manifestations of OSSN like massive surface tumours and scleral necrosis after prior surgical interventions have also been reported.\textsuperscript{[7]} Ocular surface squamous neoplasms (OSSNs) appear as fleshy, elevated, sessile lesions located adjacent to the limbus in the inter-palpebral region. The thickness of the lesion is not always an indication of invasiveness, as thick tumours have also been found to be confined within the epithelium. There are a few clinical pointers that can help in the diagnosis of OSSN: the appearance of feeder vessels, intrinsic vascularity within the tumour

\begin{center}
\textbf{Figure 1:} Slit lamp photograph of a typical limbal OSSN. Note the intrinsic vascularity of the tumour, the feeder vessels (black arrow head) and the overlying keratin (yellow arrow head)
\end{center}
and keratin specks on the tumour surface (Figure 1). Furthermore, OSSNs usually stain positively for Rose Bengal and Methylene blue. However, it should be borne in mind that these stains are not specific for OSSN and some benign lesions with devitalised epithelium can also show positive dye uptake. The overall appearance is usually gelatinous or leukoplakic, indicative of surface keratinization. Pigmented OSSNs are uncommon and need to be differentiated from conjunctival melanoma. Corneal OSSNs typically have a mottled ground glass sheet appearance. They also have clear, well-defined edges with fimbriated borders and are usually avascular (Figure 2).

**Figure 2:** Slit lamp image of a corneal OSSN. Observe the distinct fimbriated edges (Yellow arrowheads)

### 4. DIAGNOSIS OF OSSN

#### i. Impression Cytology

The diagnosis of OSSN is largely a clinical diagnosis that rarely requires additional imaging or other diagnostic modalities. Imaging is usually needed to assess the extent of involvement of adjacent structures. Exfoliative cytology using a cytobrush is useful for diagnosis of OSSNs. This is because malignant cells have poor cell to cell adherence and tend to desquamate when located on the mucosal surface. Therefore, examination of
these desquamated cells to assess their morphology can help in diagnosis. Similarly, impression cytology has been used widely as a non-invasive method for conjunctival biopsy for suspected OSSN. Impression cytology using cellulose acetate paper is a simple and inexpensive technique. However, impression cytology specimens require immediate processing and pathology expertise to accurately diagnose. Typically, cellulose acetate paper (CAP) /millimeter filter paper with pore size 0.22 mm is used. This type of filter paper removes mucous secretions as well as the sheets of epithelial cells and goblet cells from the conjunctival surface. Prior to obtaining a sample, topical anaesthesia drops are instilled, and excess tears are cleaned away. The marked filter paper strip is pressed on area to be sampled for 5-10 seconds and it is important that the lids are held away from the paper such that the filter paper does not become wet as that can reduce the yield of cells. Using CAP for specimen collection, an 80% correlation was found between impression cytology, diagnosis and histopathology specimens obtained from incisional biopsy. Biopore membrane, however, has better cell adherence and can be stored for subsequent analysis making it the procedure of choice. Reporting using biopore membrane also shows a high degree of accuracy, once the pathologist has gained expertise with the specialised cytology of the ocular surface. However, one must be aware of the limitations of this technique in dysplastic lesions with hyperkeratosis.[8]

ii. Optical Coherence Tomography

Non-invasive techniques such as Anterior Segment Optical Coherence Tomography (AS-OCT) has also been used to diagnose OSSNs. Unlike Ultrasound Biomicroscopy (UBM) and some confocal microscopy devices, AS-OCT is a non-contact investigative modality. UBM has greater depth of penetrance but lower resolution. On AS-OCT, the typical features of an OSSN include thickened, hyper-reflective epithelium over the tumour and a distinct abrupt transition zone from normal to abnormal epithelium (Figure 3). Additionally, a distinct plane between the lesion and underlying tissue can be noted in conjunctival intraepithelial neoplasia (seen in thinner tumours).[9]
Ocular Surface Squamous Neoplasia: An overview

5. PATHOLOGY

Conjunctival intraepithelial neoplasia (CIN) is a term that refers to varying degrees of conjunctival epithelial dysplasia. It is classified/graded from I to III depending on the severity of the disease (as seen histopathologically): CIN I represents mild disease, CIN II refers to moderate disease, and CIN III indicates near full-thickness epithelial dysplasia.

![Figure 3: An AS-OCT image of an OSSN showing the thickened, hyper-reflective epithelium over the tumour (white asterisk) and a distinct abrupt transition zone from normal to abnormal epithelium (yellow arrow). (Courtesy Dr. Swati Singh, L V Prasad Eye Institute, Hyderabad)](image)

![Figure 4: Histopathology of OSSN: Normal epithelium is replaced with disorganized, dyskeratotic, and acanthotic cells with penetration of the basement membrane. Multiple mitotic figures are also seen. (Haematoxylin-Eosin Stain; 400x)](image)
Ocular Surface Squamous Neoplasia: An overview

involvement. CIN involving the entire epithelium is known as to as carcinoma-in-situ. On histopathological examination, CIN lesions exhibit a mixture of spindle cells and epidermoid cells. There is disorganization of the cells, abnormal polarity, and a mild to marked increase in the nuclear to cytoplasmic ratio. However, CIN is known to be the precursor to conjunctival squamous cell carcinoma (SCC). The Bowman’s membrane acts as a barrier and therefore, the cornea is spared of subepithelial cellular invasion, which is almost exclusively limited to the conjunctiva. In SCC, Histologically, there is replacement of normal epithelium with disorganized, dyskeratotic, and acanthotic cells with penetration of the basement membrane (Figure 4). A rare variant of SCC which is particularly aggressive is mucoepidermoid carcinoma.

6. MANAGEMENT

The management of OSSN is primarily based on the size of the tumour, its invasiveness and extent of involvement of the conjunctiva. Surgical excision remains the mainstay of small tumours. Topical medications are also used for treating OSSNs. The agents used for topical therapy include Mitomycin C (MMC), 5-Fluorouracil (5-FU) and Interferon α2b (IFN-α2b). In general, when IFN-α2b is used as the primary agent for treatment – it is referred to as ‘immunotherapy’. This is typically done in small corneal or conjunctival tumours. IFN-α2b may also be used as a neoadjuvant agent, i.e. ‘immunoreduction’ in cases of diffuse tumours to reduce the size and extent of the tumour to facilitate subsequent surgical excision. Finally, it may also be used as adjuvant therapy or ‘immunoprevention’; in the presence of positive margins after resection.

While being used as a primary agent for treatment, one should begin to see a clinical response after a month (or after one to two cycles) of treatment. If no improvement is observed after this amount of time, another drug or surgery should be considered. A simplified table provided here (Table 1) can aid in choosing the appropriate management for the tumour after thorough examination of the patient.
**Table 1:** A modified table for clinical classification for ocular surface squamous neoplasia - Modified from Cicinelli et al (2018); Meel and Dhiman (2018)[10,11]

<table>
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<tr>
<th>Grade of tumour</th>
<th>Limbal involvement (clock hours)</th>
<th>Maximal diameter (mm)</th>
<th>Preferred treatment</th>
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<tr>
<td>Grade I: OSSN with no invasion into ocular coats clinically and on imaging (AS-OCT / UBM)</td>
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<td></td>
<td></td>
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<tr>
<td>A (small)</td>
<td>≤ 3</td>
<td>≤ 5</td>
<td>Surgical excision with margin control</td>
</tr>
<tr>
<td>B (large)</td>
<td>&gt;3 to &lt;6</td>
<td>&gt;5 to &lt;15</td>
<td>Immunotherapy or immunoreduction</td>
</tr>
<tr>
<td>C (diffuse)</td>
<td>≥ 6</td>
<td>≥ 15</td>
<td>Immunoreduction</td>
</tr>
<tr>
<td>Grade II: OSSN with invasion into ocular coats (sclera/corneal stroma) on imaging (UBM/AS-OCT/ Intraoperative finding)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Excision with lamellar sclerectomy or keratectomy + cryotherapy of margins and base. Adjuvant topical therapy may be considered (immunoprevention)</td>
</tr>
<tr>
<td>Grade III: OSSN with intraocular invasion</td>
<td>Any</td>
<td>Any</td>
<td>Enucleation / Extended Enucleation</td>
</tr>
<tr>
<td>Grade IV: OSSN with orbital extension confirmed on imaging (CT / MRI scanning)</td>
<td>Any</td>
<td>Any</td>
<td>Orbital Exenteration</td>
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### i. Surgical Excision

The gold standard for treatment of OSSN remains surgery. The preferred technique for excision is the ‘no touch’ technique. The ‘no touch’ technique is called so since the removal of tumour is performed without directly touching the mass and only manipulating the surrounding normal tissue as well as the avoidance of any irrigating fluid to wet the cornea as this may lead to tumour dissemination. This technique first described by Shields, incorporates large macroscopically tumour-free margins to increase the likelihood of clear margins.[12] As a result, along with the mass, at least a 4 mm of uninvolved conjunctival margin is also resected This margin of uninvolved tissue must be excised because seemingly uninvolved tissue clinically may still contain dysplastic cells. This margin is demarcated using a bipolar cautery (Figure 5A). The under-surface of the tumour along with
the surrounding demarcated conjunctiva is then dissected off, of the episclera using a mono-polar electrocautery till the limbus (Figure 5B). The corneal epithelium is also removed using absolute alcohol which loosens the epithelium from the basement membrane (Figure 5C). All involved corneal epithelium and any associated corneal pannus is then scraped off with a crescent blade (Figure 5D). The underlying Bowman’s layer should not be disturbed during this process. With the conjunctival component dissected and the corneal epithelium scraped; the only attachment of the tumour remains at the limbus. This is then removed using a crescent blade (Figure 5E and Figure 5F). A double rapid freeze-thaw technique of cryotherapy is applied to the conjunctival edges, involved limbal zone, and the bare scleral bed to kill any remaining dysplastic cells. Bleeders at the limbus may be gently cauterised with a bipolar electrocautery (Figures 6A, 6B, 6C). Cryotherapy effectively extends the surgical margins and even if margins return positive or there are any concerns for residual disease, topical chemotherapy may be used after excision. If intraoperatively, the lesion is noted to have scleral fixity - suggestive of invasiveness,
a thin lamellar scleral flap can be excised. The conjunctival defect is then closed with amniotic membrane graft after application of fibrin glue (Figure 6D and Figure 6E). The excess amniotic membrane is trimmed off (Figure 6F). Once excised, the mass should be placed on Whatman filter paper with a diagrammatic representation of the eye indicating the orientation of the mass with clear labelling to enable the pathologist to report accurately on the margins. Alternatively, margins could be sent as individual specimen as well.

Cases of invasive SCCs with intraocular extension are treated with enucleation or extended enucleation.

**Figure 6 (A-F):** Continuation of the ‘no touch technique’: double freeze-thaw cryotherapy to the conjunctival margins (Figure 6A); gentle cautery to the base of the tumour (Figure 6B); cryotherapy to the tumour bed (Figure 6C); application of fibrin glue (Figure 6D); spreading the amniotic membrane graft (Figure 6E) and finally trimming the excess amniotic membrane (Figure 6F).

**ii. Topical therapy**

Extensive surgical excision of large limbal OSSNs (involving ≥ 6 clock-hours of the limbus) carries the potential risk of causing limbal stem cell deficiency (LSCD), following removal of large amount of conjunctiva may lead to scarring and symblepharon. LSCD can be prevented with intraoperative limbal epithelial transplantation. [10] But, there is a growing body of evidence that
shows the utility of topical therapy for the treatment of OSSNs. As discussed earlier, the main topical agents used in the treatment of OSSNs are MMC, 5-FU and IFN α2b.

a. **Mitomycin C**: MMC is a potent alkylating agent used topically as a primary treatment or with the adjunction of surgical resection—before (chemoreduction), intraoperatively, or after (chemopreventive) the procedure - to reduce the risk of recurrence. [10,13] However, literature suggests that MMC has a higher incidence of reported side effects when compared to 5-FU and IFN α2b. The most commonly reported side effects are redness, ocular pain and epitheliopathy. One of the more serious side-effects include LSCD and persistent epithelial defects. Other less serious adverse effects include punctal stenosis, conjunctivitis, photosensitivity and allergic reaction; which can often lead to discontinuation of MMC as a therapeutic agent.[14]

MMC eyedrops are prescribed (0.04%) to be instilled four times daily for 3-4 weeks followed by at least one week of drug vacation; such cycles are repeated at least 3 times or until resolution is seen.

b. **5-Fluorouracil**: 5-FU is an anti-metabolite that selectively blocks thymidine synthase, thereby affecting the ability of cells to make nucleic acids. In this process, tumour cells are preferentially affected because of their rapid doubling time. For the treatment of OSSNs, 5-FU has been used topically as a 1% 5-FU formulation four times/day for 4 weeks followed by a drug holiday of 1-3 weeks.[15] When used as a primary drug for OSSN, 5-FU has a reported efficacy of 85–100% with a tumour recurrence rate ranging from 1.1 to 43%. [10,16] Although the side effects of 5-FU are lesser than those of MMC, commonly seen complaints include epitheliopathy, conjunctival inflammation and irritation.

c. **Interferon α2b**: IFN α2b, a low molecular weight glycoprotein, produced by leukocytes, has antineoplastic and antiviral properties. Interferons in general, are used as antineoplastic agents on the basis of their anti-proliferative, anti-angiogenic, and cytotoxic effects. They have the property of being a potential inducer of the host anti-tumour immunosurveillance.[17] Intralesional injections of IFN α2b enhance the production of IL-2 and IFN-γ mRNA by the immune system and lower the production of IL-10. These
mechanisms help in the recognition and targeting of neoplastic cells.\textsuperscript{[18,19]} The efficacy of topical INF in the regression of limbal epithelial dysplasia was first described in 1994 by.\textsuperscript{[20]} Since then, recombinant human IFN α2b has been used as the primary agent (immunotherapy) for treating multiple conditions including OSSN.

Topical IFN α2b is given as eyedrops which are prepared under sterile conditions by adding 4 cc of distilled water to 1 cc of INF α2b (containing 5 million IU), to achieve a dose of 1 million IU/cc. The medication is then usually packed in an icebox. Patients should be instructed to store the reconstituted drops in a refrigerator (2°C–8°C) and apply one drop four times/day. In addition to prescribing topical drops, subconjunctival IFN α2b injections (3 million IU/0.5 ml) are administered weekly until the OSSN resolution is seen. This typically requires 4 to 5 injections to achieve clinical resolution. INF α2b drops are well tolerated and have minimal side effects. While ocular discomfort is less common, some patients may report mild systemic effects. These include fatigue, myalgia and fever. These symptoms usually follow subconjunctival injection rather than topical usage; and can be treated with oral paracetamol. (\textit{Figures 7A, 7B, 7C, 7D}).

\textbf{Figure 7 (A-D):} A 45-year-old immunocompetent male patient who presented a large OSSN that extended over 6 clock hours (\textit{Figure 7A}). He was treated with topical IFN α2b drops and perilesional IFN α2b 3 Million IU. Following treatment for 4 weeks, significant improvement was noted (\textit{Figure 7B}) which continued over the next 4 weeks (\textit{Figure 7C}). The residual lesion was excised with the placement of an amniotic membrane. Pictured here is the patient 3 weeks after surgery (\textit{Figure 7D}).
d. **Other drugs:** The other drugs that have been tried in the treatment of OSSN include retinoic acid, aloe vera drops, cidofovir, anti-vascular endothelial growth factor (VEGF) agents such as bevacizumab. Large scale studies that have independently investigated the efficacy and safety of these drugs in the treatment of OSSNs are not available.[18]

- **iii. Treatment for orbital and metastatic disease.**

  Orbital extension of conjunctival SCCs is rare and if no metastatic disease is detected, orbital exenteration is usually curative. Neoadjuvant chemotherapy with 5-FU and cisplatin are useful in reduction of the size of the tumour in cases of advanced conjunctival SCCs with no systemic or lymph node metastasis.[21]

  Metastatic disease is seen in <2% of cases[7] and metastasis occurs usually to the regional lymph nodes. Rare instances of distant metastases to the lung and bone have also been documented.[22]

7. **SUMMARY**

Surgical excision with wide margins followed by cryotherapy is still considered the gold standard for the treatment of OSSN; especially small tumours that affect less than 4 clock hours of the limbus. Surgical excision has advantage of serving as both a diagnostic and therapeutic procedure, providing both an accurate histological diagnosis and rapid tumour resolution. (REF) However, as discussed earlier, surgery has potential disadvantages including LSCD or leaving behind residual disease which can lead to subsequent tumour recurrence. The use of topical chemotherapy is gaining momentum among clinicians as an effective alternative to surgery – as a tool for primary treatment, particularly for recurrent, annular and larger lesions. Additionally, topical chemotherapeutic agents are also being used preoperatively, for chemoreduction; or postoperatively, for treating positive margins or recurrent disease. The clinician should weigh multiple factors, including possible side effects, cost and compliance while deciding which topical agent to select. While there is no randomised control trial comparing the three drugs, INF α2b remains the preferred drug of choice for topical treatment.
Ocular Surface Squamous Neoplasia: An overview

REFERENCES


Neurocutaneous syndromes (or phakomatoses) are a diverse group of congenital disorders that encompass abnormalities of neuroectodermal and, sometimes, mesodermal development, hence commonly involving the skin, eye, and central nervous system. The term, phakomatoses was introduced by Jan van der Hoeve in 1920, before the distinct genetic basis of each of these diseases was understood.¹ These are often inherited conditions and typically present in early childhood or adolescence. Some of the abnormalities and clinical symptoms may be progressive, and there is an increased risk of neoplastic formation in many of the syndromes. As a group, neurocutaneous syndromes are characterized by distinctive cutaneous stigmata and neurologic symptomology, the latter often representing the most devastating and debilitating features of these diseases.² Many of these syndromes are markedly heterogeneous in nature as they affect many organ systems. Given the incurable nature of these conditions and the broad spectrum of pathologies they comprise, treatments vary on a case-by-case basis and tend to be palliative rather than curative. With the advances in molecular genetics, however, greater understanding of biologic functions of the gene products and the correlative phenotypic expression is being attained, and this knowledge may guide future therapeutic developments.

**Neurofibromatosis 1** (NF1) is an inherited neurocutaneous disorder. It is characterized by the presence of multisystem tumors throughout the skin and central nervous system (CNS), which carries a risk of malignant transformation. The hallmark clinical features of NF1 include multiple café au lait macules, neurofibromas, intertriginous freckling, osseous lesions, Lisch nodules, and optic pathway gliomas (OPGs). (Figure 1)
Figure 1: Clinical manifestations of NF1 - (A) Café-au-lait macules; (B) Ash leaf spots; (C) Neurofibroma; (D) Conjunctival Hamartoma; (E) Fundus photo right eye.

Diagnostic Criteria for Neurofibromatosis NF1\(^3\): Diagnosis by Two or More of the Following:

- Café-au-lait macules, 5 mm in diameter: six or more on the prepubertal individual and 15 or more on adults
- Neurofibromas, two or more, or one plexiform neurofibroma
- Freckling in axillary or inguinal regions
- Optic gliomas
- Lisch nodules (iris hamartomas), two or more
- Distinctive osseous lesion: sphenoid dysplasia or thinning of long bone cortex, with or without pseudoarthrosis
- First-degree relative with NF1 by above criteria

Ocular Findings are common in patients with NF1. Some of these findings are associated with visual dysfunction whereas others are not. Lisch nodules are pigmented hamartomas that project from the surface
Phakomatoses

of the iris. They are brown, clear, or yellow with sharp margins. The more common pigmented nevi of the iris are dark and flat with indistinct margins. Lisch nodules are observed in 50% of individuals by the third decade of life and are recognizable without magnification in 88–100% of affected patients over 40 years of age. They do not cause any visual symptoms. The eyelids may be affected by either isolated neurofibromas or plexiform neurofibromas. Congenital glaucoma is associated with infiltration of the upper eyelid by a neurofibroma. Gonioscopy in affected patients shows the iris insertion to be anterior to the scleral spur. In some eyes, the angle appears to be covered by a membrane. Optic nerve or chiasmal gliomas are the most significant neuro-ophthalmologic complication of NF1. The risk of vision loss depends on the location of the tumor, whether optic nerve only, extending into the chiasm, or extending to the postchiasmal visual pathways. About 10% are confined strictly to the orbit by magnetic resonance imaging (MRI). The orbit may be involved in NF1 resulting in malposition of the eye. Retinal abnormalities in patients with NF1 are uncommon and nonspecific. Abnormalities that have been described include sectoral retinal pigmentary disturbance similar to retinitis pigmentosa, hamartomas, and pigmentary change resembling cutaneous café-au-lait spots. Retinal lesions resembling those seen in patients with tuberous sclerosis also occur in some patients with NF1. Conjunctival hamartomas occur in patients with NF1. In most of these patients, the lesion is in the perilimbal conjunctiva. Although optic gliomas are the most common tumor affecting the CNS in NF1, additional tumors include other gliomas, meningiomas, and a variety of other tumors. Pheochromocytomas occur with increased frequency in patients with NF1.

**DIAGNOSIS AND MANAGEMENT**

Because of the large size of the NF1 gene and its many mutations, comprehensive genetic screening is currently not practical. Instead, the diagnosis is typically made on clinical grounds with multidisciplinary teams (MDT). The most important aspect of the management of NF1 is to recognize that most patients lead productive lives. Careful, regular examinations for malignancies, hypertension, or neurologic disability may facilitate expeditious medical or surgical intervention.
NEUROFIBROMATOSIS TYPE 2

Epidemiology: NF2 is much less common than NF1, affecting 135,000 to 150,000 persons. CNS tumors are the major feature in NF2. Meningiomas, gliomas, and schwannomas are common, but bilateral vestibular schwannomas are nearly always present. In general, there are two categories of patients with NF2: those with an early-onset, rapid course associated with multiple other tumors in addition to bilateral vestibular schwannomas, and those with a late-onset, more benign course and only bilateral vestibular schwannomas. The gene for NF2 is on chromosome 22q12. Patients with NF2 have a variety of ocular findings, including cataracts, epiretinal membranes, and retinal hamartomas. These abnormalities may cause significant visual disturbances. Optic nerve findings observed in NF2 include the morning glory disc anomaly and optic nerve neurofibroma. Molecular evaluation of NF2 eyes demonstrated that inactivation of the NF2 gene is associated with the formation of the variety of retinal and optic nerve lesions. Ocular motility abnormalities may occur from involvement of the ocular motor nerves, particularly the third nerve, by infiltration or compression by schwannomas.

Neurologic Findings: Bilateral vestibular schwannomas, also called acoustic neuromas, are the hallmark of NF2. CNS tumors other than vestibular schwannomas occur in NF2 including facial nerve schwannomas, astrocytomas, ependymomas, meningiomas, and spinal cord tumors. The increased incidence of these various tumors
reflects the loss of a tumor-suppressor gene. Bilateral vestibular schwannomas are sufficient to diagnose NF2, but they are not always present, and many patients do not have a family history of NF2. The diagnosis may also be made in a patient with a family history of NF2 who has a unilateral vestibular schwannoma detected before 30 years of age, or two of the following: meningioma, glioma, schwannoma, or juvenile posterior subcapsular cataract. MR imaging readily shows the bilateral, contrast-enhancing lesions within or adjacent to the internal auditory canal. Surgery is the definitive treatment for rapidly progressive vestibular schwannomas and for more slowly growing tumors that cause significant disability. Stereotactic radiosurgery can reduce or stabilize vestibular schwannomas in patients for whom conventional surgery may not be an option and is regarded by some as the optimum treatment modality for these tumors. Genetic counseling is a very important component in the care of patients with NF2. Offspring of a parent with NF2 have a 50% risk of being affected by the same condition.

**TUBEROUS SCLEROSIS**

Tuberous sclerosis complex is a multisystemic, autosomal dominant genetic disorder with complete penetrance that can evolve with hamartomas in multiple organs, such as skin, central nervous system, kidney and lung. Due to the wide phenotypic variability, the disease is often not recognized. Tuberous sclerosis complex affects one in 10,000 newborns and most patients are diagnosed during the first 15 months of life. The diagnostic criteria for tuberous sclerosis were reviewed in 2012, at the second International Tuberous Sclerosis Complex Consensus Conference. The diagnosis is based on genetic criteria, by the identification of inactivating pathogenic mutation of tumor suppressor genes TSC1 and TSC2, and clinical criteria, including cutaneous, renal, pulmonary, cardiac and neurological manifestations. The ophthalmic manifestations of tuberous sclerosis include a variety of nonretinal ophthalmic findings which, other than adenoma sebaceum of the lids, are uncommon. Approximately half the patients with tuberous sclerosis have retinal or optic nerve hamartomas; in half of these patients the hamartomas occur bilaterally. Three basic morphologic types of retinal hamartomas are recognized: the most common type is a subtle, relatively flat, smooth-surfaced,
Phakomatoses

salmon-colored, semitransparent, and circular or oval-shaped lesion located in the superficial retina, most commonly near or at the posterior pole. The second type is an easily recognized opaque, white, elevated, multinodular calcified lesion that is frequently described as resembling a mulberry. A third type of lesion contains features of the other two, being calcified and nodular centrally, whereas its perimeter is semitranslucent, smooth, and salmon-colored. The hamartomas may be richly vascularized. They generally do not grow, but over decades some of the lesions may become calcified. Visual loss from retinal and optic nerve hamartomas occurs rarely. Visual loss from retinal and optic nerve hamartomas occurs rarely.9 Because growth and change of the fundus lesions are rare, treatment is not indicated. The treatment of tuberous sclerosis complex consists, mainly, in management of the symptoms caused by hamartomas and in prevention of organ failure. Multidisciplinary approach is recommended, in order to obtain better clinical outcomes.

**STURGE WEBER SYNDROME**

Sturge-Weber syndrome is a sporadic congenital neurocutaneous disorder caused by a somatic activating mutation in GNAQ; it affects 1 in every 20,000 to 50,000 newborns. Although no specific inheritance pattern has been clearly defined yet, sporadic mutations in the genes at 17p1-13 loci have been shown to be involved in this syndrome.10 Associations with other rare abnormalities have also been noted which include retinitis pigmentosa, cerebral astrocytoma, phakomatosis pigmentovascularis, and Klippel–Trenaunay–Weber Syndrome. It is characterized by a facial port-wine stain, leptomeningeal angiomatosis, and glaucoma. On the basis of clinical manifestations, SWS is classified into four types: (1) presence of brain and facial angioma, with or without glaucoma, (2) portwine stain without brain involvement, with or without glaucoma, (3) isolated brain angioma, usually without glaucoma, and (4) type 1 associated with systemic manifestations such as tuberous sclerosis. Seizures are the most common neurological manifestation and typically present in the first months of life. Glaucoma may be present at birth or develop later. Neuroimaging studies show leptomeningeal angiomatosis, supporting diagnosis.11 Standard treatment for Sturge-Weber syndrome includes laser treatment for the port-wine stain, anticonvulsants, and medical or surgical treatment for the glaucoma. Prognosis depends on the extent
Phakomatoses

of leptomeningeal involvement and the severity of the glaucoma. Glaucoma secondary to SWS is very challenging as it shows very poor response to the standard medical treatment. Only latanoprost, topical propranolol and carbonic anhydrase inhibitors have shown efficacy in controlling IOP in such cases. In order to prevent the visual function loss due to increased IOP in advanced and refractory cases, surgery is usually required. Goniotomy, trabeculotomy, trabeculectomy, combined trabeculotomy–trabeculectomy, deep sclerotomy have shown success in controlling IOP post-operatively. However, surgical procedures have resulted in severe complications like choroidal effusion, hemorrhages, and exudative retinal detachment. Various appropriate modifications in the surgical approaches may prevent such grave complications, which include preoperative reduction of IOP with hyperosmotic agents, placement of posterior sclerotomies prior to entering the eye, preplacement of flap sutures during trabeculectomy, use of valved or two-step glaucoma drainage devices, or radiotherapy of choroidal hemangiomas prior to intraocular surgery. Due to multifactorial pathogenetic factors, surgical success rates are usually low.12

VON HIPPEL LINDAU SYNDROME

Von Hippel-Lindau syndrome (VHL) is a familial neoplastic condition seen in approximately 1 in 36,000 live births. It is caused by germline mutations of the tumor suppressor gene VHL, located on the short arm of chromosome 3. While the majority of the affected individuals have a positive family history, up to 20% of cases arise from de novo mutations. VHL syndrome is characterized by the presence of benign and malignant tumors affecting the central nervous system, kidneys, adrenals, pancreas, and reproductive organs.13 Common manifestations include hemangioblastomas of the brain, spinal cord, and retina; pheochromocytoma and paraganglioma; renal cell carcinoma; pancreatic cysts and neuroendocrine tumors and endolymphatic sac tumors. Increase in vascular endothelial growth factors in VHL syndrome is believed to heighten retinal capillary hemangioblastoma (RCH) formation and growth. The most common and, most often, earliest manifestations of VHL disease are RCH (Figure 2), which occur in 43 to 85% of patients. Treatment of RCH usually includes laser photocoagulation, photodynamic therapy, cryotherapy, radiation, and surgical removal. In the literature various authors recommend
Phakomatoses

early treatment of RCH when lesions tend to enlarge and become more difficult to treat with time. Nevertheless, asymptomatic peripheral RCH lesions only require observation and treatment only in case of complications. Diagnosis of VHL is prompted by clinical suspicion and confirmed by molecular testing. Management of VHL patients is complex and multidisciplinary. Routine genetic testing and surveillance using various diagnostic techniques are used to help monitor disease progression and implement treatment options. Despite recent advances in clinical diagnosis and management, life expectancy for VHL patients remains low at 40–52 years.

Figure 2: Montage fundus picture of left eye of a case of VHL showing multiple retinal capillary haemangioblastomas.

BONNET-DECHAUME-BLANC SYNDROME OR WYBURN-MASON SYNDROME

The Wyburn-Mason syndrome is characterized by unilateral, nonhereditary retinal and cerebral arteriovenous malformations (AVMs) and is occasionally associated with orbital vascular changes. Typical signs are facial and oral mucosal vascular changes, rarely with changes of the maxilla or mandible. An AVM causes high blood flow because of direct connection (shunting) of major vessels without interposition of capillaries. Ocular complications include retinal and vitreous hemorrhages, edema, and venous occlusion (risk of rubeosis iridis and secondary glaucoma). Neuroophthalmological changes comprise optic atrophy, papilledema, proptosis, pupillary changes, hemianopia, gaze paresis, nystagmus, cranial nerve palsies, strabismus, and amblyopia. Neurological complications include headache, subarachnoid hemorrhage, convulsions, cerebral
hemorrhages, increased intracranial pressure, hydrocephalus, and stroke with hemiparesis. Threatening oral hemorrhages or epistaxis may rarely occur.\textsuperscript{17}

REFERENCES


1. INTRODUCTION
Retinoblastoma represents 3% of all childhood cancers and is the most common intraocular malignancy of childhood. The management of retinoblastoma has gradually evolved over the past few decades, with an aim to not only preserve life and eye, but also optimize residual vision. The treatment of retinoblastoma is multimodal, with chemotherapy, focal treatment including trans-pupillary thermotherapy (TTT) and cryotherapy, radiation therapy and surgery, all playing a vital role. Intravenous chemotherapy has been the mainstay of treatment for the past two decades, and still continues to be the most extensively used eye-saving modality of treatment. Intra-arterial chemotherapy has emerged as a promising alternative for advanced and refractory retinoblastoma, both as a primary and secondary therapy. Periocular and intravitreal chemotherapy have specific indications in the management of retinoblastoma. Recent advances in genetics of retinoblastoma have also helped in improving the overall clinical management of this malignancy.

2. EPIDEMIOLOGY OF RETINOBLASTOMA
The incidence of retinoblastoma is 1 in every 15000 to 18000 live births.¹ There is no variation in the number among different races, although there is a diversity among different countries. There are an estimated 5000 new cases worldwide annually, with India alone contributing to 1500-2000 cases. With increasing population in Asian and African countries, the number of retinoblastoma is also rising. Unfortunately, the mortality rates for retinoblastoma is also higher in these countries owing to delay in diagnosis, advanced disease at presentation, lack of access to advanced medical facilities, and absence of standard management protocols.
3. CLINICAL FEATURES

Leukocoria (white pupil) is the most common symptom of retinoblastoma, and strabismus is the second most important presenting symptom. In majority of cases, the parents notice the white reflex first and seek the opinion of a paediatrician. This makes the paediatricians an important bridge between the retinoblastoma families and the treating ophthalmologist, making it extremely crucial that they have a basic knowledge of retinoblastoma (Table 1). Retinoblastoma is usually diagnosed at an average age of 18 months, with 95% of children diagnosed by 5 years of age. Germline retinoblastomas can present as early as first month and sporadic retinoblastomas are detected at an average age of 24 months.\(^1\) Retinoblastoma can be unilateral or bilateral. All bilateral cases have germline mutation, whereas only 10-15% patients with unilateral retinoblastoma carry a germline mutation.

<table>
<thead>
<tr>
<th>Leukocoria</th>
<th>Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor vision</td>
<td>Red painful eye</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>Phthisis bulbi</td>
</tr>
<tr>
<td>Sterile orbital cellulitis</td>
<td>Proptosis</td>
</tr>
</tbody>
</table>

A child with a suspected retinoblastoma is best examined under anesthesia for a detailed fundus evaluation (Table 2). Retinoblastoma typically manifests as a unifocal or multifocal, well-circumscribed, dome-shaped retinal mass with dilated retinal vessels. Although initially transparent and difficult to visualize as a small focal lesion, it grows to become opaque and white. When small, the tumor is entirely intraretinal. As it enlarges, it grows in a three-dimensional plane, extending away from the vitreous cavity (exophytic) or towards it (endophytic).\(^1\)
### Table 2: Examination Under Anesthesia (EUA)

**Visual acuity and slit lamp examination must be performed in the office for older children**

**Age-appropriate visual assessment must be performed in the office for all children**

#### Anesthesia Care
- Baseline investigations – Hb%, CBC, Blood Group
- Pre-anesthesia examination by the anesthesiologist/pediatrician
- Age-appropriate fasting
- Sevoflurane or isoflurane-based EUA with a laryngeal mask by a pediatric anesthesiologist or an anesthesiologist with appropriate training in techniques of pediatric anesthesia
- Monitoring is ideally performed during anesthesia and until recovery using multifunctional monitors
- An intravenous access is mandatory
- Complete recovery by an appropriately trained nurse under supervision of an anesthesiologist should be ensured before the child is handed over to the parents

#### Examination under anesthesia involves evaluation of both eyes in a detailed manner
- Anterior segment evaluation
- Corneal diameter
- Intraocular pressure measurement by Perkins applanation tonometer
- Total retinal evaluation up to ora serrata in both eyes
- Retinal drawing - all tumors, subretinal fluid, subretinal seeds and vitreous seeds are documented
- Wide-angle fundus photography

#### Instrumentation
- Hand-held slit-lamp (optional)
- Operating microscope
- Indirect ophthalmoscope with +20 diopter lens
- Eye speculum
- Perkins applanation tonometer
- Calipers
- Cryotherapy machine with retinal cryotherapy probe
- Large spot diode laser with indirect ophthalmoscope delivery
- RetCam or similar wide field fundus photography
- Facility for fluorescein angiography (optional)
- Hand-held OCT (optional)
In the exophytic growth pattern, the tumor arises from the outer retinal layers and causes diffuse retinal detachment (Figure 1A). It is most often associated with numerous small subretinal seeds. In contrast, an endophytic retinoblastoma arises from the inner retinal layers, progressively fills the vitreous cavity, and causes vitreous seeding (Figure 1B). At times, the tumor maybe a combination of these two growth patterns. Diffuse infiltrating retinoblastoma is a rare pattern of presentation where there is no obvious mass, only a placoid retinal infiltration, and is acalcific. It is generally seen in older children, and the incidence is less than 2%. Diffuse anterior retinoblastoma, a rare entity, is considered as an anterior variant of diffuse infiltrating retinoblastoma. It is thought to arise from the most peripheral parts of retina with anterior growth, and no retinal focus visible on examination.2

Patients with anterior extension of the tumor can present with white fluffy exudates in the anterior chamber resembling a hypopyon, called pseudohypopyon.1 Neovascularization of iris and glaucoma

Figure 1: Clinical presentation of retinoblastoma (A) Exophytic growth pattern with diffuse subretinal fluid (B) Endophytic growth pattern with diffuse vitreous seeds (C) Advanced retinoblastoma with neovascular glaucoma (D) Advanced retinoblastoma presenting as sterile orbital cellulitis
are other clinical presentations seen in patients with advanced tumor (Figure 1C). Orbital cellulitis-like picture occurs when a large tumor undergoes necrosis and induces inflammation in and around the eye (Figure 1D). Retinoblastoma which has extended outside the confines of the eye is known as orbital retinoblastoma and this can occur when the tumor invades either the optic nerve, or full thickness of the sclera and beyond, and the patient generally presents with proptosis.

4. DIFFERENTIAL DIAGNOSIS

The most important differential diagnosis is Coats’ disease. There are several other lesions that can simulate retinoblastoma and are known as pseudoretinoblastomas. The important differential diagnoses are listed in Table 3.

Table 3: Pseudoretinoblastoma

<table>
<thead>
<tr>
<th>Coats’ disease</th>
<th>Persistent fetal vasculature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous hemorrhage</td>
<td>Toxocariasis</td>
</tr>
<tr>
<td>Familial exudative vitreoretinopathy</td>
<td>Retinal detachment</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>Coloboma</td>
</tr>
<tr>
<td>Astrocytic hamartoma</td>
<td>Combined hamartoma</td>
</tr>
<tr>
<td>Endogenous endophthalmitis</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>Medulloepithelioma</td>
<td>X-linked retinoschisis</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>Juvenile xanthogranuloma</td>
</tr>
<tr>
<td>Norrie’s disease</td>
<td></td>
</tr>
</tbody>
</table>

5. IMAGING

While the diagnosis of retinoblastoma is mostly clinical, ancillary tests like ultrasonography, fluorescein angiography (FA), optical coherence tomography (OCT), computed tomography (CT) and magnetic resonance imaging (MRI) aid in the documentation of the disease and differentiation of pseudoretinoblastomas from retinoblastoma (Table 4). CT scan also helps diagnose extraocular extension, while MRI is most appropriate to detect optic nerve invasion and to screen for pinealoblastoma in heritable retinoblastoma.
<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RetCam</td>
<td>Wide angle fundus camera that is used in documenting fundus findings at each visit, and monitoring the treatment.</td>
</tr>
</tbody>
</table>
| Ultrasonography                      | • Detecting calcification  
    • Establishing diagnosis in an opaque media  
    • Measuring tumor thickness                                                                                                                                                                                   |
| Fluorescein Angiography (FA)         | • Visualizing tumor hyperfluorescence  
    • Detecting capillary drop-outs, neovascularization, recurrences and occlusive vasculopathy in a child with a treatment history of IAC                                                                                                                                 |
| Hand-held spectral domain OCT (SD-OCT)| • Documenting early intraretinal tumors  
    • Differentiating from pseudoretinoblastomas like astrocytic hamartoma  
    • Detecting small recurrences  
    • Assessing fovea for visual potential                                                                                                                                                                          |
| Computed Tomography (CT)             | **Need**  
    • Detecting calcification  
    • Identifying extraocular and optic nerve extension  
    **Caution**  
    • Avoid in known heritable retinoblastoma (family history, bilateral, unilateral and multifocal)  
    • Avoid “routine” CT scan in all children with retinoblastoma or for purely intraocular retinoblastoma  
    **Specifications**  
    • Spiral CT with rapid acquisition time  
    • Non-contrast  
    • Orbit  
    • Axial and coronal  
    • Sagittal reconstruction  
    • 2 mm slice thickness  
    **Indications**  
    • To diagnose in the presence of opaque media precluding visualization of the tumor  
    • To differentiate pseudoretinoblastoma or to rule out retinoblastoma in a simulating situation  
    • Baseline scan to rule out extraocular extension in the presence of clinical risk factors – corneal diameter >11 mm, asymmetry of corneal diameter >1 mm, corneal edema, neovascularization of iris, IOP >20 mm Hg, hypopyon, hyphema, vitreous exudates, vitreous hemorrhage, any media opacity precluding visualization, proptosis, phthisis bulbi  
    • To monitor response in a child with extraocular retinoblastoma treated with neoadjuvant therapy after 3 cycle |
### Imaging Modality

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Description</th>
</tr>
</thead>
</table>
| Magnetic Resonance Imaging (MRI) | Need  
• Delineating the intraocular tumor extent and detection of optic nerve or scleral extension  
• Disease staging  
• Ruling out pinealoblastoma in bilateral cases  
Caution  
• Needs monitored sedation or general anesthesia  
• Avoid “routine” MRI in all children with retinoblastoma or for purely intraocular retinoblastoma  
Specifications  
• Non-contrast for routine MRI; Gadolinium enhancement for suspected intracranial extension  
• STIR T1 and T2, with and without fat suppression  
• Surface coil  
• Axial, coronal, sagittal  
• Orbit and brain  
Indications  
• Heritable retinoblastoma - baseline scan to screen for pinealoblastoma  
• Baseline scan to rule out extraocular extension and CNS involvement in the presence of clinical risk factors – corneal diameter >11 mm, asymmetry of corneal diameter >1 mm, corneal edema, neovascularization of iris, IOP >20 mm Hg, hypopyon, hyphema, vitreous exudates, vitreous hemorrhage, any media opacity precluding visualization, proptosis, phthisis bulbi  
To monitor response in a child with extraocular retinoblastoma treated with neoadjuvant therapy after 3 cycles |
| PET-CT Scan                      | Need  
• To rule out systemic metastasis  
Caution  
• Needs monitored sedation or general anesthesia  
• Avoid “routine” PET in all children with retinoblastoma or for purely intraocular retinoblastoma  
Indications  
Clinically suspected systemic metastasis at baseline or during/following treatment |

### 6. GROUPING AND STAGING

The grouping system is for retinoblastomas confined to the eye, where eye salvage is the end point, whereas the staging system is for predicting survival in patients with retinoblastoma. International
Classification of Retinoblastoma (ICRB) was devised in 2003 and includes both grouping and staging. The grouping is based on the tumor size, location, severity and presence of subretinal and vitreous seeds (Table 5a) The latest classification is the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) system, which is novel to include an important category – Hereditary (H) (Table 5b).

### Table 5a: International Classification of Intraocular Retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: Small tumor</td>
<td>Tumor ≤3 mm in size</td>
</tr>
<tr>
<td>Group B: Larger tumor</td>
<td>Tumor &gt;3 mm, Macular location (≤3 mm to foveola), Juxta-papillary location (≤1.5 mm to disc) Clear subretinal fluid ≤3 mm from margin</td>
</tr>
<tr>
<td>Group C: Focal seeds</td>
<td>Subretinal seeds ≤3 mm from retinal tumor Vitreous seeds ≤3 mm from retinal tumor Subretinal &amp; Vitreous seeds ≤3 mm from retinal tumor</td>
</tr>
<tr>
<td>Group D: Diffuse seeds</td>
<td>Subretinal seeds &gt;3 mm from retinal tumor Vitreous seeds &gt;3 mm from retinal tumor Subretinal &amp; Vitreous seeds &gt;3 mm from retinal tumor</td>
</tr>
<tr>
<td>Group E: Extensive retinoblastoma</td>
<td>Tumor occupying 50% globe Neovascular glaucoma, Opaque media (from hemorrhage in anterior chamber, vitreous, or subretinal space) Invasion of postlaminar optic nerve, choroid (2 mm), sclera, orbit, anterior chamber</td>
</tr>
</tbody>
</table>

### Table 5b. International Staging of Retinoblastoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Unilateral or bilateral retinoblastoma and no enucleation</td>
</tr>
<tr>
<td>Stage I</td>
<td>Enucleation with complete histological resection</td>
</tr>
<tr>
<td>Stage II</td>
<td>Enucleation with microscopic tumor residual (anterior chamber, choroid, optic nerve, sclera)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Regional extension A. Overt orbital disease B. Pre-aural or cervical lymph node extension</td>
</tr>
</tbody>
</table>
Stage IV Metastatic disease  
A. Hematogenous metastasis  
   1. Single lesion  
   2. Multiple lesions  
B. CNS extension  
   1. Prechiasmatic lesion  
   2. CNS mass  
   3. Leptomeningeal disease

**Table 5c: AJCC 8 TNM Classification**

<table>
<thead>
<tr>
<th>Definition of primary tumour (cT)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cTX</td>
<td>Unknown evidence of intraocular tumour</td>
</tr>
<tr>
<td>cT0</td>
<td>No evidence of intraocular tumour</td>
</tr>
<tr>
<td>cT1</td>
<td>Intraocular tumour(s) with sub-retinal fluid ≤ 5mm from the base of any tumour</td>
</tr>
<tr>
<td>cT1a</td>
<td>Tumours ≤ 3mm and further than 1.5 mm from the disc and fovea</td>
</tr>
<tr>
<td>cT1b</td>
<td>Tumours &gt; 3 mm or closer than 1.5 mm to the disc and fovea</td>
</tr>
<tr>
<td>cT2</td>
<td>Intraocular tumour(s) with retinal detachment, vitreous seeding or sub-retinal seeding</td>
</tr>
<tr>
<td>cT2a</td>
<td>Sub-retinal fluid &gt; 5 mm from the base of any tumour</td>
</tr>
<tr>
<td>cT2b</td>
<td>Tumours with vitreous seeding and/or sub-retinal seeding</td>
</tr>
<tr>
<td>cT3</td>
<td>Advanced intraocular tumour(s)</td>
</tr>
<tr>
<td>cT3a</td>
<td>Phthisis or pre-phthisis bulbi</td>
</tr>
<tr>
<td>cT3b</td>
<td>Tumour invasion of the pars plana, ciliary body, lens, zonules, iris or anterior chamber</td>
</tr>
<tr>
<td>cT3c</td>
<td>Raised intraocular pressure with neovascularization and/or buphthalmos</td>
</tr>
<tr>
<td>cT3d</td>
<td>Hyphema and/or massive vitreous hemorrhage</td>
</tr>
<tr>
<td>cT3e</td>
<td>Aseptic orbital cellulitis</td>
</tr>
<tr>
<td>cT4</td>
<td>Extraocular tumour(s) involving the orbit, including the optic nerve</td>
</tr>
<tr>
<td>cT4a</td>
<td>Radiological evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues</td>
</tr>
<tr>
<td>cT4b</td>
<td>Extraocular tumour clinically evident with proptosis and orbital mass</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition of regional lymph nodes (cN)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cNX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>cN0</td>
<td>No regional lymph nodes involvement</td>
</tr>
<tr>
<td>cN1</td>
<td>Evidence of preauricular, submandibular, and cervical lymph node involvement</td>
</tr>
<tr>
<td>Definition of distant metastasis (M)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td>cM0</td>
<td>No signs or symptoms of intracranial or distant metastasis</td>
</tr>
<tr>
<td>cM1</td>
<td>Distant metastasis without microscopic confirmation</td>
</tr>
<tr>
<td>cM1a</td>
<td>Tumour(s) involving any distant site (e.g. bone marrow, liver) on clinical or radiological tests</td>
</tr>
<tr>
<td>cM1b</td>
<td>Tumour involving the central nervous system on radiological imaging (not including trilateral retinoblastoma)</td>
</tr>
<tr>
<td>pM1</td>
<td>Distant metastasis with microscopic confirmation</td>
</tr>
<tr>
<td>pM1a</td>
<td>Histopathological confirmation of tumour at any distant site (e.g. bone marrow, liver, or other)</td>
</tr>
<tr>
<td>pM1b</td>
<td>Histopathological confirmation of tumour in the cerebrospinal fluid or CNS parenchyma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition of heritable trait (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HX</td>
</tr>
<tr>
<td>H0</td>
</tr>
<tr>
<td>H1</td>
</tr>
</tbody>
</table>

7. MANAGEMENT

Management of a child with retinoblastoma is aimed at achieving the three sequential goals of life salvage, eye salvage and optimal vision. Management involves the identification of the tumor group and stage, decision-making regarding the appropriate therapeutic measure, and meticulous follow-up for monitoring the treatment progress and detection of any recurrence. While intravenous chemotherapy (IVC) remains the most extensively used modality of treatment, other tools available for the therapeutic intervention in retinoblastoma include chemotherapy using different delivery routes, focal treatment with cryotherapy, transpupillary thermotherapy (TTT), and laser photocoagulation, radiotherapy by teletherapy (external beam) or brachytherapy (plaque radiotherapy), and enucleation (Table 6). Those who manage retinoblastoma should be familiar with the tumor regression pattern – Type 0 is tumor resolution without a scar, Type 1 is calcific scar, Type 2 is acalcific fleshy scar, Type 3 is partially calcified partially fleshy mixed pattern and Type 4 is a flat scar. Regression
pattern is governed by the age of the patient, heredity, tumor location, tumor size, tumor type (endophytic, exophytic, diffuse infiltrative, mixed) and the mode of treatment.

**Table 6:** Decision-making in the management of Retinoblastoma: Treatment options

<table>
<thead>
<tr>
<th>Primary tumor: Options for treatment</th>
<th>Recurrent tumor: Options for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral advanced (D, E)</td>
<td>IAC, IVC, Plaque radiation, Enucleation</td>
</tr>
<tr>
<td>Unilateral less advanced (A, B, C)</td>
<td>IVC, IAC, Focal therapy</td>
</tr>
<tr>
<td>Bilateral advanced (D, E)</td>
<td>IVC + POC</td>
</tr>
<tr>
<td>Bilateral less advanced (A, B, C)</td>
<td>IVC</td>
</tr>
</tbody>
</table>

**7.1. Chemotherapy**

In recent years, there has been a trend towards targeted therapy to manage retinoblastoma with minimal adverse effects on surrounding normal retina and general systemic health. The use of intra-arterial chemotherapy (IAC), periocular chemotherapy (POC), and intravitreal chemotherapy (IVitC) has enabled to focus direct drug delivery to the tumor. Unlike IVC which can be used in the primary management of all retinoblastomas, IAC, POC and IVitC have specific indications.

**7.1a Intravenous Chemotherapy**

Currently, IVC is the most widely used treatment in India (Table 7). Used as a combination triple drug therapy of vincristine, etoposide and carboplatin, chemotherapy with focal consolidation achieves excellent success rates in the primary management of retinoblastoma. Chemotherapy alone can achieve an impressive tumor control in less advanced cases, with success rates of 100%, 93% and 90% in ICRB groups A, B and C, respectively (Figures 2A-D). Rates of regression of retinoblastoma and eye salvage with standard triple-drug chemotherapy have been suboptimal for ICRB group D and E tumors. In group D eyes, approximately
half of the eyes require either EBRT or enucleation for tumor control.\textsuperscript{11} A combination of chemotherapy and radiation in eyes with vitreous seeds has yielded globe salvage rates varying from 22-70\%.\textsuperscript{12} Periocular carboplatin and topotecan injection also resulted in higher intravitreal drug level (Table 8). Transscleral penetration of posterior sub-Tenon carboplatin leads to augmented vitreous concentration. High-dose chemotherapy with concurrent periocular carboplatin has been tried as a primary management strategy, specifically in eyes with diffuse vitreous seeds.\textsuperscript{11} This has led to better tumor control in advanced cases, with 95\% eye salvage rate in eyes with focal vitreous seeds and a 70\% eye salvage rate in those with diffuse vitreous seeds (Figure 3A-D).\textsuperscript{12,13}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Standard-dose chemotherapy in retinoblastoma (A) A group B eye (B) After 6 cycles of standard-dose chemotherapy (C) A group C eye with focal vitreous seeds (D) After 6 cycles of standard-dose chemotherapy}
\end{figure}
**Figure 3:** High-dose chemotherapy in retinoblastoma with periocular chemotherapy

(A) A group D eye with diffuse vitreous seeds (B) Clinical regression after 6 cycles of high-dose chemotherapy with 3 doses of concurrent periocular carboplatin

(C) A group D eye with fine diffuse vitreous seeds (D) Complete regression after 6 cycles of high-dose chemotherapy with 2 doses of concurrent periocular carboplatin

**Table 7:** Intravenous Chemotherapy

<table>
<thead>
<tr>
<th>Procedure:</th>
<th>IVC when given as a primary treatment for retinoblastoma causes reduction in tumor volume, and this is known as chemoreduction (CRD). Most commonly, a combination of three drugs of standard dose (SD) is used, although high dose (HD) may be necessary in advanced cases or tumors not responding to SD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
<td>Triple drug combination therapy of vincristine, etoposide and carboplatin (VEC) is employed, generally given 4 weekly for 6 cycles.</td>
</tr>
<tr>
<td></td>
<td>Day 1: Vincristine + Etoposide + Carboplatin</td>
</tr>
<tr>
<td></td>
<td>Day 2: Etoposide</td>
</tr>
<tr>
<td>Drug</td>
<td>SD-VEC (≥3 years of age)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Vincristine*</td>
<td>1.5 mg/m²</td>
</tr>
<tr>
<td>Etoposide</td>
<td>150 mg/m²</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>560 mg/m²</td>
</tr>
<tr>
<td>*maximum dose &lt; 2 mg</td>
<td></td>
</tr>
</tbody>
</table>
**Indications:**
(1) Primary tumor
(2) Recurrent tumor
(3) Recurrent subretinal seeds
(4) As adjuvant therapy in post-enucleation patients with high-risk features (discussed elsewhere)
(5) Orbital retinoblastoma
(6) As palliative therapy in metastatic retinoblastoma

**Advantages:**
(1) Long-term tumor control
(2) Reduces incidence of pinealoblastoma
(3) Reduces incidence of second cancers
(4) Reduces incidence of systemic metastasis

**Disadvantages:**
(1) Systemic side-effects including thrombocytopenia, leucopenia and anemia
(2) Allergic reactions to carboplatin and etoposide
(3) Long-term effects include hearing loss, renal toxicity and secondary leukemia

---

**Table 8: Periocular Chemotherapy**

**Procedure:**
POC is administered by posterior sub-Tenon injection of the chemotherapeutic drug in the quadrant closest to the location of the vitreous seeds. Innovative delivery systems for POC include the use of episcleral implants, fibrin sealants and nanoparticles of the drug.

**Drugs:**
Carboplatin (1.5-2.0 mg)
Topotecan (1-2 mg)

**Indication:**
Advanced groups D or E with diffuse vitreous seeds in which a higher local dose of chemotherapy is desired

**Advantages:**
(1) Achieves rapid levels within the vitreous in 30 min and can last for hours
(2) Achieves doses that are six to ten times higher than that achieved by IVC

**Disadvantages:**
(1) Orbital and eyelid edema and ecchymosis
(2) Orbital fat atrophy
(3) Muscle fibrosis leading to strabismus.
7.1b Intra-arterial Chemotherapy

IAC for the treatment of intraocular retinoblastoma was first performed by Algernon Reese with direct internal carotid artery injection of the alkylating agent triethylene melamine in 1954. Suzuki & Kaneko described the technique of ‘selective ophthalmic artery infusion’ (SOAI) in 2004 by the balloon technique, where a micro-balloon catheter is positioned by a transfemoral artery approach at the cervical segment of the internal carotid artery just distal to the orifice for the ophthalmic artery. At this point, the balloon catheter is inflated, and chemotherapy is injected with flow thereby directed into the ophthalmic artery. The authors noted there are several small, but nevertheless important, branches proximal to the origin of the ophthalmic artery (i.e. cavernous branches of the ICA) into which infused chemotherapy could flow, and concluded that this infusion method is not truly selective. In 2006, Abramson and Gobin pioneered direct intra-arterial (ophthalmic artery) infusion or superselective intra-arterial chemotherapy or “chemosurgery”.

Patient is examined under anesthesia by the treating ocular oncologist. Documentation of each affected eye is performed by wide-angle fundus photography, FFA and B-scan ultrasonography. The decision to treat with IAC is undertaken in consultation with an ocular oncology team, an endovascular neurosurgeon and a paediatric oncologist.

The procedure is performed under general anesthesia using a sterile technique (Figures 4A-D). Nasal decongestion is achieved by topical decongestant drops or spray. Anticoagulation with intravenous infusion of heparin is delivered to a target activated clotting time of 2 to 3 times baseline. Through a transfemoral approach, the ipsilateral internal carotid artery is catheterized with a 4F pediatric guide catheter. The arterial anatomy is visualized with serial angiography runs, and the ostium of the ophthalmic artery is super selectively catheterized with a Prowler 10 microcatheter by the peep-in technique. A super selective injection through the microcatheter is performed to check adequate positioning and assessing the amount of reflux, if any, into the internal carotid artery before chemotherapy is injected. Each chemotherapy dose is diluted in 30 ml of saline and administered in a pulsatile fashion over 30 minutes to prevent lamination of medication and loss of dose to peripheral tributaries. Repeat angiography is performed
immediately after the procedure to ensure patency of the vessels, and the catheter removed. At the end of the procedure, the heparin is reversed with intravenous protamine and hemostasis achieved with manual compression of the femoral artery upon removal of the catheter.15 The child is monitored for 6 hours before discharge.

Figure 4: Intra-arterial chemotherapy: Procedure in the cath lab (A) Patient under general anesthesia with a transfemoral catheter (B) An angiography performed at the beginning of the procedure, showing a patent internal carotid artery (C) An angiography performed with the microcatheter at the ostium of the ophthalmic artery, showing a patent ophthalmic artery (D) Infusion of the chemotherapeutic drug through the transfemoral cathether

IAC has emerged as an effective treatment for advanced retinoblastoma (Figures 5A-D). It is increasingly being used in tumors as a primary treatment, especially in unilateral retinoblastoma. It can be used as a secondary therapy for those cases which have recurred or have not responded adequately to IVC (Table 9). Shields et al observed 94% globe salvage in group D eyes, and 91% vitreous seed regression, when IAC was used as a primary therapy.16,17,18 In a study comparing 2-year ocular survival rate between naïve eyes with vitreous seeds (IAC as a primary therapy) and previously treated eyes with vitreous seeds (IAC as a secondary therapy), Abramson et al observed that IAC seemed to be more effective in eyes that have failed to respond
to previous therapies. In an overall study on IAC in retinoblastoma, Abramson et al observed that eyes with vitreous seeds tend to require higher treatment sessions and doses, and multiple agents, as compared to eyes without vitreous seeds.\textsuperscript{15}

**Figure 5:** Intra-arterial chemotherapy in advanced retinoblastoma (A) A group D eye with diffuse vitreous seeds (B) After 3 cycles of intra-arterial chemotherapy (C) A group E eye with a very large tumor and diffuse subretinal fluid (D) After 3 cycles of intra-arterial chemotherapy

**Table 9:** Intra-arterial Chemotherapy

<table>
<thead>
<tr>
<th>Procedure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAC involves the delivery of chemotherapeutic drugs directly in the eye through a fluoroscopy-guided microcatheter into the ostium of the ophthalmic artery, and is done in a cath lab by an interventional neuroradiologist. IAC can be a one-, two- or three-drug regimen, and each drug is delivered slowly over 30 min in a pulsatile fashion. It is repeated every 4 weeks, and most of the patients require 3 sessions to achieve complete tumor regression.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan is the most extensively used drug in IAC, and topotecan is added if there is extensive vitreous seeding. In advanced cases, three drugs including carboplatin are employed to ensure complete tumor control.</td>
</tr>
<tr>
<td>One-drug regimen: Melphalan (3-7.5 mg)</td>
</tr>
<tr>
<td>Two-drugs regimen: Melphalan (3-7.5 mg) + Topotecan (1-2 mg)</td>
</tr>
<tr>
<td>Three-drugs regimen: Melphalan (3-7.5 mg) + Topotecan (1-2 mg) + Carboplatin (15-50 mg)</td>
</tr>
</tbody>
</table>
**Indications:**

IAC can be used as a primary therapy, or secondary therapy in eyes which have not achieved tumor control after intravenous chemotherapy. In general, it is preferred in children older than 4 months of age without a germline mutation.

1. Unilateral nongermline retinoblastoma
2. Recurrent retinoblastoma following previous IVC or plaque radiotherapy
3. Recurrent extensive subretinal seeds not controlled by IVC

**Advantages:**

1. High intraocular concentration of the drug without associated systemic adverse effects of the drugs
2. Shorter time for tumor control

**Disadvantages:**

1. Expensive
2. Difficulty with catheterizations
3. Vitreous hemorrhage
4. Branch retinal artery obstruction
5. Ophthalmic artery spasm with reperfusion
6. Ophthalmic artery obstruction
7. Partial choroidal ischemia
8. Optic neuropathy
9. Complications associated with the technique including a risk for brain vascular events, hypoxia, hypotension and bradycardia

### 7.1c Intravitreal Chemotherapy

Currently, intraocular seeds are classified as vitreous seeds, prehyaloid seeds, subhyaloid seeds, epiretinal seeds, intraretinal seeds, subretinal seeds and intracameral seeds (further classified as infiltrative seeds and depository seeds). Conventionally, the term vitreous seeds includes pure vitreous seeds, prehyaloid seeds, retrohyaloid seeds and epiretinal seeds. Vitreous seeds are aggregates of tumor cells found in the avascular vitreous, which are relatively resistant to the effect of intravenous chemotherapy due to lack of blood supply (Table 10). These appear due to the disruption of the apical tumor either spontaneously (primary) or treatment-induced necrosis (secondary). Suboptimal concentration of chemotherapeutic agents in the vitreous results in persistence of vitreous seeds. Refractory vitreous seeds are the persistent or recurrent vitreous seeds which do not respond to the standard treatment modalities. Persistent
seeds are those which are present during chemoreduction, and continue to persist after the completion of chemoreduction.\textsuperscript{19,20,21} Recurrent seeds are those which appear after the completion of chemoreduction. IVitC achieves higher drug concentration within the vitreous and effectively causes regression of vitreous seeds, without associated systemic side effects.

**Table 10: Intraocular and Vitreous seeds: Classification**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary VS</td>
<td>Present at the initial diagnosis</td>
</tr>
<tr>
<td>Secondary VS</td>
<td>Those which appear during the course of treatment due to necrotic disruption of the tumor</td>
</tr>
<tr>
<td>Persistent VS</td>
<td>Primary VS which persist beyond chemoreduction</td>
</tr>
<tr>
<td>Recurrent VS</td>
<td>VS which appear after the completion of chemoreduction</td>
</tr>
<tr>
<td>Focal VS</td>
<td>Seeds located ≤ 3 mm from the main tumor</td>
</tr>
<tr>
<td>Diffuse VS</td>
<td>Seeds located &gt;3 mm from the tumor</td>
</tr>
<tr>
<td>1. Free-floating VS</td>
<td>Seeds dispersed in the vitreous</td>
</tr>
<tr>
<td>2. Pre-hyaloid VS</td>
<td>Seeds present just anterior to the hyaloid membrane</td>
</tr>
<tr>
<td>3. Retro-hyaloid VS</td>
<td>Seeds present just anterior to the internal limiting membrane of the retina</td>
</tr>
<tr>
<td>4. Epiretinal VS</td>
<td>Seeds over the internal limiting membrane with or without organic contact with the internal limiting membrane</td>
</tr>
<tr>
<td>5. Intraretinal Seeds</td>
<td>Seeds in the superficial layers of the retina</td>
</tr>
<tr>
<td>6. Subretinal Seeds</td>
<td>Seeds in the deeper layers of the retina</td>
</tr>
<tr>
<td>7. Intracameral Seeds</td>
<td>Migrated from the posterior segment and deposited in the anterior segment</td>
</tr>
<tr>
<td>a. Depository</td>
<td>Contiguous extension into the anterior chamber through ciliary body, angle and iris infiltration</td>
</tr>
<tr>
<td>b. Infiltrative</td>
<td></td>
</tr>
<tr>
<td>Dust formation</td>
<td>Minute VS formed following the apical disruption of the tumor</td>
</tr>
<tr>
<td>Sphere formation</td>
<td>Balls of VS resulting from clonal expansion of dust</td>
</tr>
<tr>
<td>Cloud formation</td>
<td>Massive VS resulting from the disruption of the tumor</td>
</tr>
<tr>
<td>Mixed</td>
<td>Combination of the above</td>
</tr>
</tbody>
</table>

IVitC in retinoblastoma was first introduced by Ericson and Rosengren using thiotepa in 1960. Methotrexate has also been tried as an intravitreal drug for retinoblastoma. In 1987, Inomata and Kaneko investigated the sensitivity of retinoblastoma to 12 anticancer drugs and found that the retinoblastoma cells were most sensitive to melphalan in-
Melphalan is now the most extensively used drug to control the vitreous disease in retinoblastoma (Table 11). Munier et al discussed a potentially safe technique to perform intravitreal injections to prevent extraocular extension of the tumor. They advocated the application of triple freeze-thaw cryotherapy at the injection site to prevent egress of the tumor cells in the needle track (Figure 6A-D).

**Figure 6:** Intravitreal chemotherapy: Safety-enhanced technique (A) Pars plana intravitreal injection of topotecan at a dose of 30 μg in 0.15 ml with a 30-gauge needle (B) Needle is withdrawn through the first ice ball of the cryotherapy (C) Triple freeze-thaw cryotherapy at the injection site (D) Forceps-assisted jiggling of the eyeball following the injection for an even dispersion of the chemotherapeutic drug

**Table 11:** Intravitreal chemotherapy

**Procedure:**
Any intraocular procedure in retinoblastoma is generally avoided for fear of extraocular extension of the tumor. However, intravitreal injections by safety-enhanced technique has proven to prevent this risk. The injection site is carefully chosen after a thorough clinical examination to rule out the presence of tumor, vitreous seeds or subretinal fluid at the injection site. The injection is given using a 30 gauge needle by the transconjunctival pars plana route. After injecting the drug, the needle is withdrawn in the first ice ball formation of the chemotherapy followed by injection site triple freeze-thaw cryotherapy. This technique reduces the extraocular escape of any tumor cell through the needle track.
**Drugs:**
Melphalan is the most widely used drug in IVitC, and topotecan is generally added if there is extensive vitreous seeding. Topotecan may also be used as a single drug. 
- Melphalan (20-30 μg)
- Topotecan (20-30 μg)
- Combination: Melphalan (20-30 μg) + Topotecan (20-30 μg)

**Indications:**
(1) Recurrent diffuse or focal vitreous seeds
(2) Persistent diffuse or focal vitreous seeds

**Advantages:**
(1) High intraocular concentration of the drug without associated systemic adverse effects of the drugs
(2) Complications associated with POC avoided

**Disadvantages:**
(1) Extraocular extension of the tumor associated with an improper technique

With melphalan, vitreous seed regression ranging from 85-100% of eyes and globe salvage in 80-100% of eyes have been reported. Intravitreal melphalan is given as a weekly injection until regression. The disadvantage of melphalan is that it is not stable in solutions, and has to be used within an hour of reconstitution of the drug. A combination of intravitreal melphalan and topotecan has also been used to achieve excellent regression in refractory vitreous seeds. Apart from melphalan, topotecan is also emerging as a potent intravitreal therapy with a safe toxicity profile (Figure 7A-D). Topotecan is a very safe drug for intraocular use, is stable in solution and can be given as a 3-weekly injection. Regression pattern of vitreous seeds includes complete disappearance (type 0), calcified seeds (type 1a), crystalline refringent dust (type 1b), amorphous nonspherical seeds, pigmented or non-pigmented (type 2), and a combination of the above (type 3).
Radiation Therapy

Retinoblastoma is a highly radio sensitive tumor, and radiation therapy can be curative. Radiation in the form of EBRT was the most popular globe-salvage therapy in retinoblastoma before the introduction of chemotherapy in 1990s. Although it is no longer the primary modality of treatment for retinoblastoma due to the associated complications, it has its own therapeutic indications (Table 12). Episcleral plaque radiotherapy is a form of brachytherapy wherein the source of radiation (commonly Iodine 125 or Ruthenium 106) is placed on the episclera adjacent to the tumor, and the tumor absorbs radiation, sparing other healthy ocular tissues from the ill-effects of radiation (Table 13).
Table 12: External Beam Radiation Therapy

Procedure:
Numerous methods and protocols to treat retinoblastoma with EBRT have been described. Lens-sparing technique with electron beam and photon beam using a linear accelerator has been traditionally employed. Newer techniques using stereotactic radiation therapy (SRT), intensity modulated radiation therapy (IMRT) and proton therapy have been described. The standard dose is 40-45 Gy, generally given in fractionated doses over 3-4 weeks.

Indications:
(1) HRF on pathology after enucleation (described elsewhere)
(2) As a part of multimodal management in orbital retinoblastoma (described elsewhere)
(3) Tumor and/or vitreous seeds refractory to other treatments

Advantages:
(1) Prevents orbital recurrence when given as an adjuvant therapy for indications 1 and 2
(2) Excellent long-term tumor control when used for refractory tumor/vitreous seeds

Disadvantages:
(1) Orbital hypoplasia
(2) Secondary cancers in the field of radiation
(3) Cataract
(4) Dry eye syndrome

Table 13: Episceral Plaque Brachytherapy

Procedure:
Radioisotopes like Iodine-125 and Ruthenium-106 that emit radiation are used for the treatment of various ocular tumors including retinoblastoma. I-125 emits gamma radiation, and Ru-106 beta radiation, which can penetrate the tumor. For this, the radioisotopes are loaded on an applicator (gold or silver), and the plaque sutured onto the episclera. The duration of the treatment is calculated by a radiation physicist, and the plaque is removed at the end of the treatment duration.

Indications:
(1) Recurrent tumor that is > 3 mm in thickness which is not suitable for treatment by other forms of focal therapy (TTT, cryotherapy or laser photocoagulation)

Advantages:
(1) Direct treatment of the tumor with minimal scarring
(2) Deeper penetration as compared with other forms of focal treatment
(3) Single treatment session
(4) Surrounding healthy tissue is not effected
(5) Overlying focal vitreous seeds are also treated simultaneously

Disadvantages:
(1) Not effective in large recurrent tumors
(2) Not ideal in multifocal recurrences
(3) Delayed radiation-related complications like radiation retinopathy
7.3 Focal Therapy

Although episcleral plaque therapy may also be considered as a form of focal therapy, the term generally refers to the use of cryotherapy, TTT and laser therapy in the treatment of retinoblastoma. These are generally used for consolidation once the tumor has attained a considerably lower volume with chemoreduction, usually after 2 or 3 cycles, or for the treatment of small recurrent tumors or subretinal seeds. However, they can also be used as the sole therapy for small retinoblastomas (Tables 14, 15, 16).

**Table 14: Cryotherapy**

<table>
<thead>
<tr>
<th>Procedure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transscleral cryotherapy involves freezing the tumor under visualization using indirect ophthalmoscopy. The cryoprobe tip is centered directly under the tumor and the ice ball formed on freezing should adequately cover the tumor and any focal vitreous seeds. Triple freeze-thaw cycles of cryotherapy are generally applied. Cryotherapy destroys the tumor cells mechanically by disruption of the cell membranes during thawing of the intracellular ice crystals. Typically the treatment is repeated every 3-4 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Peripheral tumors &lt;4 mm in diameter and &lt;3 mm in thickness</td>
</tr>
<tr>
<td>(2) Subretinal seeds</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Treatment of focal vitreous seeds overlying the tumor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Large area of retinal scarring</td>
</tr>
<tr>
<td>(2) Retinal breaks</td>
</tr>
</tbody>
</table>

**Table 15: Transpupillary thermotherapy**

<table>
<thead>
<tr>
<th>Procedure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>In thermotherapy, hyperthermia generated by infrared radiation at subphotocoagulation levels destroys the tumor. A slow and sustained temperature range of 40 to 60 degree C within the tumor is generated using a semiconductor diode laser (810 nm) delivered as a 1300-micron large spot and long burn duration (1 minute) with indirect ophthalmoscope delivery system. The tumor is heated until it turns a subtle gray. Complete tumor regression can be achieved in over 85% of tumors using 3-4 sessions of thermotherapy. Using indocyanine green dye to sensitize the tumor for TTT (ICG-enhanced TTT) is an effective alternative for tumor control, particularly for small tumors that show suboptimal response to standard TTT.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Small tumors which are 4 mm in diameter and 2 mm in thickness</td>
</tr>
<tr>
<td>(2) Subretinal seeds</td>
</tr>
</tbody>
</table>
### Advantages:
(1) Synergistic combination of thermotherapy with chemoreduction protocol (chemothermotherapy), with heat application amplifying the cytotoxic effect of platinum analogues

### Disadvantages:
(1) Focal iris atrophy
(2) Focal paraxial lens opacity
(3) Large area of retinal scarring
(4) Retinal traction and serous retinal detachment

### Table 16: Laser photocoagulation

**Procedure:**
Photocoagulation using argon green laser (532 nm) delivered with an indirect laser delivery system causes tumor apoptosis. Overlapping spots on the tumor edge are placed at a power setting of 250-350 mw for 0.3-0.5 seconds. The treatment destroys the tumor by restricting the blood supply to the tumor and also by hyperthermia. Typically the treatment is repeated every 3-4 weeks.

**Indications:**
(1) Small posterior tumors which are 4 mm in diameter and 2 mm in thickness

**Advantages:**
(1) Can be used when TTT is not available

**Disadvantages:**
(1) Retinal traction and serous retinal detachment
(2) Retinal vascular occlusion
(3) Retinal hole
(4) Large area of retinal scarring
(5) Not ideal while the patient is on active chemoreduction as it restricts the blood supply to the tumor thus reducing the intra-tumor concentration of the chemotherapeutic agent

### 7.4 Enucleation

Enucleation is the oldest form of treatment for retinoblastoma, and is still indicated in advanced cases. Unilateral disease with no salvageable vision is best treated by enucleation and the patient can be rid of the disease for life. Enucleation is a simple procedure, although special precautions need to be taken when handling an eye with retinoblastoma (Table 17). These are necessary to avoid accidental perforation that can potentially cause orbital seeding of the tumor. Use of a primary silicone or polymethylmethacrylate implant by the myoconjunctival technique provides adequate static and dynamic cosmesis. Porous polyethylene or hydroxyapatite implants don’t offer additional advantage unless pegged, and these
are best avoided if a child is likely to need adjuvant chemotherapy or EBRT following enucleation since fibrovascular integration of these implants would be impeded.

**Table 17: Enucleation**

<table>
<thead>
<tr>
<th>Enucleation by the myoconjunctival technique with a silicone orbital implant is a safe and cost-effective procedure with prosthesis motility comparable to biointegratable implants while minimizing the complications. This technique may also be used in those requiring periorbital radiotherapy following surgery.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The surgery is usually performed under general anesthesia.</td>
</tr>
<tr>
<td>A lateral canthotomy is performed.</td>
</tr>
<tr>
<td>A 360 degree peritomy is done using a blunt tipped Westcott scissors, cutting as close to the limbus as possible.</td>
</tr>
<tr>
<td>The underlying posterior Tenon’s layer is undermined in all four quadrants in a spreading action using a blunt tipped tenotomy scissors.</td>
</tr>
<tr>
<td>Each of the recti muscles is identified, hooked and double-tagged, first with 6-0 silk suture and then with 6-0 vicryl suture. 6-0 silk sutures serve as traction sutures while 6-0 vicryl sutures would later be used to suture the muscles through the conjunctiva.</td>
</tr>
<tr>
<td>Each of the recti muscles is then transected at a point between the two sutures using a radiofrequency probe.</td>
</tr>
<tr>
<td>Superior oblique and inferior oblique muscles are transected and allowed to retract posteriorly.</td>
</tr>
<tr>
<td>A conjunctival relaxing incision is made for easy manipulation.</td>
</tr>
<tr>
<td>The eyeball is then prolapsed between the blades of the speculum.</td>
</tr>
<tr>
<td>With a forward traction on the eyeball using the 4 silk sutures, a gently curved blunt tipped tenotomy scissors is passed along the lateral wall and the optic nerve is strummed along its length.</td>
</tr>
<tr>
<td>With one bold cut, the optic nerve is transected just a little anterior to the superior orbital fissure, to gain a good optic nerve length and at the same time to avoid injuring the superior orbital fissure contents.</td>
</tr>
<tr>
<td>After achieving adequate hemostasis, an appropriate sized silicone orbital implant is placed posterior to posterior Tenon’s.</td>
</tr>
<tr>
<td>Posterior Tenon’s is closed with interrupted 6-0 vicryl sutures.</td>
</tr>
<tr>
<td>Each of the Recti muscles is sutured through the conjunctiva in its respective fornix, and these sutures are called the myoconjunctival sutures.</td>
</tr>
<tr>
<td>Anterior Tenon’s is closed with interrupted 6-0 vicryl sutures.</td>
</tr>
<tr>
<td>Conjunctival closure is done in a continuous key-suturing pattern with 6-0 vicryl suture.</td>
</tr>
<tr>
<td>An appropriate sized conformer is placed and a median tarsorrhaphy done with 6-0 vicryl suture.</td>
</tr>
<tr>
<td>The suture tarsorrhaphy is removed after 1 week and a prosthesis can then be placed in the socket after 6 weeks.</td>
</tr>
</tbody>
</table>
An enucleated eyeball is always submitted for pathology to assess for high risk factors (HRF). In a landmark paper by Honavar et al, the need for adjuvant chemotherapy has been emphasized to reduce the risk of secondary orbital recurrence and systemic metastasis. The incidence of metastasis was 4% in those who received adjuvant therapy, compared with 24% in those who did not. Hence when HRF is positive, adjuvant treatment with chemotherapy and/or EBRT is indicated (Table 18). Adjuvant chemotherapy consists of a combination of vincristine, etoposide and carboplatin given 4-weekly for 6 cycles.

### Table 18: High-Risk Features in Retinoblastoma

<table>
<thead>
<tr>
<th>High Risk Features on pathology where adjuvant chemotherapy is indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anterior segment invasion</td>
</tr>
<tr>
<td>• Ciliary body infiltration</td>
</tr>
<tr>
<td>• Massive choroidal invasion (invasion $\geq$ 3 mm in basal diameter or thickness)</td>
</tr>
<tr>
<td>• Full thickness scleral extension</td>
</tr>
<tr>
<td>• Extrascleral extension</td>
</tr>
<tr>
<td>• Retrolaminar optic nerve invasion</td>
</tr>
<tr>
<td>• Optic nerve invasion at line of transection</td>
</tr>
<tr>
<td>• Combination of optic nerve infiltration till any level (pre-laminar/ laminar/ retrolaminar) and choroidal infiltration (any thickness)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High Risk Features on pathology where adjuvant radiotherapy is indicated (in addition to chemotherapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Full thickness scleral extension</td>
</tr>
<tr>
<td>• Extrascleral extension</td>
</tr>
<tr>
<td>• Optic nerve invasion at line of transection</td>
</tr>
</tbody>
</table>

### 8. ORBITAL RETINOBLASTOMA

Orbital retinoblastoma is an advanced form of retinoblastoma seen mostly in developing countries of Asia and Africa. The incidence varies among different countries, and is in the range of 18-40%. Orbital disease can be classified as listed in Table 19. Primary orbital retinoblastoma is the orbital extension of the disease which is evident at presentation either clinically or radiologically. Most of the patients present with proptosis, or a large fungating mass which bleeds on touch. Tumor necrosis causes inflammation of the surrounding tissues and the patient may present with sterile orbital cellulitis. Secondary orbital retinoblastoma occurs in an enucleated socket after an uncomplicated surgery. It may present as an orbital mass with an unexplained...
displacement of the implant, or a palpable orbital mass. Accidental retinoblastoma occurs in the event of an inadvertent perforation of the eye harboring retinoblastoma. This can occur due to improper enucleation technique, or various intraocular surgeries in an eye with unsuspected intraocular retinoblastoma. Overt orbital retinoblastoma refers to previously unrecognized extrascleral or optic nerve extension discovered during enucleation as an episcleral nodule, or an enlarged and inelastic optic nerve with or without nodular optic nerve sheath. Microscopic orbital retinoblastoma is identified on histopathological examination of the enucleated eyeball as full thickness scleral infiltration, extrascleral extension or invasion of the optic nerve.

Table 19: Orbital Retinoblastoma: Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Primary Orbital Retinoblastoma</td>
<td>Clinical or radiologically detected orbital extension of an intraocular retinoblastoma at the initial clinical presentation, with either optic nerve involvement or scleral extension of the tumor.</td>
</tr>
<tr>
<td>2. Secondary Orbital Retinoblastoma</td>
<td>Orbital recurrence following uncomplicated enucleation for intraocular retinoblastoma, presenting as unexplained displacement, bulge or extrusion of a previously well-fitting conformer or a prosthesis.</td>
</tr>
<tr>
<td>3. Accidental Orbital Retinoblastoma</td>
<td>Inadvertent perforation, fine-needle aspiration biopsy or intraocular surgery in an eye with unsuspected intraocular retinoblastoma are considered as accidental orbital retinoblastoma.</td>
</tr>
<tr>
<td>4. Overt Orbital Retinoblastoma</td>
<td>Previously unrecognized extrascleral or optic nerve extension discovered during enucleation as an episcleral nodule, or an enlarged and inelastic optic nerve with or without nodular optic nerve sheath.</td>
</tr>
<tr>
<td>5. Microscopic Orbital Retinoblastoma</td>
<td>Full thickness scleral infiltration, extrascleral extension or invasion of the optic nerve on histopathologic evaluation of an eye enucleated for intraocular retinoblastoma.</td>
</tr>
</tbody>
</table>

The presence of orbital disease is generally known to carry a poor prognosis. Orbital disease increases the risk of systemic metastasis by 10-27 times and the mortality rates range from 25 to 100%. However, with an intensive multimodal management and careful monitoring, patients with orbital disease are known to do well (Table 20) (Figures 8A-D).
Figure 8: Multimodal management in orbital retinoblastoma (A) External photograph of primary orbital retinoblastoma taken during examination under anesthesia (B) Axial computed tomography image displaying extraocular extension of the intraocular tumor (C) After 12 cycles of doses of high-dose chemotherapy, external beam radiotherapy and enucleation (D) Healthy child cured of orbital retinoblastoma, with a well-fitting prosthesis

Table 20: Orbital Retinoblastoma: Treatment

<table>
<thead>
<tr>
<th>Baseline investigations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CT or MRI to assess the tumor extent</td>
</tr>
<tr>
<td>• Bone marrow biopsy</td>
</tr>
<tr>
<td>• Cerebrospinal fluid cytology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multimodal management involving chemotherapy, surgery and radiation therapy is employed. Chemotherapy is essential for chemoreduction and to prevent systemic metastasis, surgery to reduce the tumor load and clear the orbit of most of the tumor, and radiation to take care of the residual disease and prevent orbital recurrence.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Orbital Retinoblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neoadjuvant high dose chemotherapy is given for 3 cycles</td>
</tr>
<tr>
<td>• Residual disease is assessed by CT or MRI</td>
</tr>
<tr>
<td>• If orbital retinoblastoma has resolved, enucleation is performed. If orbital retinoblastoma has not resolved, no surgery is done at this stage and 3 more cycles of high dose chemotherapy are given</td>
</tr>
<tr>
<td>• Residual disease is again assessed by CT or MRI</td>
</tr>
<tr>
<td>• If orbital retinoblastoma has resolved, enucleation is performed at this stage. In case there is residual orbital disease even after 6 cycles, exenteration is performed</td>
</tr>
<tr>
<td>• EBRT given to the orbit (45-50 Gy)</td>
</tr>
<tr>
<td>• Adjuvant high dose chemotherapy are given for 6 or 9 cycles, to complete a total of 12 cycles</td>
</tr>
</tbody>
</table>
### Secondary Orbital Retinoblastoma
- Neoadjuvant high dose chemotherapy is given for 3 cycles
- Residual disease is assessed by CT or MRI
- If orbital retinoblastoma has regressed significantly, excision of the residual mass is performed. If orbital retinoblastoma has not resolved, no surgery is done at this stage and 3 more cycles of high dose chemotherapy are given
- Residual disease is again assessed by CT or MRI
- If orbital retinoblastoma has resolved, excision of the orbital mass is performed at this stage. In case there is significant orbital disease even after 6 cycles, exenteration is performed
- EBRT given to the orbit (45-50 Gy)
- Adjuvant high dose chemotherapy are given for 6 or 9 cycles, to complete a total of 12 cycles

### Accidental Orbital Retinoblastoma
- If the intervention is limited such as a needle biopsy and the tumor is not advanced, high dose chemotherapy is given for 6 cycles and the patient carefully monitored at frequent intervals
- If the intervention is limited such as a needle biopsy and the tumor is advanced, enucleation with an en bloc excision of the conjunctiva at the needle site is performed and adjuvant high dose chemotherapy is given for 6 cycles and the patient carefully monitored at frequent intervals
- If the intervention is extensive such as pars plana vitrectomy, enucleation with an en bloc excision of the conjunctiva overlying the ports is performed and adjuvant high dose chemotherapy is given for 6 cycles and the patient carefully monitored at frequent intervals
- EBRT may be given in each case depending on the nature of the disease, type and extent of the intervention and the findings at subsequent follow-ups, a decision best left on the treating doctor’s expertise

### Overt Orbital Retinoblastoma
- If an extrascleral extension is macroscopically visualized during enucleation, special precaution is taken to excise the nodule completely along with the eyeball, also with the overlying Tenon’s capsule in the involved area
- If optic nerve extension is suspected during enucleation and the nerve stump obtained is short, extra efforts to excise an additional length is made
- In both cases, EBRT is given followed by 12 cycles of adjuvant high dose chemotherapy

### Microscopic Orbital Retinoblastoma
- If microscopic full thickness scleral involvement and/or extrascleral extension and/or optic nerve involvement up to the level of transection is detected, EBRT is given followed by 12 cycles of adjuvant high dose chemotherapy

### Follow-up
- CT or MRI 6-monthly to look for tumor recurrence
- Bone marrow biopsy 6-monthly
- Cerebrospinal fluid cytology 6-monthly
9. METASTATIC RETINOBLASTOMA

With an incidence of less than 5% of all retinoblastoma cases, metastatic retinoblastoma is rare, but most often seen in developing countries. It usually occurs as a relapse following enucleation for intraocular retinoblastoma, especially in those who had high risk pathologic features. Most commonly, metastasis occurs to the central nervous system (CNS), bone and bone marrow. The metastasis occurs in one of the three ways- by direct dissemination into the CNS via the optic nerve, choroidal invasion and hematogenous spread, or orbital extension with lymph node involvement and hematogenous spread. Bony metastasis, usually involving the long bones or the craniofacial bones, causes non-tender palpable mass.

Cerebrospinal fluid cytology, bone marrow evaluation and whole-body imaging are done in all cases of metastatic retinoblastoma for staging the disease. Use of high-dose chemotherapy with autologous stem cell rescue (ASCR) has offered some encouraging results. However, most of the experience is in stage 4a disease that does not involve the CNS. The use of radiotherapy and intrathecal chemotherapy for CNS lesions have been recommended, although the prognosis for such advanced metastatic retinoblastoma continues to remain grim.

10. PRENATAL GENETICS

Retinoblastoma is a malignancy associated with somatic mutation or germline mutation. Knudson proposed the two-hit hypothesis where he described the occurrence of two consecutive mutations for the conversion of a normal retinal cell into a malignant cell. In heritable retinoblastoma, the first mutation is in the germ cell, and this ‘first hit’ is carried in every cell in the body, making them prone not only for retinoblastoma, but also for other second cancers (most commonly pinealoblastoma, osteosarcoma and soft tissue sarcomas). The ‘second hit’ occurring in the retinal cells during retinal development causes retinoblastoma. In non-heritable retinoblastoma, both hits occur in the retinal cell, and thus the mutation is confined to one single cell in the retina. Heritable retinoblastoma constitutes 30-40% of all retinoblastomas, while the rest 60-70% are non-heritable. One-fourths of the germline mutations are familial with autosomal dominant inheritance pattern, and the others are de-novo non-familial germline mutations.
RB1 is a tumor suppressor gene that was identified in association with retinoblastoma and it validated the two-hit hypothesis. RB1 gene is located in the long arm of chromosome 13 (13q), and most of the mutations are nonsense codons or frame shifts. Sometimes retinoblastomas are caused by genomic deletion of chromosome 13q, a syndrome known as RB1 gene deletion syndrome, where the affected individual has varying degrees of dysmorphic features and neurodevelopmental delays.2

To prevent transmission of the disease from parents to offspring, genetic testing for germline mutations can be done at specialized laboratories (Figure 9). RB1 is the only gene that is implicated in retinoblastoma. However, there are different types of mutations affecting this gene. Direct DNA sequencing detects 75% of the mutations, and PCR amplification detects yet another 20% of the mutations. Peripheral blood lymphocytes or tumor tissue, when available, are sampled for the detection of the mutation.

Figure 9: Canadian national guidelines for genetic screening
In heritable retinoblastoma, once the mutation is identified in the lymphocytes, the presence of the same mutation is tested in the fetus (sibling or offspring) by chorionic villus biopsy or amniocentesis. If the mutation is found, a decision to terminate the pregnancy can be made.

In non-heritable retinoblastoma, if the tumor tissue is available from an affected individual, it can be sampled to detect the type of mutation. If the same mutation is also found in the blood of the patient, the individual is positive for germline mutation and an offspring can be tested for the same mutation. However, if no mutation is found in the blood, the tumor is nongermline (sporadic), without any risk of transmission of the disease to the offspring. In case no tumor tissue is available, lymphocytes are sampled for the type of RB1 mutation, but the interpretation of a negative result in these cases is difficult. Either the patient has a sporadic retinoblastoma, or a germline mutation that escaped detection by the currently available techniques.

Preimplantation genetic testing for carriers of mutation involves the identification of RB1 mutation in a blastomere (8-cell embryo) which is obtained by in vitro fertilization (IVF) technique. The small material is amplified by polymerase chain reaction (PCR) and the blastomere without the RB1 mutation maybe implanted for a successful pregnancy.34

11. SCREENING FOR RETINOBLASTOMA

Vision screening in new-born babies and children at appropriate ages and intervals can help identify tumors at early stages, when more effective treatment modalities can be applied, increasing the chances of cure. A thorough history is obtained from the parent (Table 21). Vision-screening is simple and effective when appropriately performed (Table 22). The red reflex is a popular method to confirm leukocoria among the pediatricians. The tumors are generally located in the macular region in the newborn, and are much easier to detect. In older children, the tumors tend to be more peripheral. For this reason, the test is performed in all gazes.
Table 21: History-taking

Presenting history
- Presenting symptom - leukocoria, strabismus, reduced vision, red painful eye, protruding eye
- Duration of symptoms

Perinatal history
- Weight and gestational age at birth of the child
- Need for oxygen administration (rule out possibility of ROP)

Family history
- History of intraocular tumor in any of the family members
- History of blindness in the family - at birth or in childhood
- History of any other cancers in the family
- Family tree should be charted for three generations indicating the ages of all the Siblings

Treatment history
- Age at first diagnosis
- Complete details of previous treatment received, with the dates of examination and type of treatment received, including the names and dosage of drugs
- Details of the treating doctor, including the name and address

Table 22: Vision Screening

Complete examination of the ocular adnexa, conjunctiva, cornea, iris, and pupils.

Red reflex test
- In a darkened room (to maximize pupillary dilation), a direct ophthalmoscope is focused on each pupil individually, 50 cm away from the eye. The red reflex obtained from each pupil is observed. It is useful to set the ophthalmoscope on +4 diopter setting for a focused image of the red reflex.
- After each eye has been assessed separately, the eyes are viewed together with the child focusing on the ophthalmoscope light (Bruckner test) at a distance of 1 m. Any asymmetry in pupil colour, brightness or size warrants a referral. A white reflex that is ominous sign that warrants an urgent referral to an ophthalmologist to rule out retinoblastoma. (It should be noted that if the child is looking 15 degrees nasal to the path of the viewer, the optic nerve head can cause leukocoria, resulting in a false positive red reflex test.
- Dilated direct ophthalmoscopic examination may improve the ability to detect early retinoblastoma. One drop of 0.5% cyclopentolate and one drop of 2.5% phenylephrine placed in both eyes 20–40 minutes before the red reflex test should provide an adequate pupillary dilation in those children with smaller resting pupil diameters.

Urgent referral to an ophthalmologist is indicated when a white pupillary reflex is detected.
12. SIBLING SURVEY

Once retinoblastoma is diagnosed in a child, it is important that the treating doctor charts out a family tree, and lists every sibling of the affected child, with age and details of any prior eye exam. This is crucial in familial retinoblastoma and for children in the family aged less than 5 years of age. With careful clinical screening alone, 50% cases can be diagnosed by 2 months of age, 85% by 6 months, and nearly 100 % by 12 months. The frequency of screening depends on the age of the sibling (Table 23). These are empiric guidelines for sibling survey. Use of genetics-guided sibling survey would be ideal.

### Table 23: Sibling Survey in Retinoblastoma

<table>
<thead>
<tr>
<th>Age of the child</th>
<th>Frequency of examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>First exam within 2 weeks of birth</td>
</tr>
<tr>
<td>Birth-3 months</td>
<td>Every 1 month</td>
</tr>
<tr>
<td>3 months-1 year</td>
<td>Every 2 months</td>
</tr>
<tr>
<td>1-2 years</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>2-3 years</td>
<td>Every 4 months</td>
</tr>
<tr>
<td>3-5 years</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

13. FOLLOW-UP

All retinoblastoma survivors should receive individualized, lifelong follow-up and surveillance for late effects of disease and treatment. Following completion of treatment, EUAs for children at risk of developing new tumours continue as often as every 4 weeks, or at longer intervals as tumour activity decreases, until risk for new tumours and recurrences are low, and the child is able to cooperate in clinic (at about 5 years of age). Upon complete and stable event-free regression, the child is evaluated every 3 months for a year and every 6 months for 3 years and every year thereafter by age-appropriate means (EUA or clinic exam). Following the end of EUAs at 5 years of age, clinic visits for retinal exam should continue every 6 months to age 10, and then annually for lifelong. Examination of an enucleated socket for infection, fit of prosthesis and implant exposure should be assessed at every EUA and clinic visit. The use of protective polycarbonate glasses is recommended in all children. Visual rehabilitation is important in children with low vision. Those with RB1 germline mutation, or
14. CONCLUSION

The management of retinoblastoma revolves around having a sound knowledge of the disease, choosing the best treatment for the patient among the various available options and careful monitoring for recurrences. Enucleation should be performed when deemed necessary in advanced retinoblastoma with no visual prognosis, without needless overenthusiasm for globe salvage in advanced tumors. Specific precautions during the surgery, use of a primary implant for cosmesis, and post-enucleation evaluation of histopathologic HRFs and adjuvant therapy, as appropriate, achieve optimal life salvage. Primary focal therapy with laser, TTT or cryotherapy for peripheral tumors can be used for ICRB group A tumors in visually noncritical locations. IVC continues to be the standard treatment for ICRB groups B to D, and for bilateral retinoblastoma. Appropriate use of high-dose protocol and concurrent POC can help salvage group D and E eyes with diffuse vitreous seeds. Figures 10-16 summarize the current treatment algorithms. IAC is a very promising treatment with high success for advanced retinoblastoma, but the cost factor must also be taken into consideration. IVitC should be performed with safety-enhanced technique. Radiation therapy should be employed only when indicated. Retinoblastoma has a very high cure rate, and is best managed in an integrated retinoblastoma clinic under the watchful monitoring of an expert ocular oncologist. The recent advances in management of retinoblastoma and a holistic approach have rendered it eminently curable - prognosis for life salvage is now around 98%, with 90% eye salvage and 80% vision salvage.
Figure 10: Treatment algorithm for intraocular retinoblastoma, group A.

Figure 11: Treatment algorithm for intraocular retinoblastoma, group B.

Figure 12: Treatment algorithm for intraocular retinoblastoma, group C.
Figure 13: Treatment algorithm for intraocular retinoblastoma, group D.

Figure 14: Treatment algorithm for intraocular retinoblastoma, group E.
**Figure 15:** Treatment algorithm for extraocular retinoblastoma. For stage II with optic nerve transection positive, we recommend external beam radiotherapy after 6 cycles of high-dose chemotherapy, followed by 6 more cycles of high-dose chemotherapy.

**Figure 16:** Treatment algorithm for extraocular/metastatic retinoblastoma.
REFERENCES:


15. Abramson DH, Marr BP, Dunkel IJ, et al. Intra-arterial chemotherapy for retinoblastoma in eyes with vitreous and/or subretinal seeding: 2-year results. Br


INTRODUCTION

Melanoma is a rare but dangerous malignancy arising from pigmented neural crest derived melanocytes situated at various anatomic sites like skin, mucosa and eye (uvea, conjunctiva, eyelid, orbit). Of all melanomas 5% are reported to arise from eye and adnexal structures in USA. Of these ocular melanomas 85% are uveal (iris, ciliary body and choroid) in origin of which choroidal melanoma is most common. Uveal melanoma is the most common primary intraocular tumor in adults, predominantly affecting Caucasians and Hispanic population compared to Asians and Africans. In their series of 8033 patients with uveal melanoma Shields et al reported the tumor location in iris in 285 (4%), ciliary body in 492 (6%) and choroid in 7256 (90%) patients. Analysis of the Surveillance, Epidemiology, and End Results (SEER) program database from the National Institute of Health (Maryland, USA) revealed an age adjusted incidence of uveal melanoma of 5.2 cases per million population per year which remained stable over the last four decades. Overall, there has been a significant shift in treatment modality from surgery (local tumor resection or enucleation) to vision sparing radiotherapy (brachytherapy and proton beam). However, despite this change in treatment trend the 5 year relative survival rate remained unchanged (80.9%), a finding similar to the Collaborative Ocular Melanoma Study (COMS) where brachytherapy was offered in place of enucleation as a treatment modality for medium-sized tumors. In Europe similarly a stable incidence of uveal melanoma was reported from the European Cancer registry based study on survival and care of cancer patients (EUROCARE) revealing an age standardized incidence rate of 1.3-8.6 per million per year. Moreover, they reported a decreasing gradient of uveal
melanoma from north to south Europe supporting a protective role of ocular pigmentation. The incidence rate of uveal melanoma has been found to be low from regions like Asia (0.2-0.3/million/year), Africa (0.2-0.3/million/year)\(^9\) and South Korea (0.6/million/year).\(^{10}\) However, it seems across continents the overall incidence of uveal melanoma has remained unchanged or showing a decreasing trend over the years.\(^{1,6,7,8,11}\) Currently, in order to improve prognostication and aid therapy significant research work is being done focusing on molecular diagnostics. Herein, we discuss the various epidemiology and predisposing factors, clinical features, diagnostic and treatment modalities, recent advances in the management of uveal melanoma.

**Epidemiology**

**Age**

Uveal melanoma is more common in elderly population with median age at diagnosis being 62 years, with a range of 6 to 100 years.\(^7\) The age specific incidence rises progressively and peaks between 70-74 years decreasing thereafter.\(^1,5,8\) Uveal melanoma in children is rare. Based on large cohort of 8033 eyes with uveal melanoma only 1% were <20 years of age. However, these children manifested a higher proportion of iris melanoma compared to adults and had a better prognosis than adults.\(^{12-14}\) Congenital uveal melanoma has also been reported in some anecdotal case reports.\(^{15,16}\) In a large cohort of 7043 cases from the SEER database showed an increase in the mean age of diagnosis from 59 to 62 years over a span of 37 years which they attributed to the increase in life expectancy and increased frequency of ocular examinations in elderly population.\(^{17}\) However, multiple reports show a decade or more lower age at diagnosis in Asian countries, with mean age of 46.1 in Indians,\(^{18-21}\) 44.6 in Chinese,\(^22\) 50.9 in Taiwanese,\(^23\) 54 in Korean\(^{10}\) and 55.2 in Japanese.\(^{24}\)

**Gender**

According to the population-based sources the age adjusted incidence rate of uveal melanoma is more in males compared to females. According to the SEER registry database although the overall age adjusted incidence of uveal melanoma in USA over the last 41 years remained stable there was a significant higher age adjusted incidence in males at 6 per million compared to females with 4.5
per million population. In places like Australia, Denmark, Norway the incidence of ocular melanoma has been reported to be higher in males especially in older ages (>65 years) which they attribute to the greater sun exposure and hours of outdoor work in males compared to females. It is noteworthy that significant gender difference has not been reported in younger patients (<65 years) and in large patient cohorts with no age standardization.

**Temporal stability**

In contrast to the global trends of rising cutaneous melanoma incidence, uveal melanoma incidence has either remained stable or declined in different regions over the last several decades. The stable difference in uveal melanoma incidence rate population-wise points towards the underlying susceptibility of the tumor to an individual’s region of origin.

**Race**

Melanomas are classically known to occur in the Caucasian population. The ratio of incidence in Black to white has been reported as 1:8 to 1:143. It has been found that for primary cutaneous melanoma non-Caucasians are more likely to present with a more advanced disease and has a higher disease-specific mortality rate compared to whites. In contrast based on their case series of 8100 patients with uveal melanoma where Caucasians comprised 98%, Hispanics 1%, Asians and African-Americans <1% Shields and associates commented that uveal melanoma has similar prognosis for all races (Caucasians, Hispanics, Asian, African-American). This decreased incidence in blacks may be because of protective effect of dark pigmentation or unknown socioeconomic or environmental factors.

**ETIOLOGICAL FACTORS**

Early diagnosis of uveal melanoma is extremely crucial as each millimeter increase in melanoma thickness leads to 5% increased risk of systemic metastasis by 10 years. Thus, significant research work is being conducted to improve our understanding of risk factors of uveal melanoma to aid early diagnosis and prompt treatment.
A. Host factors

1. Skin, hair, eye colour and ability to tan

A meta-analysis by Weis et al highlighted strong association between host susceptibility factors of light (blue or gray) iris colour (OR=1.75), fair skin colour (OR=1.8) and increased sun burning (OR=1.64) to uveal melanoma. The probable explanation for this association is that people with light iris color or fair skin or decreased ability to tan may have less melanin in their choroid and retinal pigment epithelium thus providing less protection to UV rays causing uveal melanoma. Further, it is possible that people with these factors are phenotypically predisposed unrelated to the amount of melanin. However, this meta-analysis did not find an association between light hair colour and uveal melanoma. This they attributed to the fact that hair colour is not a true surrogate marker for follicular melanin production and the difference in response to UV light of follicular and epidermal melanocytes.

2. Oculodermalmelanocytosis

Ocular and dermal congenital slate-gray hyperpigmentation along the distribution of first and second division of trigeminal nerve is known as Oculodermalmelanocytosis (ODM) or Nevus of Ota. The melanocytosis predominantly involves unilateral sclera, uvea, eyelid, orbit, meninges, tympanic membrane and temporal fossa. ODM is an important predisposing factor for uveal melanoma. 1 out of every 400 people with ODM develop uveal melanoma in their lifetime. ODM is noted in ~1.4 to 3% of patents with uveal melanoma. Higher number of melanocytes in their uvea is responsible for the increased susceptibility of ODM to uveal melanoma. Patients of uveal melanoma with ODM have double risk of systemic metastasis compared to those with no ODM. This highlights the importance of twice yearly ophthalmic examination in patients with ODM to rule out uveal melanoma.

3. Cutaneous, iris and choroidal nevus

Atypical cutaneous nevus (dysplastic nevus), common cutaneous nevus, cutaneous freckles, iris and choroidal nevus are recognized risk factors for developing uveal melanoma. Atypical cutaneous nevi are often found in Atypical mole syndrome (AMS) or Familial atypical Mole and melanoma (FAM-M) syndrome. The
National Institute of Health consensus report defined FAM-M as occurrence of a large number of atypical cutaneous moles (often >50) with distinct histologic features and cutaneous melanoma in first or second degree relatives. These patients are at higher risk of developing both cutaneous and ocular melanoma. Further patients with eye melanoma are at higher risk of developing cutaneous melanoma. Thus skin examination to rule out AMS and cutaneous melanoma is a mandate in all patients with uveal melanoma.

Iris nevus apart from being a risk factor for transformation into iris melanoma also serves as an independent predisposing phenotype for developing uveal melanoma in general. The rate of transformation of iris nevus to iris melanoma has been differently stated as 5% at 5 years to 8% at 15 years. Features predictive of growth can be remembered by the mnemonic ABCDEF standing for A- young Age (<40 years), B- Blood (hyphema), C- inferior Clock hours of iris involvement, D- Diffuse iris involvement, E- Ectropion uveae, F- Feathery margins. Ultrasound biomicroscopy features predictive of growth for iris melanocytic lesions are greater baseline thickness, corneal touch, irregular internal structure and presence of dots and linear streaks.

Choroidal nevus is a common intraocular lesion with a prevalence of 4.6 to 7.9% in USA. The annual rate of transformation of a choroidal nevus to melanoma is 1 in 8845 (assuming that all choroidal melanoma arise from choroidal nevus). Factors predictive of growth of a choroidal nevus into melanoma can be remembered by the mnemonic ‘To Find Small Ocular Melanoma Using Helpful Hints Daily’ (TFSOM UHHD) where T-tumor Thickness greater than 2 mm, F-subretinal Fluid, S-Symptoms (vision loss, field defect, flashes/floaters), O-Orange pigment, M-tumor Margin within 3 mm of the optic disc, UH-Ultrasonographic Hollowness, H- Halo absence, and D-Drusen absence. The risk of tumor growth increases from 4% with none of these factors to >50% with the presence of >3 risk factors.

4. Genetic predisposition

Uveal melanoma predominantly occurs as a sporadic disease. However, reports of familial uveal melanoma, young age at diagnosis, congenital uveal melanoma, bilateral or multifocal primary uveal melanoma supports an underlying
genetic predisposition of uveal melanoma. Familial uveal melanoma is extremely uncommon and reported to be <1% of all uveal melanomas. Amongst the different genes studied BAP1 (BRCA1-associated protein 1) is the only gene known to confer significant risk to uveal melanoma. BAP1 mutation is found in around 22% of familial uveal melanomas and ~5% patients with uveal melanoma. Moreover, patients with BAP1 mutations are found to have larger tumors with ciliary body involvement, both of which are risk factors for systemic metastasis. Uveal melanoma is rare (~1%) in young patients (<20 years) with a better 5-year survival compared to adults. However, ODM has been found to be 9 times more common in young patients with uveal melanoma compared to older patients. Bilateral primary uveal melanoma although extremely rare, occurs more frequently than expected by chance alone. However, no specific clinical evidence of an inherited genetic predisposition has been found yet. Unknown germline mutations may be involved in the pathogenesis.

B. Environmental factors

1. Sunlight exposure

Ultraviolet (UV) light exposure is an established risk factor for cutaneous melanoma. Intermittent UV light exposure has been found to be a risk factor for cutaneous melanoma, whereas chronic UV light exposure seems to have a protective role. In contrast with regards to uveal melanoma there is contradicting evidence in literature to support and refute the role of sunlight exposure in the development of uveal melanoma. The most common location of choroidal melanoma being the macula and temporal retina and of iris melanoma being the inferior iris had supported the proposition that incident solar radiation is a causative factor for uveal melanoma, because these ocular locations receive the largest dose of incident solar radiation and also has the greatest concentration of melanocytes. However, a meta-analysis by Shah et al found inconsistent association between ultraviolet light exposure and development of uveal melanoma. Factors like outdoor leisure, occupational sunlight exposure and latitude of birth were not significant for uveal melanoma.
2. Occupation

Higher risk of uveal melanoma is established in welders.\textsuperscript{25,59,65} Intermittent exposure to artificial ultraviolet light along with other factors like exposure to radio frequency radiation, electric field, asbestos, carcinogenic welding fumes may account for this association.\textsuperscript{59} Excess risk of uveal melanoma has also been found in occupational cooks.\textsuperscript{65,66,67} Workers being exposed to antifreeze agents, carbon tetrachloride, formaldehyde and pesticides are also speculated to be at increased risk for uveal melanoma.\textsuperscript{68}

3. Radio frequency radiation

Possible association between radio frequency radiation exposure to radio sets, mobile phones and uveal melanoma although reported could not be corroborated in further studies.\textsuperscript{69,70}

IRIS MELANOMA

Iris melanoma has a more benign course compared to posterior uveal melanoma with slower growth and infrequent metastasis.\textsuperscript{4}

Symptoms

Iris melanoma patients are usually asymptomatic. Rarely patients complain of growing black spot on the iris or change in iris color or ocular pain because of secondary glaucoma.\textsuperscript{1,71,72} Chronic glaucoma may also lead to visual field loss and blurred vision.

Clinical features

Iris melanoma arises from the iris stroma. Iris melanoma occurs most commonly in mid-adults (20-60 years) around one to two decades earlier than cilio-choroidal melanomas.\textsuperscript{1,71} Clinically it can present as circumscribed, diffuse, tapioca or trabecular meshwork (ring) types.\textsuperscript{71,72} The tumor is melanotic (82%), amelanotic (10%) or mixed variant (8%).\textsuperscript{71}

It is most commonly located in the inferior quadrant below the horizontal meridian with associated features of corectopia (45%), ectropion uvea (24%), glaucoma (35%), hyphema (3%), angle seeding (28%) and extraocular extension (3%). The mean tumor basal diameter is 6.2 mm and thickness 2.3 mm.\textsuperscript{71} Secondary glaucoma is caused by direct mechanical compression or, invasion of the angle
structures by the tumor or, tumor cells blocking the trabecular meshwork or, iris neovascularization with angle closure or, inflammatory posterior synechiae with iris bombe or, necrotic pigment or pigment-laden macrophages blocking the anterior chamber angle and causing outflow obstruction.\textsuperscript{1,71,72}

\textit{Circumscribed} iris melanoma appears as a dome shaped well-defined nodule with variable pigmentation with irregular surface with prominent vasculature with documented growth. They can grow anteriorly or posteriorly or both causing complications like hyphema, sectoral cataract, glaucoma or rarely, corneal decompensation, edema and band shaped keratopathy.

\textit{Diffuse} iris melanoma infiltrates the iris stroma, causing thickening of the entire iris without any obvious nodule formation. There is progressive heterogeneous iris pigmentation with disappearance of the iris crypts, distorted pupil and pigment accumulation at the angle. The classical presentation of diffuse iris melanoma is of acquired hyperchromic heterochromia with unilateral secondary glaucoma.

\textit{Ring} melanoma is a rare variant where iris melanoma involves the trabecular meshwork and anterior chamber angle structures circumferentially causing secondary glaucoma without any iris involvement. This type of iris melanoma can only be diagnosed on gonioscopy.

\textit{Tapioca} melanoma is a rare type of iris melanoma where multiple tiny amelanotic transparent tumor nodules are found on the iris surface. Algernon Reese coined the term in 1972 because of the similarity of the tumor to tapioca pudding.\textsuperscript{71-75}

\section*{Classification}

The American Joint committee on cancer classification (8\textsuperscript{th} edition) has classified iris melanoma based on tumor extent in clock hours, presence of secondary glaucoma, involvement of ciliary body and/or choroid and scleral, extrascleral extension (Table 1).\textsuperscript{3}
### Table 1: American Joint Cancer Committee on Cancer Classification of Iris Melanoma

<table>
<thead>
<tr>
<th>T criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Tumor limited to the iris</td>
<td></td>
</tr>
<tr>
<td>T1a Tumor limited to the iris 3 clock hours in size</td>
<td></td>
</tr>
<tr>
<td>T1b Tumor limited to the iris &gt;3 clock hours in size</td>
<td></td>
</tr>
<tr>
<td>T1c Tumor limited to the iris with secondary glaucoma</td>
<td></td>
</tr>
<tr>
<td>T2 Tumor confluent with or extending into the ciliary body, choroid, or both</td>
<td></td>
</tr>
<tr>
<td>T2a Tumor confluent with or extending into the ciliary body, without secondary glaucoma</td>
<td></td>
</tr>
<tr>
<td>T2b Tumor confluent with or extending into the ciliary body and choroid, without secondary glaucoma</td>
<td></td>
</tr>
<tr>
<td>T2c Tumor confluent with or extending into the ciliary body, choroid, or both, with secondary glaucoma</td>
<td></td>
</tr>
<tr>
<td>T3 Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension</td>
<td></td>
</tr>
<tr>
<td>T4 Tumor with extrascleral extension</td>
<td></td>
</tr>
<tr>
<td>T4a Tumor with extrascleral extension 5 mm in diameter</td>
<td></td>
</tr>
<tr>
<td>T4b Tumor with extrascleral extension &gt;5 mm in diameter</td>
<td></td>
</tr>
</tbody>
</table>


### Investigations

Diagnosis of iris melanoma can often be challenging as spontaneous hyphema or corneal decompensation because of raised intraocular pressure can obscure visibility of the tumor, or tumor necrosis may cause inflammation, mimicking iridocyclitis. Moreover, no clinical feature is pathognomonic. Diagnosis of iris melanoma is based on slit lamp biomicroscopy. Gonioscopy is an useful adjunct to rule out angle involvement or tumor seeding or a ring melanoma.

Anterior segment optical coherence tomography (AS-OCT) is an useful modality for anterior and lateral surface characterization of smaller iris melanomas. For larger tumors UBM is preferred for visualization of the posterior surface because of increased penetration compared to AS-OCT.76-78

Ultrasound biomicroscopy (UBM) is required to delineate the tumor.
margins and extent or to differentiate melanoma from iris cysts. Iris melanoma appears as a stromal mass with medium echogenicity. Different characteristics assessed on UBM are- Surface plaque (hypo or hyper reflective band on surface corresponding to predominant spindle cell or epithelioid cell morphology respectively on histopathology), tumor vascularity (hyperechoic dots for small caliber blood vessels and hypoechoic spaces relating to large caliber vessels), tumor and ciliary body interface (visible as a line of change of the internal reflectivity), focal disruption of the highly reflective iris pigment epithelium by tumor indicating posterior growth and hypoechoic intrascleral emissary canal connecting tumor with sclera suggestive of extrascleral extension. The advantages of UBM over AS-OCT because of higher penetration are visualization of ciliary body extension, lesser posterior shadowing for pigmented tumors and better imaging of posterior tumor margin.

Fine needle aspiration biopsy (FNAB) is rarely required for histopathology confirmation of atypical diagnostically challenging cases of iris melanoma and for cytogenetic testing. It may be used for confirmation of diagnosis where enucleation or plaque brachytherapy is being planned. However, FNAB can be inconclusive or falsely reassuring as spindle cell nevus and melanoma both may look similar. With modern techniques FNAB achieve high yields and complications like persistent hyphema, prolonged hypotony, cataract, endophthalmitis are extremely rare.

Differential diagnosis
The differentials of a circumscribed iris melanoma are iris nevus (most common), melanocytoma, metastasis, iris cysts, leiomyoma, lymphoma, iris epithelioma (adenoma) of iris pigment epithelium (IPE), granuloma (sarcoidosis, xanthogranuloma), iridocorneal endothelial (ICE) syndrome and foreign body. A diffuse iris melanoma should be differentiated from diffuse iris nevus, pigmentary glaucoma, congenital heterochromia, congenital ectropion iridis, siderosis bulbi and ICE syndrome. Iris nevus is usually a flat lesion with variable extent that usually lacks tumor angiogenesis, do not invade angle, and do not distort the pupil or cause ectropion uveae. A more deeply pigmented variant of iris nevus is melanocytoma that can undergo spontaneous necrosis with pigment dispersion and
secondary glaucoma. Iris metastasis is always amelanotic unless from skin melanoma. Iris stromal cysts are thin walled cysts with clear or turbid fluid inside arising from the stroma. UBM helps in differentiating iris cyst from a solid iris melanoma. Adenoma of the iris pigment epithelium is darkly pigmented and pushes the iris stroma from behind as it arises from the IPE. ICE syndrome has associated corneal endothelial guttae changes with edema, multidirectional ectropion uveae, peripheral anterior synechiae, and iris atrophy.\cite{1,72,74,84}

**Treatment**

Treatment of iris melanoma depends on tumor size, location, secondary glaucoma, tumor seeding, visual acuity and patient preference.\cite{86} All melanocytic iris nevus are monitored until growth is documented. Once growth is noted treatment of iris melanoma is either surgical (local resection, enucleation) or radiotherapy (plaque brachy therapy, proton beam therapy). Incomplete surgical resection can lead to tumor recurrence whereas with radiotherapy there are risks of cataract, glaucoma, iritis, hyphema, keratitis, limbal stem cell deficiency and others. However, a recent review by Shields et al shows a favorable outcome for both the therapeutic modalities for iris melanoma.\cite{86}

Circumscribed iris melanoma with documented growth <6 mm in size is best managed by local resection. The different techniques of local resection are partial iridectomy (removal of a part of the iris), iridotrabeculectomy (removal of a part of the iris along with trabecular meshwork when tumor invades the angle of the anterior chamber) and iridocyclectomy (removal of a part of the iris and ciliary body when the tumor invades the ciliary body).\cite{1,72,86} For diffuse iris melanoma, ring melanoma, eyes with large tumor, uncontrolled secondary glaucoma, eyes with poor visual potential, recurrent tumor enucleation is preferred.\cite{1,72}

Primary plaque brachytherapy is considered for tumors >6 mm or eyes with extensive tumor seeding. Brachytherapy is reserved for patients with unresectable tumors or if tumor is in the only seeing eye of the patient.\cite{72,87} Proton beam radiotherapy involves collimated beams of external beam radiotherapy being very precisely delivered on to the tumor through the cornea. It has been reported to have excellent tumor control in iris melanoma with acceptable complication rate.\cite{88}
Prognosis
Iris melanoma prognosis is better than posterior uveal melanoma with 5 to 10 times less mortality rates.\textsuperscript{1,4,89,90} Reason for better prognosis are possible less tumor activity, younger age of presentation and smaller tumor size.\textsuperscript{1} Factors predictive of poor prognosis are old age, iris root/angle location, increased tumor thickness, secondary glaucoma and extra ocular extension.\textsuperscript{1,71,90} Systemic metastasis in iris melanoma occurs in 0.5%, 4% and 7% at 3, 5 and 10 years respectively.\textsuperscript{4}

POSTERIOR UVEAL MELANOMA (CILIAR-CHOROIDAL MELANOMA)

Symptoms
The symptoms of choroidal melanoma are vision loss, persistent flashes, floaters, visual field loss, ocular pain, metamorphopsia or micropsia.\textsuperscript{1,74,92} However, ~30% patients can be asymptomatic.\textsuperscript{1} Ciliary body melanomas are mostly asymptomatic. Sometimes pressure on the lens induce astigmatism leading to visual distortion and frequent change of glasses as the initial presenting symptom of ciliary body melanoma.\textsuperscript{73}

Clinical features
\textit{Ciliary body melanomas} usually attain a large size at the time of diagnosis as the iris initially hides them. They are either circumscribed or annular (ring). The circumscribed ciliary body melanoma appears as a brown dome-shaped mass because of the overlying pigmented epithelium. In the early stages the tumor is confined to the ciliary body and subsequently spread anteriorly to the angle and iris (iridociliary melanoma) causing secondary glaucoma or posteriorly into choroid (ciliochoroidal melanoma) or on the lens causing subluxation or cataract. The mean basal diameter is 11.7 mm and tumor thickness is 6.6 mm.\textsuperscript{4} In the initial stages they are only visible on full pupillary dilatation. However, there can be external signs of an underlying ciliary body melanoma like one or more dilated episcleral vessels overlying the mass (sentinel vessel) or epibulbar pigmented lesion overlying the intraocular mass because of trans-scleral spread of tumor. Transillumination can be an useful diagnostic test to evaluate pigmented ciliary body and anterior choroidal melanoma. A bright
focused light source is placed in the conjunctival fornix opposite the location of the intraocular melanoma with dim room lighting. Normally the sclera transmits light. The area with a pigmented melanoma will cast a shadow. Ciliary body cysts, leiomyoma and other tumors transmit light and do not cast shadow. Rarely, (0.3% of all uveal melanomas) tumor can spread circumferentially without nodule formation (ring melanoma) and limited anteroposterior spread. All cases with sentinel vessels, sectoral cataract, localized iris neovascularization, localized anterior chamber shallowing, unexplained iridocyclitis ring melanoma needs to be ruled out.

Choroidal melanoma has two configurations- circumscribed and diffuse. Circumscribed choroidal melanoma presents as a dome shaped (75%) or mushroom shaped (20%) or diffuse (5%) mass underlying the sensory retina without feeder vessels. Progressive growth of choroidal melanoma can rupture the Bruch’s membrane and give rise to a mushroom shape. With this configuration the tumor has a greater tendency to cause subretinal or vitreous hemorrhage, which obscures visibility of the tumor. Tumor can be pigmented (55%), amelanotic (15%) or mixed (30%). Clinically a choroidal melanoma which has ruptured the Bruch’s membrane with retinal invasion looks darkly pigmented almost black. The mean basal dimension is 11.3 mm and tumor thickness is 5.5 mm. A secondary exudative retinal detachment frequently occurs in choroidal melanoma most commonly involving the macula and the inferior quadrant. With positional changes in the patient’s head the fluid shifts. In supine position the fluid shifts to the macula accounting for the vision loss. Retinal pigment epithelium alterations are frequently seen on tumor surface irrespective of the tumor size. For small melanoma confluent orange pigment is seen on tumor surface corresponding to macrophages with engulfed lipofuscin or melanin from retinal pigment epithelium. This is suggestive of choroidal melanoma in most cases. Secondary glaucoma rarely happens in choroidal melanoma (3%) by tumor infiltration of angle of anterior chamber, forward movement of the lens iris diaphragm due to anterior tumor pressure, iris neovascularization. However, extremely rarely there may be hypotony because of ciliary body involvement with decreased aqueous production. Tumor necrosis can rarely cause inflammatory reaction causing orbital cellulitis like clinical picture. Extrascleral extension of choroidal melanoma is also
very rare. The diffuse configuration of the tumor is flat or has only minimal elevation with predominant horizontal growth pattern. It has been defined as tumor thickness less than 20% of tumor base. It has irregular surface with pseudopodia like scalloped margins with variable pigmentation.

**Classification**

The American Joint committee on cancer classification (8th edition) has classified choroidal and ciliary body melanomas based on tumor size (combination of basal diameter and tumor thickness), ciliary body involvement and extra ocular extension (Table 2).

### Table 2: American Joint Cancer Committee classification of Posterior uveal melanoma

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>Tumor dimensions (mm)</th>
<th>Ciliary body involvement</th>
<th>Extraocular extension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor base ≤3–9 mm with thickness ≤ 6 mm</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T1b</td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor base 9.1–12 mm with thickness ≤ 3 mm</td>
<td>No</td>
<td>Yes &lt;5mm in diameter</td>
</tr>
<tr>
<td>T1d</td>
<td></td>
<td>Yes</td>
<td>Yes &lt;5mm in diameter</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor base ≤9 mm with thickness 6–9 mm</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T2b</td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumor base 9.1–12 mm with thickness 3.1–9 mm</td>
<td>No</td>
<td>Yes &lt;5mm in diameter</td>
</tr>
</tbody>
</table>
| T2d           | Tumor base 12.1–15 mm with thickness ≤ 6 mm  
Tumor base 15.1–18 mm with thickness ≤ 3 mm | Yes                       | Yes <5mm in diameter  |
| **T3**        |                 |                          |                       |
| T3a           | Tumor base 3.1–9 mm with thickness 9.1–12 mm | No                       | No                    |
| T3b           |                 | Yes                      | No                    |
| T3c           | Tumor base 9.1–12 mm with thickness 9.1–15 mm | No                       | Yes <5mm in diameter  |
| T3d           | Tumor base 12.1–15 mm with thickness 6.1–15 mm  
Tumor base 15.1–18 mm with thickness 3.1–12 mm | Yes                       | Yes <5mm in diameter  |
<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>Tumor dimensions (mm)</th>
<th>Ciliary body involvement</th>
<th>Extraocular extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td></td>
<td>Yes or no</td>
<td>Yes or no</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor base 12.1–15 mm with thickness &gt;15 mm</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor base 15.1–18 mm with thickness &gt;12 mm</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>T4c</td>
<td>Tumor base &gt;18 mm with any thickness</td>
<td>No</td>
<td>Yes &lt;5mm in diameter</td>
</tr>
<tr>
<td>T4d</td>
<td></td>
<td>Yes</td>
<td>Yes &lt;5mm in diameter</td>
</tr>
<tr>
<td>T4e</td>
<td>Any tumor size</td>
<td>Yes or no</td>
<td>Yes &gt;5mm in diameter</td>
</tr>
</tbody>
</table>


**Figure 1:** Choroidal melanoma: Fundus picture and ancillary tests

A 32-year-old female presented with decreased vision in the right eye since 6 months. (A) Fundus examination revealed a 8mm x 7mm x3mm pigmented lesion inferotemporal to fovea. Central darkly pigmented portion was suggestive of retinal invasion. (B) B-scan showed a classic dome-shaped lesion with acoustic hollowing and choroidal excavation. (C) Optical coherence tomography revealed a smooth (D) Venous phase of fundus fluorescein angiography revealed central hypofluorescence corresponding to the area of retinal invasion with hyperfluorescence of the surrounding tumor. Subretinal fluid can be is seen as an area of mild hyperfluorescence surrounding the lesion. (E) There was increased intensity of hyperfluorescent areas in the late phase.
Investigations

The diagnosis of posterior uveal melanoma is predominantly clinical based on the classical clinical features on slit lamp biomicroscopy and indirect ophthalmoscopy. However, for atypical cases where there is a diagnostic dilemma some ancillary investigations like ultrasound biomicroscopy, ultrasound B scan, Optical coherence tomography, Fluorescein angiography, Indocyanine green angiography, Computed tomography scan, Magnetic resonance imaging and fine needle aspiration biopsy are more useful.

**Ultrasound biomicroscopy (UBM)** uses a much higher frequency transducer (35-100 mHz) resulting in a higher resolution than conventional ultrasound (USG) although the depth of penetration is much lower. UBM is extremely useful in demonstrating small ciliary body melanomas (<4 mm) which otherwise won’t be visible by conventional USG. It helps in planning surgery and plaque brachytherapy. It also helps in differentiating cavitary melanoma from cysts and other ciliary body tumors.

**Ultrasound B scan (USG)** is an important investigation to diagnose posterior uveal melanoma, define its extent and for tumor biometry. The cardinal features of posterior uveal melanoma on B scan are solid consistency, dome or collar button (mushroom) shape, acoustic hollowness, regular internal structure, internal vascularity, choroidal excavation, orbital shadowing and posterior scleral bowing (in young patients). The associated features can be serous retinal detachment, vitreous hemorrhage, and surface focus of calcification. On A scan the characteristic features are low to medium internal reflectivity, inner tumor spikes with similar height or regular decrease in height (positive angle Kappa sign), fast spontaneous continuous low amplitude flickering vertical motion of single tumor spikes indicating vascularity of the tumor and solid consistency with no after movement of tumor spikes. The pathognomonic collar button shape of choroidal melanoma occurs when the tumor breaks the Bruch’s membrane at the apex. When the Bruch’s membrane is broken at the tumor rim an irregular or inclined shape is found. Acoustic hollowing refers to the decreased reflectivity at the tumor base region. Both acoustic hollowing on B scan and low reflectivity on A scan is because of the homogeneous cellular architecture on histopathology in this region.
Choroidal excavation at the tumor base is thought to be because of homogeneous tumor infiltration of the normal choroid. Increased concavity of the sclera posterior to the tumor (scleral bowing) is associated with scleral invasion of the tumor in young individuals. Sound attenuation may at times cause decreased reflectivity of the orbital echoes behind the tumor (shadowing). Choroidal excavation and scleral bowing is not specific for choroidal melanoma. Large choroidal melanomas may develop irregular internal structure in presence of necrosis and hemorrhage. Extraocular extension appears as one or more nodule near the sclera adjacent to the base of the tumor.95

Enhanced depth Optical coherence Tomography (ED-OCT) is particularly helpful in evaluating small choroidal melanomas (<3 mm in greatest dimension) and differentiating them from choroidal nevus. Small choroidal melanomas have dome shape with smooth surface with overlying shallow subretinal fluid with subretinal lipofuscin deposits and shaggy photo receptors. ED-OCT has limited role in thicker tumors and in pigmented tumors because of significant back shadowing.1,96 OCT angiography also demonstrates vascular network inside the tumor.97

Fluorescein angiography (FFA) and Indocyanine Green angiography (ICG) have minimal role in diagnosis of choroidal melanoma. FFA illustrates gradually increasing hyperfluorescence at or before the arterial phase, which increases in intensity in the recirculation phase, causes diffuse late staining of the mass along with subretinal fluid till atleast 45 mins.98 Cases of choroidal melanoma that has breached the Bruch’s membrane with retinal invasion, show either the double circulation pattern as the fluorescence of the retinal vessels superimposes on the fluorescence of the intratumor blood vessels or the area of retinal invasion appears as non fluorescence surrounded by a ring of hyperfluorescence due to leakage from the damaged intraretinal capillaries present at the margin of invaded retina.99,100 ICG helps to demonstrate the intrinsic vascularity of the choroidal tumor better than FFA. It demonstrates hypofluorescence in thin, less vascular tumors and hyperfluorescence in thicker, larger tumors with average maximal fluorescence achieved at 18.2 minutes after injection.101

Autofluorescence is useful in early detection of small choroidal
melanoma. Corresponding to clinically visible orange pigment bright geographic hyperautofluorescence is demonstrated on the tumor because of overlying lipofuscin in the retinal pigment epithelium.\textsuperscript{72}

*Computed tomography (CT) scan and Magnetic Resonance imaging (MRI)* eye and orbit has limited utility in diagnosing uveal melanoma because in most of the cases diagnosis is primarily based on simple fundus evaluation and USG finding. CT has role in delineating orbital extension of the tumor. On CT choroidal melanoma is hyperdense with mild to moderate contrast enhancement.\textsuperscript{1,72} In MRI melanoma appears hyperintense on T1 and hypointense on T2 weighted images. MRI is used to differentiate subretinal hemorrhage from melanoma. Blood doesn’t enhance with contrast whereas melanoma enhances with gadolinium contrast injection.\textsuperscript{1,72}

*Fine needle aspiration biopsy* (FNAB) is a safe and reliable method in cases where the diagnosis of posterior uveal melanoma has not been confirmed by less invasive techniques or for cytogenetic study for prognostication.\textsuperscript{72,102} The procedure is performed through pars-plana approach using 25-27 gauge needle.

**Differential diagnosis**

Multiple fundus lesions can mimic posterior uveal melanoma. In a study done by Shields et al out of 12,000 patients referred with the diagnosis of posterior uveal melanoma 1739 were found to have a simulating lesion. The most frequent mimickers were choroidal nevus (most common), Peripheral exudative hemorrhagic chorioretinopathy, Congenital hypertrophy of retinal pigment epithelium (RPE), idiopathic hemorrhagic detachment of retina or pigment epithelium, Circumscribed choroidal hemangioma, Age-related macular degeneration, Hyperplasia of RPE, Optic disc melanocytoma, Choroidal metastasis, hemorrhagic choroidal detachment and vaso proliferative tumor.

**Treatment**

The treatment of posterior uveal melanoma depends on tumor size, extent, location, visual potential of the eye, status of the other eye, age and systemic status. The details of the tumor should be accurately documented with drawings and fundus photographs at each visit. The different treatment options used to treat posterior uveal melanoma
are transpupillary thermotherapy for small choroidal melanomas, Photodynamic therapy for small amelanotic choroidal melanoma, Plaque brachytherapy and Proton beam therapy for small and medium ciliary and choroidal melanoma, Enucleation for large posterior uveal melanoma and orbital Exenteration for tumors with orbital extension.1

**Observation**

In borderline cases of small melanocytic choroidal lesions with a doubt in the diagnosis of choroidal melanoma versus nevus observation with regular monitoring with fundus photography and B scan is recommended.72 Moreover, observation may be preferred for terminally ill patients with systemic metastasis.1

**Figure 2:** Transpupillary thermotherapy for choroidal melanoma (A) A 50-year-old male presented with decreased vision in the right eye since 6 months. Fundus examination revealed a 9mm x 6mm x 3.2mm pigmented lesion inferotemporal to the fovea with associated subretinal fluid. (B) B-scan ultrasonography revealed a dome-shaped choroidal lesion with acoustic hollowness and choroidal excavation. A diagnosis of choroidal melanoma was established and the patient underwent transpupillary thermotherapy. (C, D) The lesion reduced in size and the subretinal fluid resolved post-treatment.

**Transpupillary thermotherapy (TTT)**

Oosterhius first reported the use of TTT in uveal melanoma in 1994.104 TTT is a non-invasive technique of tumor heating with infrared radiation (diode 810 nm) delivered through the pupil on the surface of the tumor. Heating upto 45-65°C causes blockage of tumor-related
blood vessels and cause tumor necrosis in choroidal melanomas up to 4mm of thickness.\textsuperscript{1,72,74,105} Laser photocoagulation with argon, krypton light sources which were used earlier has been abandoned because they raise the tumor temperature >65\textdegree\textsuperscript{C} and cause excessive retinal complications with inadequate tumor control.\textsuperscript{74} The advantage of TTT over plaque brachytherapy are focused delivery of laser on the tumor with lesser surrounding collateral damage, immediate tumor necrosis and outpatient procedure.\textsuperscript{1,74} TTT is not suitable as sole therapy in cases with media opacity obscuring visibility of tumor, insufficiently dilating pupils, peripherally located tumors, tumor basal diameter >10 mm and thickness more than 4 mm and subretinal fluid elevation >3 mm.\textsuperscript{74}

The potential complications are retinal vascular obstruction, retinal traction, foveal dragging, retinal hole, retinal detachment (rhegmatogenous, tractional, transient serous), retinal neovascularization, macular edema, epiretinal membrane, chorioretinal scar at fovea, vitreous hemorrhage, optic disc atrophy, optic disc edema and focal cortical cataract.\textsuperscript{105,106} Tumor recurrence rates post primary TTT for small choroidal melanomas has been reported to be 9-28\%.\textsuperscript{105,106} A direct correlation between number of high risk factors predictive of tumor growth present (FSOM UHHD) and rate of tumor recurrence has been reported making TTT a less preferable treatment modality in high risk tumors.\textsuperscript{106}

**Photodynamic therapy (PDT)**

PDT is a minimally invasive technique in which a light sensitive compound (most commonly used- Verteporfin 6 mg/m\textsuperscript{2}) injected intravenously accumulates in the target tissue. On light activation by laser beam (light emitting diode 690 nm) the photosensitive compound releases reactive oxygen species causing direct targeted cytotoxic effect, local inflammation triggering autophagy and destruction of peritumoral vessels.\textsuperscript{1,107} Tumor pigmentation prevents light penetration into tumor. Standard PDT starts 15 mins post dye injection with 600 mW/cm\textsuperscript{2} for 83 secs and reaches a total energy of 50J/cm\textsuperscript{2}. Double fluence (100J/cm\textsuperscript{2}) and double duration (166 secs) PDT is also used. PDT is most useful in amelanotic choroidal melanoma with tumor thickness <4 mm. TTT uptake is poor in these tumor because of lack of pigmentation. Local tumor control rate for PDT for choroidal melanoma is 80-89\%.\textsuperscript{108} Complications with PDT are uncommon.\textsuperscript{109}
Radiotherapy

Radiotherapy in posterior uveal melanoma can be administered as Plaque brachytherapy, proton beam radiotherapy and stereotactic radiotherapy. For uveal melanoma Moore first used brachytherapy in 1930 by implanting radon-222 seeds into the tumor. Brachytherapy means implantation of a radioactive substance close to or within the tumor. Radioisotopes decay into stable forms by emitting ionizing radiation which when absorbed by tumor tissue forms free radicals causing DNA damage and loss of mitotic ability causing cell death.

For posterior uveal melanoma one of the most dominant treatment modality is plaque brachytherapy with an apical dose of 80-100 Gy. It requires close collaboration between ocular oncologist, radiation oncologist and radiation physicist. Presently Iodine-125 and Ruthenium-106 are the most commonly used isotopes. Custom designed plaques can be used for any shape of uveal melanoma at any ocular location (upto diameter <18 mm and thickness <12 mm). The extended indications for using plaque brachytherapy are large posterior uveal melanomas, ciliary body and macular...
melanomas and extraocular extension of uveal melanoma.\textsuperscript{111,112} However, vision is severely compromised post-therapy in all these cases.\textsuperscript{72,111,112} According to the Collaborative Ocular Melanoma Study (COMS) plaque brachytherapy with Iodine 125 is equivalent to enucleation for medium sized tumors (basal diameter <16 mm and thickness 2.5-10 mm) in terms of prevention of systemic metastasis and death.\textsuperscript{113} Another study from the same group showed no mortality advantage with pre-enucleation radiotherapy for large tumors (basal diameter >16 mm and thickness >2 or any basal diameter with thickness >10 mm).\textsuperscript{114} Local tumor control with brachytherapy is excellent (~98%).\textsuperscript{73} Combination of plaque brachytherapy with TTT also has excellent local tumor control with a tumor recurrence rate of 3%.\textsuperscript{115} The radiation related potential complications are dry eye, diplopia, keratitis, cataract, iris neovascularization, scleral necrosis, retinopathy, maculopathy, neovascular glaucoma, optic neuropathy, choroidal atrophy and vitreous hemorrhage.\textsuperscript{1,74}

Another form of radiotherapy is \textit{charged particle radiotherapy} using proton beam or helium ion to deliver focused radiation on the tumor minimizing collateral damage. It is comparable to plaque brachytherapy in terms of local tumor control (~97%), visual outcome and systemic metastasis. It is well suited for medium and large sized tumors and tumors close to optic nerve and fovea with visual potential.\textsuperscript{74,116} However, the limited availability and cost limits its use.

\textit{Stereotactic radiotherapy} with cyber knife or gamma knife or linear accelerator is also a treatment modality for uveal melanoma. The local tumor control, visual outcome and survival rates are similar to proton beam radiotherapy.\textsuperscript{117}

**Local resection**

Local resection of ciliary body or peripheral choroidal melanoma can be performed either transclerally (exoresection) or transretinally (endoresection). Years back, exoresection was performed by removing full thickness sclera along with the tumor and placing a scleral graft.\textsuperscript{118} More recently, partial lamellar sclerouvectomy (PLSU) is being done where uveal tumor is removed leaving behind outer sclera and sensory retina.\textsuperscript{119} This surgery is technically very difficult and requires lot of skill and expertise. Adjunctive plaque brachytherapy can be used post resection in cases of high-grade melanoma.\textsuperscript{74} Currently, there has been
some interest in removing the tumor piecemeal with a vitrectomy cutter transretinally. However, this technique is controversial as it has concerns of iatrogenic tumor spread both local and systemic.\textsuperscript{120} Endoresection is usually performed after proton beam radiotherapy to prevent development of toxic tumor syndrome from radiation induced tumor necrosis and intratumoral vasculopathy which causes intraocular inflammation and neovascular glaucoma.\textsuperscript{121}

**Enucleation**

Enucleation is performed for large melanomas (>18 mm in basal diameter and >12 mm in thickness) with poor visual potential and with moderate extraocular extension.\textsuperscript{1,72} The lost orbital volume is replaced with an orbital implant (porous or nonporous). The original Zimmerman’s hypothesis stating that enucleation for uveal melanoma may cause tumor cell dissemination promoting metastatic disease was reviewed in the light of current evidence and nullified.\textsuperscript{122}

**Orbital exenteration**

Eyelid sparing orbital exenteration is performed in cases of uveal melanoma with large orbital extension.\textsuperscript{1,72}

**Systemic work up**

A positron emission tomography/ computed tomography scan (PET-CT Scan) is ideal to rule out systemic spread of uveal melanoma at 6 monthly intervals. In developing countries considering socioeconomic constraints a chest imaging (CT scan or X ray) and an abdominal imaging (MRI/CT/USG) may be considered to rule out metastasis.

**Prognosis**

Despite having an excellent local tumor control posterior uveal melanoma has a high mortality rate owing to the high tendency to metastasize to the liver (~90\%) and other sites like lung, bone, skin, subcutaneous tissue and lymph node.\textsuperscript{123} Long term follow up of treated patients show that the uveal melanoma-related mortality was 31\% by 5 years, 45\% by 15 years, 49\% by 25 years, and 52\% by 35 years.\textsuperscript{124} Out of patients dying of uveal melanoma 90\% dies within 15 years and 98\% within 25 years.\textsuperscript{1,124} The factors predicting poor prognosis and thus increased risk of metastasis are (Table 3).\textsuperscript{124}
### Table 3: Features predictive of poor prognosis for uveal melanoma

<table>
<thead>
<tr>
<th><strong>Clinical features</strong></th>
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<td>Older age at presentation</td>
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<td>Male gender</td>
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<td>Larger tumor basal diameter</td>
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<td>Increased tumor thickness</td>
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<td>Ciliary body tumor location</td>
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<td>Diffuse tumor configuration</td>
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<td>Association with ocular/oculodermalmelanocytosis</td>
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<td>Extraocular tumor extension at presentation</td>
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<td>Advanced AJCC category and staging</td>
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<th><strong>Histopathologic features</strong></th>
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<td>Epithelioid cytology on histopathology</td>
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<td>High mitotic activity/PC-10/Ki-67</td>
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<td>High values of mean diameter of 10 largest nucleoli</td>
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<td>High microvascular density</td>
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<td>Microvascular loops and patterns</td>
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<td>Tumor-infiltrating lymphocytes</td>
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<td>Tumor-infiltrating macrophages</td>
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<td>High expression of insulin-like growth factor 1 receptor</td>
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<td>High expression of HLA class I and II</td>
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<th><strong>Cytogenetic features</strong></th>
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<td>Chromosome 3-loss (monosomy 3)</td>
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<td>Chromosome 8q-gain or 8p-loss</td>
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<td>Chromosome 1p-loss</td>
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<td>Chromosome 6q-loss</td>
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<th><strong>Transcriptomic feature</strong></th>
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<td>Gene expression profile class 2</td>
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### 1. Clinical features

Cases with initial presentation at an older age have poor prognosis. This is probably because of smaller tumor size, better immune system and fewer genetic mutations inside the tumor in young patients. In some studies, females have been reported to have better prognosis than males. Hormones possibly estrogen may have a role in inhibiting metastasis. Out of all the clinical features, tumor size is the most important factor predicting metastasis. Each mm increase in tumor thickness is associated with ~5%
increased risk of systemic metastasis. Ciliary body melanomas have a more aggressive course in comparison to iris and choroidal melanoma. This is probably because of delayed presentation as they are hidden by the iris, increased blood supply in the ciliary region favoring hematogeneous spread of tumor cells, susceptibility for monosomy 3 and 8q gain and microvascular patterns. Ocular/oculodermal melanocytosis, diffuse growth pattern and extraocular extension have poor prognosis.

2. Histopathology features
   The different histopathology features predicting poor prognosis are epithelioid cell type, increased mitotic activity, microvascular loops, large mean diameter of the 10 largest nucleoli, increased tumor-infiltrating lymphocytes and macrophages, increased microvascular density, and greater expression of insulin-like growth factor 1 receptor, and HLA class I and II antigens.

3. Cytogenetic features
   Chromosome 1, 3, 6 and 8 aberrations are linked to survival in uveal melanoma. BAP1 is on chromosome 3p21.1. Loss of chromosome 3, 8p, 1p, 6q and gain of chromosome 8q is associated with poorer prognosis in uveal melanoma patients. The most important predictor of metastasis is cytogenetics and not histopathology.

4. Transcriptomic features
   mRNA analysis by Gene expression profiling of tumor biopsies reveal 2 classes of uveal melanoma- Class 1 and 2. The rate of metastasis in class 1 cases have been reported as 1% whereas in class 2 is 26% after a duration of 17 months. Thus class 2 tumors which usually have a monosomy 3 are high risk tumors with greater risk of metastasis and mortality.

WHAT'S NEW?

Despite great progress in the clinical management of uveal melanoma and effective primary therapy the mortality rate remains high owing to the high rate of systemic metastasis (~50%). Recent advances in understanding the cytogenetics of the tumor help in predicting
prognosis and identifying patients who are at highest risk of metastasis. At present there is no approved targeted therapy for early treatment of uveal melanoma and effective management for metastatic uveal melanoma. Targeted treatment strategies in preclinical development for uveal melanoma are-

Melanoma cells over express tissue factor (transmembrane cytokine receptor) in comparison to normal uveal melanocytes. *ICON 1* is an immuno conjugate protein molecule, which binds to cells that over express tissue factor eliminating pathologic neovascularization and causing tumor cell removal. An ongoing study is evaluating the safety and efficacy of intravitreal ICON1 as primary treatment for uveal melanoma.127

*AU-011* consists of viral nanoparticles clubbed to infrared activated photosensitizer dye. Following intravitreal injection the particles bind to cancer cell surface heparin proteoglycans. On activation by infrared light at 689 nm causes selective tumor cell destruction.128,129

Ongoing efforts seeking novel therapeutic approaches to improve the survival outcome in adjuvant and metastatic setting are-

1. **Targeted therapy**
   Targeted blockage of growth signaling pathways highly expressed in metastatic melanoma may play a role in controlling metastatic melanoma. Currently agents against the mitogen activated protein kinase pathway (*MAPK inhibitors*) like Selumetinib, Trametinib are in preclinical trials. Similarly other protein kinase inhibitors like Sorafenib, Crizotinib, Sunitinib are being evaluated in preclinical models for uveal melanoma.

2. **Immunotherapy**
   Recently, *checkpoint inhibitors* have gained importance owing to favorable results by targeting cytotoxic T lymphocyte associated antigen 4 (CTLA-4) (Ipilimumab, Tremilimumab) and Programmed cell death 1 (PD 1) (Pembrolizumab). The goal of immunotherapy is to surround the tumor or metastasis with an immunogenic environment with tumor specific antibodies. Lamentably, like cutaneous melanoma similar benefits have not been observed in uveal melanoma probably because eye is an immune privileged organ.
Effect of infusion of autologous dendritic cell vaccines loaded with tumor peptides to improve patient survival in uveal melanoma is also being studied.\textsuperscript{130}

3. Epigenetic approaches
Alteration of tumor suppressor genes or oncogenes can be done by mutations or transcription regulation by DNA (de)methylation and/or histone (de)acetylation as epigenetic mechanisms. Histone deacetylase inhibitors (HDAC inhibitors) have been shown to reverse the phenotypic effects of BAP 1 loss in melanoma cells. Valproic acid and Vorinostat are being evaluated in ongoing trials.\textsuperscript{131}

REFERENCES
10. Park SJ, Oh CM, Kim BW, Woo SJ, Cho H, Park KH. Nationwide Incidence of Ocular Melanoma in South Korea by Using the National Cancer Registry
Uveal Melanoma


1. INTRODUCTION

The first case of choroidal metastasis was documented by Perls in 1872.\(^1\) Although Choroidal Metastasis (CM) has been considered a rare entity, they are now known to be the most common intraocular malignancy.\(^2\) The increasing survival of patients with metastases and better diagnostic tools may explain these findings, yet the incidence of CM is probably even higher than reported due to underdiagnoses. Presence of intraocular metastasis usually indicates poor systemic prognosis with increased risk of mortality in the ensuing months.

Choroidal metastasis is the first sign of a systemic malignancy in up to a third of patients presenting to the oncological services.\(^3\) Thereby ophthalmologists play a pivotal role in suspecting and diagnosing systemic malignancy. The methods for diagnosis have improved over recent decades. Fundoscopy, ultrasonography (USG), and fluorescein angiography are now complemented by indocyanine green angiography (ICGA), more recently, spectral domain-OCT (SD-OCT) and OCTA (OCT Angiography).

Histopathological diagnosis is also made possible by choroidal tumor biopsy that can confirm the nature of the tumor and help determine the site of the primary cancer.

There is still debate as to the best way to treat these patients. As most patients have a limited life expectancy, complex treatments are generally not recommended. Ocular treatment is more of palliative and as such primarily aimed to avert or treat possible complications such as pain in order to improve quality of life.

Fulfilling this objective provides a double challenge: on the one hand, the treatment should be easy to implement and should have a
low risk of complication, and on the other hand it should be effective and improve or stabilize vision, which is essential for end-of-life well-being. However, recent advances in systemic therapies have significantly improved the survival of metastatic patients.

2. EPIDEMIOLOGY OF CHOROIDAL METASTASIS:

Prevalence: Until recently, the most popular belief was that the incidence of choroidal metastasis was relatively rare. This has been proved to be incorrect by various well-documented recent articles. The prevalence has been studied using two models:

a. Cadaver: post-mortem examination of the globes from patients who deceased due to oncological reasons.

b. Ophthalmic evaluation: universal eye evaluation of all oncological patients.

c. Primary neoplasms associated with choroidal metastasis: the primary sites in descending order
   i. Breast – 40%-53%
   ii. Lungs – 20%-29%
   iii. GIT – 4%
   iv. Prostate – 2%
   v. Kidney – 2%
   vi. Skin – 2%

Isolated reports of metastasis from salivary glands, thyroid, testes, female genital organs, and urothelial tract has been reported in literature. Ocular metastases from neuroendocrine tumors are rare, but given the scarcity of this cancer, ocular spread should be investigated. Sarcomas even more rarely metastasize to the choroid (Fig. 1).

Most patients have known systemic cancer at the time of choroidal metastasis, but in 8–30% of cases the diagnosis of choroidal metastasis precedes that of systemic cancer. In these cases, a complete workup revealed lung cancer in 35–59% of cases and breast cancer in 7–15% of cases. These findings suggest that the presence of uveal metastases in a patient without history of cancer should prompt a thorough investigation for lung and breast cancer. However, some studies have reported the primary site was not found after initial general work-up in 51% of such patients.
3. Other ocular localisation: Uveal metastasis involve the choroid in 88-89%. Other sites include
   a. Iris – 9%
   b. Ciliary body – 2%
   c. Isolated retina, optic disc or vitreous is rare. (figure 1)

![Figure 1: a- Small yellow dot lesion noted at the ONH with similar lesions noted inferior to the lower vascular arcade  b- Same patient after 1 week of the initial presentation. Large lesion at the ONH with combined occlusion.]

4. PATHOPHYSIOLOGY
   a. Anatomical – mechanical mechanism: suggest tumour cells follow the vascular and lymphatic drainage channels from the site of the primary tumour. Duke-Elder hypothesized short posterior ciliary arteries as most preferential for tumour cells.
   b. Seed and soil: proposed by Paget, states that metastatic cells does not grow randomly but have preferential to particular tissue
   c. Wound oncogene – wound healing model: WOWH. According to this metastasis is the result of the body to heal a wound. At the site of the wound abnormal oncogenes are activated which circulates and are able to activate oncogenes.

5. DIAGNOSIS:
   a. Symptoms – decreased vision due to either foveal or juxtafoveal involvement or exudative retinal detachment caused by adjacent metastatic lesion which involves the fovea.
      Floaters and visual field loss is less frequent. Secondary glaucoma due to increase in the size of the lesion and bleeding may also be encountered.
      A fraction of patients can be asymptomatic, and metastasis is diagnosed on routine examination.
b. Signs – generally seen as creamish-white lesions with accompanying subretinal fluid which is usually dis-proportionate to the lesion size. The lesion can also have orange colour when its origin is from carcinoid tumor, renal or thyroid tumors. Dark brown appearance is noted in cases of metastasis from cutaneous melanoma. Some lesions have dark pigment patched resembling leopard spots (Figure 2).

![Figure 2: Leopard spot sign in a patient with choroidal metastasis](image)

The most common associated feature with choroidal metastasis is subretinal fluid and as already mentioned is always dis-proportionate to the lesion per se (Figure 3).

![Figure 3: Excessive exudative retinal detachment in a patient with choroidal metastasis](image)
Most of the metastatic lesions are posterior to the equator and nearly 40% are seen involving the equator.

Bilateral (15–50% of cases), multifocal, and diffuse forms are more commonly associated with breast cancer (Figure 4).

![Figure 4: Bilateral multiple foci of choroidal metastatic lesions secondary to breast carcinoma.](image)

6. ULTRASONOGRAPHY (USG):

Ultrasonography (USG) is helpful in differentiating choroidal metastasis from other lesions which have a similar clinical appearance. The twofold importance of USG include:

a. Localisation of the lesions and their dimensions, internal reflectivity.

b. Their response to treatment given, by sequential measurements.

The US features of choroidal metastasis are characterized by:

a. Flat or a slightly dome shaped mass with a medium-to-high non-homogeneous reflectivity, unlike choroidal melanomas.

b. Choroidal metastasis are often multilobular with an irregular surface.

c. Exudative retinal detachment can be seen with rare choroidal detachment.

d. Choroidal metastasis are found as flat tumors with a large infiltration of the choroid resulting in an irregular shape in USG.

e. Choroidal excavation is very rarely associated with metastatic lesion

f. Another application of US associated with Doppler technology is color flow mapping that can display blood flow on the background
of the USG image. Vascular features, such as hypovascularity, with a dominant centrally located vessel with blood flow is typically associated with choroidal melanoma, whereas hypervascularity with lack of dominant vessel is typically associated with CM. Neudorfer et al. have described this ‘central pattern’ of blood flow in melanoma, contrasting with the ‘peripheral pattern’ in metastasis.

7. FLUORESCEIN ANGIOGRAPHY (FA)

They are usually hypofluorescent in the early phase and heterogeneously hyperfluorescent in the late phase with leakage.

Indo-cyanine green angiography (ICGA) helps in the differential diagnosis of choroidal tumors. Metastatic lesions are usually show hypofluorescence at all phases on an underlying isofluorescent background. Double circulation and other specific patterns are not seen in metastatic lesion.

Furthermore, due to better visualization of the choroid, ICGA generally shows a larger area of choroidal involvement of the metastases than does clinical examination or FA.

8. OPTICAL COHERENCE TOMOGRAPHY (OCT):

The small size and posterior location of most choroidal metastasis make these tumors ideal candidates for investigation using OCT. SD-OCT with EDI, and more recently swept-source OCT, have improved our understanding of the choroid and provided detailed information about the morphological features of choroidal tumors.

a. In EDI-OCT, CM has a low internal optical reflectivity, with an enlarged suprachoroidal space.

b. The internal reflectivity can increase after treatment.

c. The most noticeable feature is the irregular or “lumpy bumpy” anterior surface of the lesion, despite an apparently smooth surface on USG.

d. Another sign frequently associated with choroidal metastasis is subretinal fluid. This is found in 67–95% of cases, mostly with hyper-reflective dots known as speckles.
e. The optical density or substance reflectivity of the subretinal fluid can also be measured by OCT, and can be indicative of the cause of SRF as the optical density ratio of SRF was found to be significantly lower in CM than in melanoma. This suggests that the composition of the SRF, mainly its protein content, is different between tumor types.

f. Other OCT features of metastatic tumors include shaggy photoreceptors, alteration of the ellipsoid zone, RPE changes (atrophy or hyperplasia), and choriocapillaris compression.

g. OCTA may help differentiate tumors as in choroidal metastasis there is a lack of flow at the level of the lesion and absence of pathological blood flow in the outer retinal layer, whereas in choroidal melanoma, hemangioma, and osteoma there may be a dense, irregular vascular network inside the tumor and even increased flow in the outer nuclear layer.

9. DIFFERENTIALS:

a. Posterior Scleritis:

Differentiating between choroidal metastases and posterior scleritis remains a diagnostic challenge. Failure to make the correct diagnosis could lead to misguided treatment. Symptoms of pain are rarely found in patients with choroidal tumor, and direct questioning of this symptom may be helpful. The subtle ocular redness may be easily overlooked, but this sign is often suggestive of an inflammatory condition. Other features which help us to differentiate posterior scleritis from an amelanotic choroidal mass include orange color of the mass (Figure 5); light transmission on transillumination; hypofluorescence and absence of double circulation on fluorescein angiography; and the presence of scleral thickening, fluid in Tenon’s space and absence of posterior acoustic shadowing on B-scan ultrasonography.

On MRI, hyperintensity in T1 images reflects paramagnetic substances such as blood, melanin or inflammatory cells. In addition, increased T2 signal intensity adjacent to the nodular lesion is suggestive of an inflammatory process.
b. Amelanotic melanoma:

As enumerated earlier, several clinical and investigational modalities can be of value in distinguishing these two lesions. Clinically the greater height, dome or mushroom shape, and associated minimal SRF forms important clue in diagnosing amelanotic melanoma from choroidal metastasis.

USG can also be of great importance. High amplitude spikes of the surface and low inside with choroidal excavation rules in the diagnosis of melanoma (Figure 6).

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**Figure 5:** Montage and posterior pole fundus photo of a patient with Giant Nodular Scleritis.

**Figure 6:** USG B scan of a melanoma:
- Mushroom shaped,
- High surface and low internal reflectivity
- Choroidal excavation
- No Shadowing
FFA also plays an important role. Double circulation and increased lesional vascularity again points towards melanoma.

c. Tubercular granuloma of choroid:

Choroidal tuberculomas or tuberculous choroidal granulomas are solitary elevated cream or yellow coloured mass-like lesions ranging from 4 to 14 mm in size (Figure 7). These result from rapid multiplication of tubercle bacilli and progressive liquefactive caseative necrosis. Ultrasonography shows low to moderate internal reflectivity.

![Figure 7: colour photo shows a Tubercular choroidal granuloma involving the disc with surrounding exudative RD](image)

d. Osteoma:

Osteomas are flat orange-yellow lesions distinct geographic borders with branching vessels. On USG it shows up as high intensity echo spike (Figure 8 & 9). FFA shows patchy hyper-fluorescent choroidal filling with late diffuse staining.

![Figure 8: Colour fundus photo of osteoma](image)
10. DIAGNOSTIC WORK-UP:

Up to a third of patients presenting with intraocular metastases have no known history of cancer.\textsuperscript{2-3} It is therefore important to perform a systemic work-up to identify the primary site of neoplasia. Physical examination by an oncologist, imaging with CT or MRI of relevant organ systems, serology for cancer markers and PET scan comprise the systemic work-up. If no primary tumor is found, biopsy for cytological or histopathological analysis should be considered.

Unlike most organs, retrieving a biopsy from a small choroidal lesion is tedious and carries a risk of intraocular injury. Biopsy is further limited by often insufficient or inadequate retrieved material.

**Fine Needle Aspiration Biopsy (FNAB):**

Jacobiec et al\textsuperscript{15} first proposed FNAB of intraocular tumors in 1979. The advantage of a needle aspiration biopsy is that it allows a histopathological correlation in atypical presentations of intraocular
tumors, avoiding the need for an open biopsy or sacrificing the eye. It is a safe procedure in trained hands and in spite of a theoretical risk of dissemination through the needle track; no such case has been documented yet.16 A sensitivity and specificity of 84% and 98% respectively has been reported.15 False negative results are known; hence do not rule out a malignancy.

Tumor thickness is a crucial factor in obtaining a positive result of a biopsy (< 1.9 mm: 40% [4/10]; > 4 mm: 98% [42/43]; 1.9–4 mm: 90% [27/30]) 17 Fine-needle aspiration biopsy can be expected to give useful information in lesions > 3 mm in thickness, but is unreliable in lesions thinner than 2 mm. A tumor of >3mm will allow the bevel of the needle to enter the tumor completely thereby increasing the chances of obtaining an adequate specimen.

a. Indications-
   i. Suspected masquerade syndrome (ex: intraocular lymphoma)
   ii. Solitary choroidal metastasis with undetectable primary.
   iii. Amelanotic choroidal lesion with discrepancy between clinical findings and ancillary investigations
   iv. Atypical presentations.

FNAB provides sufficient material as open biopsy in tumors >3mm in thickness and the results were reliable for FISH analysis of chromosome abnormalities.26-27 FNAB specimens also allow studying the cell type of the tumor.

b. Prerequisites-
   i. Clear media for good visualization.
   ii. Skilled surgeon and cytopathologist with good coordination. It is preferable to have the cytopathologist in the operating room or nearby to process the specimen quickly and to assess the need for resampling.
   iii. Well-equipped laboratory facility.
   iv. Availability of possible treatment options.
   v. Prompt treatment of the malignancy once the diagnosis is established.
c. **Materials**-

i. 25 gauge 1-1.5 inch disposable needle

ii. 30 gauge needle is preferred by some authors for a transcleral biopsy and a 27 gauge for transvitreal biopsy.\(^{22,24-26}\)

iii. 10cc disposable syringe

iv. Extension silicon tubing with luer lock (to allow safe aspiration without needle movement)

v. Indirect ophthalmoscope/ Wide angle viewing system

One end of the silicone tubing is attached to the syringe and the other end to the FNAB needle. Using a tubing will allow the assistant to aspirate and avoid inadvertent movement of the needle within the eye, thereby complications associated with it.

**Procedure**-

FNAB is usually performed in an operation theatre under peribulbar or retrobulbar anaesthesia after pre-operative dilation of pupils. The patient is prepared as for any intraocular surgery. The approach to the lesion depends on the site and type of lesion, visualization, and lens status.

d. **Routes of approach for FNAB:**

i. limbal

ii. clear corneal

iii. direct – trans-scleral/ subretinal

iv. parsplana- trans-vitreal

i. **Limbal approach**- Limbal approach is used for FANB of anterior segment mass lesions. Anterior chamber is inflated with viscoelastic placed through a limbal wound placed 90-120 degrees away from the mass lesion. The needle enters the anterior chamber through the limbal wound and in to the mass, avoiding traversing the pupil where possible. As the volume of the anterior segment tumors is likely to be small, a 30/27 gauge 1 inch needle is used to obtain the biopsy. Inadvertent aspiration of the aqueous may result in flattening the anterior chamber and is preferably avoided by placing the needle within the mass and stopping aspiration before withdrawing the needle from the mass.
ii. **Clear corneal approach**- A clear corneal approach is indicated when obtaining a biopsy of friable tumors to decrease the chances of tumor dissemination (Figure 10). The needle is inserted through the peripheral clear cornea, 2-3mm within the limbus, through the iris root, zonules, vitreous and into the mass. The multiple interphases the needle passes through when withdrawn out of the eye restrict the risk of needle track seeding of tumor cells.

iii. **Transscleral approach**-

   I. **Direct approach**– Tumors >10mm in diameter and >3mm in height and localized with the anterior border between the equator and optic disc can be sampled transclerally (Figure 11). Limited peritomy and tagging of the rectii in the quadrant of the tumor will allow access to transcleral biopsy. Meticulous localization of the tumor on the scleral surface by both transillumination and indirect ophthalmoscopy is performed. The needle is inserted in to the tumor under a partial thickness scleral flap, under direct visualization through an operating microscope. The depth of penetration of the needle depends on the thickness of the tumor. The partial thickness scleral flap is secured using the pre-placed sutures and peritomy closed after removal of the sutures used to tag the muscles.
II. Subretinal approach- Subretinal approach is preferred when the mass is accompanied by a bullous retinal detachment, thereby making placement of the needle within the mass tricky and also increasing the risk of the exudative detachment converting into a rhegmatogenous retinal detachment (Figure 11). Limited peritomy and tagging of the rectii in the quadrant of the tumor will allow placement of an anterior sclerotomy, placed behind the muscle ring. The needle enters the subretinal space through the anterior sclerotomy, traverses the subretinal space into the mass, under direct visualization with an indirect ophthalmoscope or an operating microscope. Rest of the procedure is similar to a transvitreal biopsy.

iv. Parsplana approach-
Small lesions with a posterior location and, especially, those which are thin are more safely biopsied with a transvitreal approach (Figure 12). FNAB can be performed transconjunctivally. Limited peritomy and cauterization of the episcleral vessels however offer the advantage of visualizing the sclerotomy site and controlling extraocular spillage of the vitreous or tumor cells at the site of sclerotomy. Peritomy approach is particularly advisable if the specimen is likely to flow easily as in a previously vitrectomised eye, extensive subretinal fluid or predominantly liquefied vitreous. The globe is stabilized with a traction suture/forceps. An indirect
ophthalmoscope or an operating microscope with a wide angle viewing system may be used for visualizing the tumor. The latter has the advantage of a bimanual approach if needed, though for only biopsy purposes a fibre optic endoilluminator is not placed within the eye. Using an indirect ophthalmoscope for transvitreal FNAB needs practice, adapting to the inverted view and counterintuitive intraocular movement of the needle. This difficulty can be avoided by using an operating microscope.

For transvitreal access the needle is often bent 2–3 mm from its bevelled tip to an angle of 60–90 relative to the shaft. This allows entry to the neoplasm with the needle tip parallel to the retinal plane, across the breadth of the lesion, thereby increasing the yield of biopsy and decreasing the risk of inadvertent globe perforation in small tumors.19

For transvitreal biopsy, the needle is inserted into the thickest part of the mass lesion transretinally, avoiding large retinal vessels, macular region, optic disc and areas of retinal detachment. The iatrogenic retinal break created at the entry site is usually self-sealing in an area of attached retina in absence of any vitreoretinal traction. Once within the mass, the assistant applies abrupt aspiration by pulling the plunger of attached syringe. When obtaining biopsy of a solid mass lesion, no specimen will be seen traversing the needle hub, tubing of the syringe; a sliver of tissue is gathered in the bore of the needle. The needle is advanced further into the mass and the suction is gently released. This
cycle is repeated 2-3 times with the needle in place. The needle is gently withdrawn out of the mass after cessation of the suction force to prevent inadvertent aspiration of the retina or vitreous. Laser retinopexy to the retinal break further decreases the risk of a subsequent rhegmatogenous retinal detachment, but is not mandatory. The sclerotomy self-seals if a 23 - 25g needle was used to obtain the biopsy. The eye is patched with topical antibiotics and steroid.

e. **Specimen handling**- Once the needle is removed from the eye, the tip of the needle is placed in a bowl with ringer lactate solution and 2cc of fluid is aspirated through the needle and the silicon tubing into the syringe. This will move the biopsy specimen from the bore of the needle into the syringe and can often be seen as a sliver of tissue within the barrel of the syringe. A rubber cork is applied to the needle tip and the specimen is promptly delivered to the pathologist. Alternately, the tissue can be expressed out on to a slide and alcohol-fixed. The material may be stained with May–Grünwald–Giemsa procedure. Usage of immunocytochemistry and immunohistochemistry techniques may be routine or selectively depending on a particular laboratory’s protocol.

f. **Complications** Fine-needle aspiration biopsy can cause severe complications. The potential risks include tumour seeding, haemorrhage, retinal detachment, cataract and endophthalmitis; however exact data to define their incidence are not available.

**MANAGEMENT OF CHOROIDAL METASTASIS:**

Choroidal metastasis can be treated with systemic chemotherapy, external beam radiation or rarely focal treatment options such as brachytherapy, transpupillary thermotherapy or photodynamic therapy. The treatment option is selected based on the nature of the primary tumor and what it is most responsive to.

**Systemic chemotherapy:** Metastatic lesions arising from the Lung and Breast are both amenable for systemic chemotherapy (Fig 13). Systemic chemotherapy treats the choroidal metastasis in addition to treating metastatic lesions elsewhere in the body and the primary tumor. Even choroidal lymphoma lesions respond well to systemic chemotherapy and steroids.
**EBRT**: external beam radiotherapy (EBRT) at a dosage of 40-60 Gy causes tumor regression in 85-93% of patients with vision improvement or stabilization in 56% of eyes (Figure 14). However, the extended treatment period of EBRT makes the treatment inconvenient and impractical in critically ill-patients with poor life prognosis. Radiation related complications include cataract (7%), radiation retinopathy (3%), exposure keratopathy (3%), optic neuropathy (2%), and neovascularization of iris (2%).

![Figure 13: Fundus images before and after systemic chemotherapy. Choroidal lesions have regressed completely.](image1)

![Figure 14: Choroidal metastatic lesion with exudative retinal detachment responded very well to EBRT with completely regressed lesions and resolution of the exudative RD.](image2)
Local Chemotherapy: Intravitreal injection of chemotherapy in appropriate dosages causes regression of some metastatic lesions. The rationale of intravitreal injections being circumventing the blood retinal barrier and achieving high concentrations intravitreally (Figure 15).

![Figure 15: Metastatic lesion secondary to breast CA. The lesion progressed despite the lady being on systemic chemotherapy. Single intravitreal injection of Bevacizumab and Carboplatin caused complete regression.](image)

Vision of the patient did not recover owing to the combined occlusion of the blood vessel.

Other modalities for approaching choroidal metastatic lesions include:
- a. Gamma Knife
- b. Proton beam Therapy
- c. Plaque radiotherapy
- d. TTT & PDT – Plaque brachytherapy is used to treat radiosensitive focal choroidal metastasis. TTT and PDT can be used small metastatic lesions.

CONCLUSION

Choroidal metastasis is the most common intraocular malignancy in the adult population. Choroidal metastases frequently occur in the later stages of disseminated disease and are considered a poor prognostic sign. With increasing treatments available leading to longer survival rates for cancer patients, metastases have the potential to become more prevalent. Effective control of these lesions is imperative. Systemic
chemotherapy allows tumor control in some cases, while focal therapy is advised in tumors causing visual loss or is unresponsive to systemic treatment.

**BIBLIOGRAPHY**


INTRODUCTION:

Choroidal osteoma is a rare benign intraocular tumor composed of mature cancellous bone involving the choroid.\(^1\) It was first presented at the meeting of the Verhoeff Society in 1975 and reported by Gass et al.\(^1,^2\) It typically occurs in young healthy females in their second and third decade of life. It is unilateral in majority of cases.\(^3,^4,^5\) However it can also occur in males, young children and adults. There is no racial predilection. It is usually sporadic though familial cases have also been reported.\(^6,^7,^8\)

Figure: Fundus image reveals choroidal osteoma over the posterior pole with area of orange-pink appearance representing calcified portion, while the yellow-brown areas represent the decalcified portion. Fresh subretinal haemorrhage is seen along superotemporal arcade.
ETIOLOGY:
The exact etiology is unknown. Possible theories include choristomatous, inflammatory, traumatic, hormonal, metabolic, environmental, and hereditary causes. No association between choroidal osteoma and any abnormality in blood chemistries such as calcium, phosphorus, alkaline phosphatase, complete blood count, and urinalysis.

SYMPTOMS:
It is asymptomatic in majority of the cases. Symptoms include diminution of vision, metamorphopsia, and visual field defects depending on the location of the tumor. Diminution of vision is a result of macular location of the tumor, development of choroidal neovascularization (CNV), decalcification, and atrophy of overlying retinal pigment epithelium and photoreceptors.

MORPHOLOGICAL APPEARANCE:
Choroidal osteoma is identified as an orange-yellow sub-retinal deep lesion with distinct geographic or scalloped borders. Spider-like branching vessels may be seen on the tumor surface. Calcified lesions have an orange-red color, whereas decalcification in later stages results in a yellowish tint from RPE depigmentation. In majority of cases it is juxta-papillary with some extension into the macular region. Slight enlargement of the tumor occurs over a period of 5-10 years in 40-60% of the cases.

Trimble et al in 1988, described tumor decalcification and resolution. It appears as a greyish-yellow lesion with atrophy of overlying retinal pigment epithelium (RPE) and choriocapillaris. Decalcification of a sub-foveal lesion is associated with poor visual outcome. Photodynamic therapy (PDT) and laser photocoagulation induce decalcification within the lesion by stimulating osteoclastic activity, and hence reserved for extrafoveal tumors with growth.

COMPLICATIONS:
CNV is found to occur in 31% cases over 5 years, 31-47% cases over 10 years and 46-56% cases over 20 years. Disruption of RPE
and Bruchs membrane allows growth of underlying choroidal vessels. Choroidal osteoma is also associated with serous retinal detachments, sub-retinal fluid and sub-retinal hemorrhage. It is postulated that it occurs as result of pinpoint RPE leakage points over the tumor surface and associated atrophy of the RPE and choriocapillaris.

**INVESTIGATIONS:**

1. Fundus fluorescein angiography: Early patchy hyperfluorescent choroidal filling pattern with late diffuse staining is seen. RPE atrophy and CNV can also be identified.\(^3,18,19\)

2. Fundus auto-fluorescence: It depends on the presence of decalcification, lipofuscin accumulation, outer retina and RPE atrophy. It is increased in metabolically stressed outer retina and RPE, and absent in atrophic or dysfunctional RPE. Calcified choroidal osteomas show fluorescence on blue-light autofluorescence, whereas the decalcified areas has reduced overall fluorescence.\(^19,22\)

3. Indocyanine green angiography: Choroidal osteomas show early hypo-fluorescence, followed by fine diffuse multifocal fluorescence that becomes confluent in late phase.\(^23\)

4. OCT: Choroidal osteoma shows dense, abrupt reflection of light on OCT. It is also useful in detecting CNV, subretinal fluid, retinal edema, and retinal thinning. The retinal architecture is relatively preserved in calcified areas whereas outer-layer thinning and photoreceptor loss is seen over decalcified osteoma.\(^21,26\) Spectral-domain SD-OCT and fourier domain FD-OCT having higher resolution and penetration, have demonstrated a wide range of tumor reflectivity patterns varying from hypo-reflective to iso-reflective to hyper-reflective.\(^24,25\) Furthermore, a latticework reflective pattern has been demonstrated in calcified tumor regions which is similar to the original osteoma spongy bone.\(^19,24\)

5. Ultrasonography: “Pseudo-optic nerve sign” on B-scan: Choroidal osteoma is seen as slightly elevated, highly reflective choroidal mass which persists on low gain causing acoustic shadowing of the orbit and appearance of pseudo-optic nerve.\(^5,21\)

6. X-ray of the orbit: Radiodense lesion may be seen corresponding to the ossified tumor.\(^5\)
7. Computed tomography: Crescentic radiopaque plaque is seen in the choroid.
8. Magnetic resonance imaging: Choroidal osteoma is seen as a bright signal on T1-weighted images and an area of relative low intensity on T2-weighted images.22

**DIFFERENTIAL DIAGNOSIS:**

- *Amelanotic choroidal melanoma:* yellow-brown, dome or mushroom shaped, ill-defined margins
- *Amelanotic choroidal nevus:* flat, grey, brown, ill-defined margins31
- *Metastatic choroidal carcinoma:* may be multifocal, placoid, non-pigmented, indistinct margins, serous retinal detachment out of proportion to the size of the tumor27
- *Circumscribed choroidal hemangioma:* red-orange, ill-defined margins23
- *Disciform macular degeneration:* In elderly patients with associated features of age-related macular degeneration.
- *Posterior scleritis:* red-brown lesion, ill-defined with associated features of uveitis, cloudy sub-retinal fluid, thickened sclera and choroid. Possible ‘T’ sign on ultrasound.
- *Idiopathic sclerochoroidal calcification:* multi-focal, irregular calcific plaque, usually outside the retinal vascular arcades
- *Peripapillary serpiginous choroiditis:* bilateral, chronic, progressive, and recurrent inflammatory disease which progresses centrifugally from the disc and involves macula. Resolution of the lesion results in fibrous scarring and retinal pigment epithelium hyperplasia or hypoplasia.33

**MANAGEMENT:**

**Goals of treatment are;**

1. Treatment of associated complications: Subfoveal CNV is treated with anti-vegf agents 28,29,30 and extrafoveal CNV with PDT18 or laser photocoagulation.
2. Prevention of tumor growth and promoting decalcification in extrafoveal lesion to prevent further growth of the tumor by photodynamic therapy or laser photocoagulation are being considered but are yet to come in to practice.

**Prognosis:**

Variable. Spontaneous resolution is seen in about 64% cases over a period of 10 years.4

Factors for poor visual outcome:

1. Sub-foveal location
2. Atrophy of overlying RPE
3. Presence of CNV
4. Sub-retinal fluid and sub-retinal hemorrhage

**What’s new:**

Enhanced depth imaging OCT (EDI-OCT), has revealed unique, intrinsic features of choroidal osteoma. These features include hyperreflective horizontal lamella representing bone lamella, intermittent horizontal lines that are brighter and slightly thicker representing cement lines. Other features are horizontal tubules (Haversian canals) and vertical tubules (Volkmann canals). Speckled hyperreflective dots are suggestive of spongy, cancellous tissue.32

**REFERENCES:**


INTRODUCTION:
Congenital hypertrophy of retinal pigment epithelium (CHRPE) is a benign condition which is frequently confused with choroidal melanoma. It was first described by Jones and Reese in 1956 as ‘benign melanoma of the RPE’. Kurz and Zimmerman found on histopathology the hypertrophy of the RPE cells but it was Buettener who named it ‘congenital hypertrophy of the retinal pigment epithelium’ in 1975. It is characterized by the presence of oval, pigmented dark gray - dark brown lesions at the level of retinal pigment epithelium usually distributed in the retinal mid-periphery, but may also occur in the posterior pole involving the macula.
CLINICAL FEATURES:

Symptoms:
It is usually asymptomatic, discovered incidentally on fundus examination.

Morphological features:
CHRPE is characterized by the presence of oval to round, well circumscribed, flat, pigmented lesion in the mid-periphery of retina with smooth or scalloped margins. It may be surrounded by a halo of depigmentation with punched-out hypopigmented lacunae within the body of the lesion.4,5,6

Based on the number and distribution of the lesions, it is classified as follows:

1. Solitary. It can be found anywhere in the fundus but is usually observed in the supero-temporal and equatorial regions. Solitary CHRPE, believed to be stationary, can grow to become elevated nodular tumors and even turn into malignant epithelioma (adenocarcinoma).

2. Multifocal (Congenital grouped pigmentation; Bear tracks). Several lesions distributed in a cluster giving the appearance of footprint of an animal, described as ”bear-track”. When they appear clinically nonpigmented, they have been called ‘polar bear tracks’. They assume a sectoral distribution in the fundus with no predilection for any quadrant. These lesions have a meridional orientation towards the optic disc. These lesions have no relationship to familial adenomatous polyposis or Gardner syndrome, despite its similarity to the pigmented fundus lesions seen with those conditions.7,8,9 It is RPE hamartomas, which are ‘CHRPE-like lesions’ that are associated with familial adenomatous polyposis (FAP) and Gardner syndrome.10,11,12

Histology13:
- Increase in RPE cell density
- Abnormal RPE cells showing increase in the height of individual
cells and multiple granules with increase in pigment density. Hypertrophy and hyperplasia of RPE.

- Degeneration of overlying photoreceptors
- RPE cells adjacent to the CHRPE lesion slowly become broad and flat and induce pressure on the hypertrophic RPE cells present within the CHRPE lesion, creating areas of micro-trauma at the junction between the two. This may be associated with RPE cell migration into the inner retina and may allow the subretinal fibrovascular growth associated with neovascular membranes.

Investigations:

- Fundus autofluorescence (FAF): Hypoautofluorescence is seen as CHRPE contains predominantly melanin and only small amounts of lipofuscin. Lacunae or nonpigmented halos show a trace to moderate autofluorescence.14
- Fluorescence angiography (FA): blocked fluorescence is seen in pigmented areas and a transmission defect in depigmented portions. No intrinsic vessels or dye flush are seen, as with a true tumor. Leakage from retinal vessels overlying CHRPE may be seen during late phases of the angiogram.
- Spectral domain optical coherence tomography (SD-OCT): Thinning of neural retina with overlying photoreceptor is seen. Hypertrophied pigmented RPE shadows the underlying choroidal structures. Areas of lacunae show absence of RPE and thus increased transmission of light.15 Sub-retinal cleft is seen at the site of loss of photoreceptors.

Differential diagnosis:

- Choroidal malignant melanoma: elevated, less homogenously pigmented and less sharply demarcated as compared with CHRPE, and usually exhibiting growth in all three dimensions.
- Choroidal nevus: flat or minimally elevated and located below the RPE varying light to dark brown in colour. The borders are ill-defined and feathery. It is associated with drusen and pigmentary mottling on the surface.
- Melanocytoma: Homogeneously black in color (jet black).
black sunburst lesions in sickle cell retinopathy: dark gray to brown convex shaped lesions predominantly in the midperiphery.

- True hyperplasia of the RPE: Has ill-defined borders and invades the retina, resulting in retinal distortion.

- CHRPE-like lesion: multifocal lesions with irregular border, associated with a white tail of depigmentation on one margin, located peripherally. Unlike typical CHRPE that follows sectoral distribution, these lesions have a haphazard distribution. They are hamartomatous malformation of the RPE seen in Gardner’s syndrome and familial adenomatous polyposis (FAP).16

**Management:**

CHRPE has good visual prognosis and no treatment is required. Regular follow-up is required due to possibility of conversion to adenoma or adenocarcinoma.

**REFERENCES**


INTRODUCTION

Combined hamartomas of the retina and retinal pigment epithelium (CHRRPE) are benign tumours and are usually solitary unilateral lesions, most commonly located at posterior pole. They appear as slightly elevated lesions and have varying amounts of pigmentation, retinal vascular tortuosity, and epiretinal membrane (ERM) formation. The lesions are characterized by predominant tissue subtype, including pigment epithelium, vascular, or glial. Historically, combined hamartomas describe lesions that were clinically mistaken for choroidal malignancy. Gass reported these lesions and used the term “combined hamartoma”.

CLINICAL FEATURES

The Macula Society reported a series of 60 patients with combined hamartomas, with the mean age of 15 years, ranging from 10 months to 66 years. There was no apparent predilection based on sex or race. Diagnosis is more likely delayed relative to the appearance of the lesions due to the gradual impact on vision of non-macular lesions. Generally, the patients complain of painless visual loss as the major symptom followed by strabismus, floaters, leukocoria, and ocular pain. Visual acuity depends on the location of lesion being more profoundly decreased in the lesions involving macular area and optic nerve.

Other causes of visual loss include choroidal neovascularization, vitreous hemorrhage, exudative retinal detachments, retinoschisis, and macular hole formation.
Lesions of the posterior pole have variable amounts of retinal pigment epithelial, vascular, and glial components (Figure 1). The lesion appears as an elevated pigmented mass involving the RPE, retina, and overlying vitreous with fan-like extensions extending towards periphery.

The Macular Society study has reported retinal vascular tortuosity (93%) within the lesion, hyperpigmentation (87%), slight elevation in retina (80%), ERM formation (78%), and exudation (7%). In patients with peripheral lesions, dragged disc appearance has been described. Combined hamartomas are mostly solitary, unilateral tumors; however, cases of bilateral involvement have been reported in association with neurofibromatosis. CHRRPE lesions have also been associated with optic nerve colobomas, optic nerve head drusen, X-linked juvenile retinoschisis, optic nerve head pits.

**Figure 1:** Combined hamartoma of retina & RPE with retinal vascular tortuosity, epiretinal membrane, deep pigmentation and exudation.

**INVESTIGATIONS**

The diagnosis of CHRRPE is based upon clinical appearance and confirmed by characteristic features of fluorescein angiography (FA) and optical coherence tomography (OCT). In FA, during the early phase the degree of hyperpigmentation determines the degree
Combined Hamartoma of Retina and Retinal Pigment Epithelium (CHRRPE)

of hypofluorescence. Tractional distortion of the retina may produce marked vascular tortuosity. During the mid-phase of the FA other vascular anomalies are highlighted and in the late phase of FA, late hyperfluorescence is observed due to leakage from tortuous vessels or associated choroidal neovascularization.

OCT imaging (Figure 2) shows characteristic findings like vitreoretinal traction, retinal distortion, retinal thickening at the level of the RPE, and preretinal vitreoretinal interface abnormalities, and choroidal thinning. The intraretinal extension of epiretinal glial tissue is seen as omega-shaped, hyper-reflective tissue that causes disorganization of retinal layers and limited posteriorly by the outer plexiform layer (OPL). This OCT finding has been termed as ‘Omega sign’. Autofluorescence imaging shows hypoautofluorescence over the lesion and hyperautofluorescence in areas with macular edema and overlying ERM. Ultrasonography is not of much use in diagnosing these minimally elevated lesions.

![Figure 2: SD-OCT scan of the eye above reveals epiretinal membrane with vitreoretinal traction and retinal folds. RPE is variably thickened and undulating in appearance.](image)

**DIFFERENTIAL DIAGNOSIS**

CHRRPE lesions are often confused with epiretinal membranes (ERMs) which also show vitreoretinal interface disruption and vascular tortuosity but the hyperpigmentation in CHRRPE lesions is rarely present. OCT testing differentiates CHRRPE and ERMs. The intraretinal component of CHRRPE lesions is often difficult to
Combined Hamartoma of Retina and Retinal Pigment Epithelium (CHRRPE)

discriminate by FA or clinical examination, but is easily apparent with high-resolution OCT imaging.13

Choroidal lesions like melanoma, nevus, congenital hypertrophy of the retinal pigment epithelium (CHRPE), adenoma and adenocarcinoma of the RPE can be misidentified as a CHRRPE lesion. Choroidal melanomas are subretinal, elevated, and lack vitreoretinal interface changes and vascular tortuosity. Choroidal nevi lack vitreoretinal interface changes and vascular tortuosity as well. Congenital hypertrophy of the retinal pigment epithelium is subretinal and flat with normal retinal vessels. Adenoma and adenocarcinoma of the retinal pigment epithelium are quite rare and usually jet-black in colour.17

MANAGEMENT

In patients with CHRRPE, treatment depends upon the cause of visual loss. Choroidal neovascular membrane causing progressive visual loss and vascular leakage is treated with photodynamic therapy (PDT) and anti-VEGF injections. Macular lesions which cause visual loss with glial proliferation and vitreous traction need surgical treatment.18 OCT imaging is an invaluable tool for identifying any vitreoretinal interface abnormalities and determining the presence of a surgical plane. A combination of pars plana vitrectomy, membrane peeling, intravitreal triamcinolone, and laser reduces the vascular activity and reduce traction associated with the abnormal vitreoretinal interface.19 Interventional outcome depends on early surgical intervention and improvement in retinal architecture and underlying amblyopia. Use of preoperative autologous plasmin-assisted vitrectomy showed significant architectural and functional improvement.20 Even though tractional distortion of the macula can be relieved by vitrectomy and epiretinal membrane surgery, the hamartoma generally persists or recurs in eyes with CHRRPE, as the hamartomatous tissue cannot be completely removed. Aggressive amblyopia therapy is an important component of the postsurgical care of such patients.

REFERENCES


Glial Tumors of Retina and Optic Disc

Glial tumor of the retina and optic disc include the following:

1. Retinal astrocytic hamartoma
2. Retinal astrocytoma
3. Presumed solitary circumscribed retinal astrocytic proliferation (PSCRAP)
4. Multiple circumscribed retinal astrocytic proliferation (MPRAP)

1. RETINAL ASTROCYTIC HAMARTOMA

Retinal astrocytic hamartoma is a benign tumor composed of proliferation of well-differentiated astrocytes.\(^1\) It is congenital and associated with Tuberous Sclerosis in majority of the cases. It is undetermined whether it is a separate entity, or form fruste or partial expression of tuberous sclerosis.\(^2,3,4,5\) Genetic alterations of chromosome 9 and 16 have been identified. Some cases have been reported in association with neurofibromatosis-1 (NF-1).\(^6\)
Glial Tumors Of Retina and Optic Disc

**Clinical features:**
Following variants have been identified:

- Non-calcified: gray-yellow, sessile, transparent lesion
- Calcified: glistening yellow spherules of calcification are present in contrast with chalky white calcification in retinoblastoma.
- Combination of both (Figure)

Unlike retinoblastoma, there are no prominent feeder vessels. It is associated with adjacent glial proliferation and retinal traction.

Histopathology: well-differentiated astrocytes are seen. Calciospheres are observed in areas of calcification.

**Complications:** Progressive growth of the tumor is associated with exudative retinal detachment and neovascular glaucoma, vitreous seeding of tumor cells, vitreous hemorrhage, and proliferative retinopathy. Extra-ocular extension into orbit and epi-bulbar tissues is observed in cases of rapid progression.

**Investigations:**

**Fundus fluorescein angiography:** demonstrates network of small vessels in venous phase with late staining.

**Autofluorescence:** calcified areas demonstrate hyper-autofluorescence.

**Ultrasonography:** Calcified plaque is seen.

**OCT:** Following variants have been identified on SD-OCT

- Type 1: flat and within the nerve fiber layer
- Type 2: slight elevation with retinal traction
- Type 3: typical ‘moth-eaten’ areas caused by calcification
- Type 4: optically empty intra-lesional cavities

**Differential diagnosis:**

- Atypical choroidal melanoma
- Retinoblastoma
Contraindications to cataract surgery include:

- Severe glaucoma
- Severe corneal disease
- Severe retinal disease
- Severe systemic disease

**References:**


2. ACQUIRED RETINAL ASTROCYTOMA

Retinal Astrocytoma is a glial tumor of the sensory retina. It represents the retinal equivalent of a low-grade central nervous system astrocytoma. It is an acquired tumor similar to the congenital astrocytic hamartoma associated with tuberous sclerosis.

Clinical features

It appears as a solitary yellow mass with abundant intrinsic vascularity. Unlike congenital astrocytic hamartoma, it lacks calcification and is unassociated with tuberous sclerosis. The tumor exhibits slow
progressive growth and as the tumor enlarges intraretinal exudates and exudative retinal detachment occur.\textsuperscript{6,7}

**Investigations:**
- Fundus Fluorescein angiography: The tumor shows early hyperfluorescence depicting fine, intrinsic vascularity with diffuse staining in late phase.
- Ultrasonography: reveals noncalcified retinal mass with high internal reflectivity.
- FNAC: shows glial cells that are positive for glial fibrillary acid protein (GFAP) stain

**Differential diagnosis**
- Atypical choroidal melanoma
- Retinoblastoma
- Retinal hemangioblastoma

**Management**
Photodynamic therapy in case of progressive tumor associated with sub-retinal exudates, cryotherapy for peripherally located tumor, and radiation therapy when the conventional treatment fails.\textsuperscript{8,9,10,11}

**REFERENCES**


3. PRESUMED SOLITARY CIRCUMSCRIBED RETINAL ASTROCYTIC PROLIFERATION (PSCRAP)

It is a benign, solitary well circumscribed lesion that generally occurs in an eye with clear media and prior ocular insults. It is diagnosed in middle-age or older people with no personal or family history of tuberous sclerosis.

Clinical features: It appears as solitary, well-defined, white opaque lesion with obscuration of view of deeper retinal vessels. It is not associated with subretinal fluid, exudation, or feeder vessel. There is no adjacent retinal gliosis and retinal dragging and it lacks calcification.1,2,3

Investigations:

- Fundus fluorescein angiography: The tumor shows early hypofluorescence with mild staining in late phase.
- Ultrasonography: reveals dome shaped noncalcified retinal mass with medium to high internal reflectivity.
- OCT: shows dome shaped mass with posterior shadowing. It was previously believed to arise in the nerve fiber layer, the site where most astrocytes reside. However, with higher resolution SD-OCT, it is now believed that the tumor is derived from RPE or deeper retina. SD-OCT also demonstrates retinal tenting at tumor margins.4-10
• OCT angiography: shows lack of intrinsic or paralesional vascular flow, indicating that this lesion is fibrous and likely derived from the RPE or deep retina and not the retinal astrocytes.11

**Differential diagnosis:**

• Astrocytic hamartoma: Usually multiple or bilateral, ill-defined, white-yellow lesion, located peripapillary, calcified or non-calcified, and associated with tuberous sclerosis.12,13,14

• Acquired retinal astrocytoma: Solitary mass with abundant intrinsic vessels, tends to be progressive, and may be associated with exudation or exudative retinal detachment.15,16

• Retinoblastoma (RB): Solitary or multiple white calcified lesion with feeder vessels, seen in children. Family history of RB may be present.

• Myelinated fibers: Benign, idiopathic, chalk-white, sharply demarcated patches on the superficial retina with feathery margins.17

• Granuloma and reactive gliosis.18,19,20

**Management**

It requires periodic observation. It is usually stable on follow-up, with no tendency to grow or to cause local complications. Spontaneous involution of the lesion has also been reported.21,22

**REFERENCES**


4. MULTIPLE PRESUMED RETINAL ASTROCYTIC PROLIFERATION (MPRAP):

The features are similar to presumed solitary circumscribed retinal astrocytic proliferation (PSCRAP) but with occurrence of multiple lesions. A single case report of MPRAP associated with CHRRPE and NF-2 in a 9-year-old male child has been described by Rishi et al (Figure).

REFERENCES

INTRODUCTION

Medulloepithelioma (diktyoma, teratoneuroma) is a rare congenital tumor that arises from the epithelium of the medullary tube. This tumor usually arises from the ciliary body epithelium, but medulloepitheliomas of the retina and the optic nerve have also known to occur. Fuchs2 reported it as diktyoma because of the presence of netlike appearance of cells in the tumor. Grinker3 was first to use the term “medulloepithelioma”.

Medulloepithelioma has its origin from nonpigmented ciliary epithelium. Its appearance is like that of primitive retina and medullary epithelium of brain.4 Benign medulloepithelioma is detected late after years of gradual growth when it eventually manifests clinically or represents delayed malignant transformation of preexistent lesion. Medulloepithelioma can rarely arise from the optic disc, iris, and retinal stalk.5-7 Most common age of presentation of medulloepithelioma is between 2-10 years, with 75-90% of tumors presenting in the first decade of life. There have also been documented cases of medulloepithelioma manifesting in adulthood. It is typically unilateral, with no preference for either eye and there seem to be no racial or gender predilection.6,8-13

Clinical features

Initially, patients are asymptomatic as small tumors rarely cause any significant functional change to be noticed. Patients often present when the tumors are large enough to be seen through the pupil or causing any other symptomatic secondary effect. Patients present with symptoms of loss of vision, unilateral astigmatism, leukocoria, pain, red eye, or visible intraocular mass. Subluxation of lens, cataract,
retrolental membrane, or neovascular glaucoma can be the reason for vision loss in these patients.

Presence of cysts is the most classic feature of medulloepithelioma, formed by the production of mucopolysaccharide by the epithelial cells. These cysts are seen within the tumor or free-floating in the anterior/posterior chamber. Thus, the presence of anterior/posterior chamber cysts should be considered as a possibility of a differential diagnosis of medulloepithelioma. The tumor may show pigmentation, episcleral feeder vessels or chalky, grey white areas representing the presence of cartilage. There may be loss of zonular fibers adjacent to the tumor, resulting in a notch of the adjoining area of lens, also known as ‘pseudo-lens coloboma’. It may also lead to lens subluxation with accompanying sectoral or occasionally total cataract. The ciliary body next to the tumor may show long ciliary processes and may be covered by a neoplastic cyclitic membrane. Neovascular glaucoma can also be associated with it.

**Systemic Associations**

Medulloepithelioma has been found to be associated with DICER 1 gene and inherited as an autosomal dominant trait located at chromosome 14q32.29 It manifests as Pleuropulmonary Blastoma Family Tumor and Dysplasia Syndrome (PPBFTDS). The tumors reported with this mutation include pleuropulmonary blastoma, ovarian Sertoli–Leydig cell tumor, cystic nephroma, and thyroid hyperplasia or goiter. Medulloepithelioma, rhabdomyosarcoma, medulloblastoma, primitive neuroectodermal tumor, thyroid cancer, and papillary Wilms’ tumor (nephroblastoma) are also known to be associated. PPB is a rare tumour of lung presenting with lung cysts arising from embryonal cells. and it represents pulmonary analogue of childhood embryonal tumors like retinoblastoma, Wilms tumour, medulloblastoma and neuroblastoma.

**Investigations**

USG examination of medulloepithelioma shows heterogeneous, highly echogenic mass localized to ciliary body, with irregular cystic areas within.15 It can show calcification, if there is cartilage component within the tumor. Ultrasound biomicroscopy (UBM)
delineates the exact radial and circumferential extent and the height of the ciliary body mass and demonstrates intratumoral cysts, neoplastic cyclitic membrane, anterior chamber cysts and sequelae, such as lens subluxation. On fluorescein angiography, large branching arteries and veins arising from the ciliary body tumor peripherally and haphazardly crisscrossing within the retrolenticular tissue are seen. Magnetic resonance imaging (MRI) is the standard preoperative investigative modality for the tumor. The tumor appears as a heterogeneous mass composed of both solid and cystic components arising from a lateral retrolental location. T1 weighted MRI imaging depicts tumor as isointense to mildly hyperintense to vitreous, with avid enhancement with contrast.

**Differential diagnosis**

Since the tumor can present as neovascular glaucoma, total cataract, and anterior chamber seeds, it may lead to misdiagnosis of the tumour. It can be misdiagnosed as retinoblastoma. Patients of retinoblastoma present less than 6 years of age with unilateral or bilateral, grey-white to yellow intraocular retinal mass, associated with or without seeds. Presence of cartilage within medulloepithelioma may mimic calcification of retinoblastoma.

Coats disease is another differential diagnosis, but absence of involvement of ciliary body is the differentiating feature from the tumor. The retrolental neoplastic cyclitic membrane differentiates medulloepithelioma from retinoblastoma and Coats disease. On fluorescein angiography, the neoplastic cyclitic membrane shows rapid filling of large, haphazard vessels emanating from the ciliary body across the hyaloid face. Persistent fetal vasculature (PFV) has been reported to be associated with about 20% of cases of medulloepithelioma. The retrolental membrane in medulloepithelioma can be confused with PFV but the membrane in medulloepithelioma represents a sheet of neoplastic tissue that has migrated from the main tumor across the anterior vitreous face, using the hyaloid as a scaffold and the vessels on the neoplastic membrane arise from the periphery and vascular stalk is absent. Juvenile xanthogranuloma appears as fleshy involvement of the iris and can have spontaneous hyphema.
Management

Treatment for ciliary body medulloepithelioma include various options like cryotherapy, plaque radiotherapy,27 external beam radiotherapy, local resection, and enucleation.6,8,9,20-24 Smaller tumors up to 4 clock hours may be treated with cryotherapy, radiotherapy, or local resection. Plaque brachytherapy is employed with I-125 and R-106,28 for small to medium sized tumors. Treatment for advanced or large tumors or presenting with neovascular glaucoma undergo enucleation.6,8,9 Enucleation should be done with minimum manipulation to avoid accidental perforation or spillage of tumor cells into the orbit. Orbital exenteration may be required for cases with orbital extension. Since the tumor is often misdiagnosed as glaucoma, uveitis, or cataract, the intervention is usually late and thereby prognosis is poor.25,26

REFERENCES


INTRODUCTION

Melanocytoma is a benign melanocytic tumor that appears dark-brown or black in colour. Most commonly, it is located at the optic disc and may cause extension into the surrounding tissues. The term melanocytoma was coined by Zimmerman,\(^1,2\) and its clinical and histopathological description was given by Zimmerman and Garron.\(^1\) Originally, the tumour was described as melanocytoma of the optic disc but subsequently, similar melanocytomas of the iris, ciliary body, and choroid have been described.\(^3-5\) Historically, the tumour was confused with uveal malignant melanoma. Melanocytoma is now defined as a specific variant of melanocytic nevus which is located at the optic disc or elsewhere in the uveal tract, characterized clinically by a dark brown to black colour and composed histopathologically of deeply pigmented round to oval cells with small, round, uniform nuclei, often termed ‘magnocellular nevus’.

Figure: Fundus photograph of right eye shows an optic disc melanocytoma, jet-black in colour with deeper extension.
**CLINICAL FEATURES**

Most ocular melanocytoma remain relatively stable and do not cause central visual impairment. Mild visual loss related to the tumor can occur in nearly 26%, mainly due to mild retinal exudation and subretinal fluid. Cause of severe visual loss, though rare, can be attributed to central retinal vein obstruction, spontaneous tumor necrosis, or malignant transformation. Melanocytoma is usually unilateral but bilateral cases have been rarely reported in children but these cases may not be true melanocytoma. The typical features of this tumour include a mass characteristically dark brown to black in colour and situated partly on the optic disc. The tumor is relatively small in size and can be confined to the disc in 15% or extends over the margin of the optic disc to involve the adjacent choroid (54%) or into the adjacent sensory retina (30%).

Melanocytoma can undergo tumour necrosis and vitreous seeds can extend into the anterior chamber, producing a black pseudohypopyon. Other complications include disc edema (25%), intraretinal edema (16%), subretinal fluid (14%), intraretinal exudation (12%), focal hemorrhage (5%), vitreous seeds (4%), and retinal vein obstruction (3%). These complications can produce visual loss in 26% of cases. The degree of visual loss depends on extent of extension of the tumor into the retina and the presence of surrounding subretinal fluid. There have also been reports of choroidal neovascularization adjacent to optic disc melanocytoma. Melanocytoma of the optic disc traditionally was recognized to be a stable lesion with no tendency to grow. The main predictive risk factor for growth is an initial thickness of ≥1.5 mm at the time of first diagnosis. The tumor can grow slowly and result in severe visual loss due to secondary effects like ischemic optic neuropathy associated with tumor necrosis, central retinal vein obstruction, neovascular glaucoma, central retinal artery occlusion and neuroretinitis. There has been a report of simultaneous occurrence of optic nerve melanocytoma and pituitary adenoma resulting in severe visual field loss.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of melanocytoma of the optic disc includes choroidal nevus, juxtapapillary choroidal melanoma, hypertrophy...
Melanocytoma

of the RPE, hyperplasia of the retinal pigment epithelium (RPE), adenoma of the RPE, and combined hamartoma of the retina and RPE. Rarely, malignant melanoma can occur in the optic nerve and may be difficult to differentiate clinically from melanocytoma.25

INVESTIGATIONS

The diagnosis of melanocytoma of the optic nerve is usually made its characteristic clinical features. Investigations like fundus photography, fluorescein angiography, optical coherence tomography (OCT), OCT angiography, autofluorescence, and visual field examinations can assist the clinical features in the diagnosing and helping in follow-up evaluations. Fluorescein angiography of a melanocytoma of the optic nerve shows hypofluorescence throughout the angiogram.5 In cases with optic disc edema, there is hyperfluorescence of the optic disc adjacent to the tumour. OCT imaging shows a smooth dome-shaped pre-papillary mass with dense shadowing and occasional vitreous seeds overlying the mass.12,20,21 OCT angiography demonstrates that radial peripapillary capillary network that is prominent overlying the mass, if there is no retinal invasion. Deeper vessels are not seen. Indocyanine green angiography (ICGA) shows the lesion to be hypofluorescent.19 Autofluorescence imaging also shows the tumour to be hypoautofluorescent.8 The visual field analysis shows variable field loss, depending on the size and extent of the lesion, as well as degree of optic nerve compression and atrophy and include arcuate scotoma, enlarged blind spot, and others.19 Melanocytoma greater than 0.5 mm in elevation, can be diagnosed with ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). MRI with gadolinium enhancement can determine gross extent of melanocytoma involvement in the retrolaminar portion of the optic nerve.28 Extensive involvement in the optic nerve with severe visual loss suggests malignant transformation of the lesion.25–31 Malignant change is estimated to occur in about 1–2% of cases.7

MANAGEMENT

Melanocytomas are observed to look for the rare possiblity of malignant transformation. Tumor necrosis induced inflammation resulting in optic neuritis / neuroretinitis can be treated with systemic steroids.33 Progressive growth and visual loss should suggest
malignant transformation, and fine needle biopsy confirmation followed by enucleation should be considered. Since melanocytoma of the optic disc can rarely evolve into malignant melanoma, thorough examination and fundus photography should be performed routinely.

REFERENCES

Melanocytoma


INTRODUCTION

Intraocular lymphoma, a great non-infective masquerader occurs intraocularly in either the vitreoretinal (primary vitreoretinal lymphoma PVRL)) or in the uveal space (primary choroidal, iris lymphoma). By definition PVRL denotes presence of pathology limited to vitreoretinal space without its occurrence in the central nervous system. The term ‘primary’ is however controversial as almost 56-90% of PVRL patients will ultimately go on to involve the CNS over few months to years (8-29 months) and is considered a subset of primary CNS lymphoma (PCNSL). Incidentally 25% of patients with PCNSL will have concurrent ocular involvement at presentation. Primary choroidal and iridial lymphomas are rarer, less aggressive as compared to its vitreoretinal counterpart and due its rarity, the following section will deal primarily with PVRL.
PATHOPHYSIOLOGY OF PRIMARY VITREORETINAL LYMPHOMA

Origin of lymphoma cells in the retina is a point of debate. Two etiologies have been proposed: infectious and hematogenous. Infectious etiology proposes an agent which triggers B cell migration to CNS which subsequently undergoes clonal expansion.3 This theory is particularly true in immunocompromised individuals who have increased incidence of lymphoma. Role of viral agents like EBV (Epstein-Barr virus) seen commonly in immunocompromised patients and its association with CNS lymphoma has already been documented.4 Hematogenous theory suggests spread of lymphoma cells from extraocular foci to eye via the central retinal artery.5 Preferential entry to retina rather than choroid has been attributed to selective receptive retinal endothelial receptors.6

Once in the retina space; cells then move anteriorly towards the vitreal space and also posteriorly where Bruch membrane acts as a natural barrier preventing it from reaching the choroid. Lymphoma cells then get accumulated in the subRPE space (retinal pigment epithelium)

CLINICAL FEATURES

Although PVRL is aggressive in nature, the presentation is insidious. It generally presents between the fifth and eight decade without racial predilection with slightly more occurrence in females (female to male ratio of 2:1).7 It is mostly bilateral although asymmetrical. The
Primary Intraocular Lymphoma

Insidious nature of the condition can be summed up as the average time to diagnose a case of PVRL from its onset of symptoms is approximately 1 year. This contradicts to a case of CNS lymphoma where the average time to diagnosis is approximately 3 months. Since PVRL is closely related to CNS lymphoma its imperative to elicit any recent CNS signs in a patient suspected to have PVRL. CNS lymphoma most commonly affects the frontal lobe, so enquiring for recent behavioral changes, or history of recent hemiparesis or ataxia is a good way to begin examination of any suspected case of PVRL.

PVRL is painless clinical condition with generally no signs of inflammation like pain and redness. The most common symptom is blurring of vision present in 90% of cases. Patients also complain of floaters, which are intermittent. Patients may have already visited few ophthalmologists with multiple courses of systemic and topical steroids. Typically patients will report decrease in floaters and blurring with steroids, which again reappears. This is a important clinical clue which is because steroids are lympholytic in nature.

Clinical signs typically will show a quiet eye with no scleral/ocular tenderness. Anterior chamber may be absolutely quiet or present with cells/flare and keratic precipitates(KP). Rarely PVRL can present with pseudohypopyon. Although presence of cells and KP mimics other uveitic entity, a close examination of these KP and cells yield important clinical clues. Cells in PVRL will be larger and so will be the KP, which are typically found throughout the corneal endothelial surface. With time these KP will not show changes of pigmentation or change its shape. These features are because cells are not true inflammatory cells but individual lymphoma cells which then conglomerate to form the KP. Posterior synechiae is typically absent.

Posterior examination reveals presence of vitreous haze secondary to vitreous cells. Depending on the state of vitreous syneresis, vitreous haze can be divided into 3 types. Aurora Borealis variety of vitreous haze was reported to be the most common where the individual lymphoma cells align themselves along the vitreous fibrils. The other 2 types are string of pearls where lymphoma cells align akin to a string of pearls and non-specific variety.

The most typical sign are multiple foci or single foci of yellowish
subRPE deposits (figure 1). An earliest retinal sign is perivascular infiltration, which mimics vascular sheathing (figure 2). These deposits are individual clusters of lymphoma cells. Since Bruch’s membrane acts as a natural barrier to spread of cells towards choroid, these cells then gradually rests under the RPE. Gradually over time with varying degrees of RPE atrophy, a typical ‘leopard spot’ appearance is seen. An important clinical sign is absence of cystoid macular edema in spite of long standing cells.

PVRL comprised mainly of B cell has increased interleukin 10 levels (IL10) in aqueous and vitreous. IL10 in turn helps in B cell proliferation and decreases host immunity. This explains the absence of typical inflammatory signs like redness, pain and cystoid edema.11

<table>
<thead>
<tr>
<th>Suspect PVRL when</th>
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<tr>
<td>1) Regression of anterior/ vitreal cells with steroids which reappears on withdrawal specially in an older person</td>
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<tr>
<td>2) Multiple previous visits to different ophthalmologists with waxing and waning clinical course</td>
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<td>3) Recent behavioral and cognitive changes in a patient with clinical signs of uveitis</td>
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<tr>
<td>4) Presence of vitreal cells in a ‘aurora borealis’ or ‘string of pearls’ fashion</td>
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<td>5) Multiple confluent subRPE yellowish deposit with typical absence of redness/ pain</td>
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<tr>
<td>6) In all patients with recurrent uveitis older than 50 years with varying response to steroids</td>
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**Figure1:** Typical appearance of subRPE lymphoma
DIFFERENTIAL DIAGNOSIS

Being a great masquerader, following ocular conditions needs to be kept in mind when examining a case of PVRL

| Inflammatory conditions: | 1) Intermediate uveitis |
| | 2) Posterior uveitis |
| | 3) Multifocal choroiditis |
| | 4) APMPPE |
| | 5) Frosted branch angitis |
| | 6) MEWDS |

| Infectious entities | 1) Tuberculosis |
| | 2) Cytomegalovirus infection |
| | 3) Toxoplasmosis |
| | 4) Acute retinal necrosis |
| | 5) Herpetic uveitis |

| Neoplastic conditions | 1) Choroidal melanoma |
| | 2) Uveal metastasis |

IMAGING IN PVRL

Although a typical clinical appearance of yellowish subretinal / subRPE deposits is very much suggestive of PVRL, early retinal lesions are very much confusing even to the best of the clinician.

**Fundus Autofluorescence (FAF):** Since the lymphoma cells rests
in the subRPE space, FAF plays an important role. Typically on FAF, early lesions appear hyper-autofluorescent and as the overlying RPE undergoes atrophy FAF lesions become to hypo autofluorescent. FAF findings are not pathognomical although its useful for follow up to detect new lesions and should be corroborated with other imaging modalities.¹²

**Optical Coherence tomography (OCT):** No other retinal imaging modality provides so many novel markers for early detection of PVRL as does OCT. Since the pathology in PVRL is mainly concentrated in the subRPE space, OCT scans specifically documenting the same is useful. Lesions may not be in the macula; hence it is important to convey to the OCT technician the area in retina to scan through. Multiple nodular saw tooth like elevations of RPE with hyper-reflective areas beneath RPE is typical which denotes infiltration of lymphoma cells. As the disease progresses, there occurs disruption of the interdigitation and ellipsoid zone with multiple hypereffective and confluent bands in the subretinal space.¹³ Presence of these hypereffective bands along with nodular RPE elevations have reported to be typical of PVRL (figure 3).¹³ Vertical hyper-reflective lesions (VHRL) is a recent OCT biomarker described in PVRL.¹⁴ These are hypereffective columnar lesions extending from inner retina (ganglion cell/ nerve fibre layer) to RPE. Pathophysiology of VHRL is not known although they have been postulated to be early lymphocytic infiltrations of sensory retina

**Fundus Fluorescein angiography (FFA):** FFA features of PVRL are not diagnostic. Window defects, staining and blocked fluorescence are some of the features seen in PVRL. Features of leakage are typically not observed. Capillary dropout a feature seen in FFA has been described by Ramesh et al secondary to tumor infiltration of sensory retina leading to ischemia.¹⁵ Although an interesting find it may not be pathognomic.

**Ultrasound (USG):** B scan USG yields no additional result in cases of PVRL although it may be an useful adjunct in cases of optic nerve infiltration.

**Neuroimaging:** 16-34% of PVRL patients will have concurrent CNS disease. When suspecting any case of PVRL, it is important to order a MRI of the brain with orbit with contrast. Lesions are typically hypodense on T1 and hyperdense on T2 weighted scales. Since
absence of CNS lesions does not rule out the pathology in CNS, an MRI should be ordered every 3 months for the first 2 years followed by at every 6 months thereafter.\textsuperscript{9}

![Figure 3: Typical OCT in PVRL showing subRPE hyperreflectivity and nodular RPE elevations](image)

**DIAGNOSTIC TESTS IN PVRL**

Like any other cancer in the body a definitive diagnosis is important to start treatment; and herein lies the most difficult aspect when dealing with patients of PVRL. Vitreous being the most accessible and common site for PVRL, vitreous biopsy is the most preferred method to diagnose or refute a case.

**Method of biopsy:** Before performing biopsy, it is absolutely necessary to stop any form of steroids be it oral or topical. Although no fixed schedule is prescribed, a general consensus is to withdraw steroids for a minimal of 2 weeks. Biopsy can be performed either with 23 or 25 gauge vitrectomy system. Whatever the gauge, while performing the same a low cut rate (approximately 600 cpm) is essential to prevent mutilation of lymphoma cells. Initially undiluted sample is taken. To maximize undiluted vitreous yield once the globe starts collapsing, air can be introduced through the infusion cannula and vitrectomy can proceed under air. Once sufficient material is obtained, fluid can then be turned on. It is important to send both undiluted and diluted fluid for further test, including the fluid in the cassette. Sample should ideally be processed with an hour (preferably $< 30$ min) to get the best possible outcome. In case no in-house pathologist is available, sample can then be send via RPMI( Rosewell Park Memorial institute) solution or HOPE solution( Hepes Glutamic acid buffer mediated solution).
organic solvent effect) in a ratio of 2:1. If none exists, commercially available Ctyolyt solution can be used. It is best not to transfer sample in alcohol solution. It is important to remember that lymphoma cells are fragile and gets destroyed easily, hence prior intimation to pathologist is crucial. If vitreous yield is less a retinal biopsy with aspiration of subretinal material is warranted.

Sample obtained ideally needs to undergo five assessments. They are a) cytological b) immunohistochemical analysis c) Flow cytometry d) Molecular analysis e) assessing cytokine levels.

Cytological exam is the most commonly performed test whereby a morphological assessment of the vitreous sample is performed. Typically pathological lymphoma cells appear large with a scanty cytoplasm and prominent nucleus and nucleoli. If seen, diagnosis of PVRL is certain, but alone, confirms < 50% cases. Poor tissue handling, improper trained personnel, lack of sample are some of the causes for a negative result.

Cytokine analysis is another test commonly performed. That lymphoma cells generate more of IL10 than IL6 forms the basis of this test. IL6 levels are seen more in uveitic pathologies and comparing the two helps not only to differentiate between the two but also support a diagnosis of PVRL. A ratio of IL10: IL6 >1 supports a diagnosis of PVRL although IL10 levels have also been higher in uveitic entities. That IL10 levels are variable also puts this test in the spotlight. Immunohistochemical analysis and flow cytometry are useful tools to study cell surface markers mainly CD20 positivity. CD20 positivity not only confirms presence of B type lymphoma cells but also is useful in therapeutic intervention, as we will see later.

Molecular analysis by PCR to confirm clonal expansion of B cells is newer test being employed to confirm diagnosis of PVRL.

A recent marker known as myeloid differentiation primary response 88 protein (MYD88) and its mutation detected by PCR analysis is emerging to be an important diagnostic tool to confirm cases of PVRL. Detecting MYD88 mutation is specially important when routine cytological and immunohistochemical tests yield negative results.
### Checklist before Vitreous Biopsy

1. Stop steroids in any form for at least 2 weeks
2. Inform pathologist before sample is taken
3. Use a cut rate of 600cpm
4. Do not transfer sample in alcohol based solutions
5. Send undiluted, diluted and the entire cassette fluid for analysis
6. Use RPMI, HOPE or cytolyt for transfer

### TREATMENT

Unlike other ocular tumors, treatment in a case of PVRL needs a thorough systemic evaluation to rule out CNS involvement.

To begin with laterality of the condition along with whether CNS is involved or not is of paramount necessity.

Broadly treatment can be divided into local and systemic therapy.

Local therapy includes intravitreal agents and ocular radiation. Systemic therapy involves use of chemotherapeutic agents, whole brain radiotherapy (WBRT) and stem cell therapy. Treatment strategies are not universal and the following description provides an approximate guide.

**Uniocular disease without CNS involvement:**

The choice is local intravitreal agents. Most common drugs are Methotrexate (MTX) and Rituximab although Melphalan use has also been reported.20 Intravitreal agents are given under aseptic and sterile environment preferably in a OR setting like any other retinal intravitreal injections. Anterior chamber paracentesis prior to injection is not must.

**IVM (Intravitreal MTX):** MTX is generally used as 400µg/0.1m dose. The ideal regimen involves: INDUCTION phase comprising of bi-weekly injection for 1 month, CONSOLIDATION phase of weekly injection of 2 months and MAINTENANCE phase of monthly injection for 9 months. Due to its large number of injections, many patients opt out. Most common side effect of IVM is corneal epithelial toxicity, which is reversible once injections are withdrawn.
A mean of 6.4 injections are needed to induce remission \( [21] \)

**IVR:** Intravitreal Rituximab. As discussed earlier, CD20 positivity plays an important role in therapeutics. Luckily and thankfully 95% of PVRL are large B cell with CD20 positivity. Rituximab, a monoclonal antibody against CD20 has been in use and slowly gaining popularity due to its less toxic effects and less number of injections. Mechanism of action is disputed although it is believed to act by inducing apoptosis and complement mediated cell death.\( [22] \) Regimen involves weekly injections for 4 weeks. Most common side effect is increase in intraocular pressure. With either of agent, recurrences have been reported and once the same happens, its then time to switch treatment regimen.

**Ocular radiation:** Once the most common modality of treatment, ocular radiation is now reserved in unioocular condition when intravitreal agents fail or PVRL recurs after completion of intravitreal regimen. Current regimen uses 30-36 Gy.\( [23] \) Complication of radiation includes cataract, radiation retinopathy and neuropathy. These complications have been seen even with dose as low as 20Gy.

**Local ocular treatment does not alter survival time neither does it prevent CNS or other eye disease.**

If during the course of treatment, CNS disease occurs or the other eye gets affected, immediate systemic treatment in consultation with systemic oncologist is warranted. Systemic therapy with chemotherapy in unioocular disease without CNS involvement is now being thought of as an alternate as it offers the option to treat before CNS disease manifests.

**Bilateral ocular disease without CNS involvement**

With bilateral disease it is a question of time before the CNS gets involved, hence the need for systemic therapy. Systemic chemotherapeutic agents include MTX, Rituximab, Ibrutinib or Pomalidomide. Lenalidomide a newer drug with immunostimulant property holds promising results for systemic therapy.\( [24] \) Local therapy with intravitreal agents is also used along with systemic therapy in bilateral disease.
Ocular disease with concurrent CNS involvement

With primary CNS involvement multiple therapeutic strategies gets involved. Systemic chemotherapy, WBRT is used initially. Stem cell therapy is currently employed when the initial treatment fails with or without use of high dose MTX.

Role of therapeutic vitrectomy: Apart from a few incidental case reports, complete vitrectomy as a therapeutic modality has never been looked into. The author here and many other retinal surgeons will however concur regression of ocular disease when a complete vitrectomy is performed. It is postulated a complete vitrectomy not only reduces ocular load but also helps better penetration of systemic chemotherapeutic agents. It is preferable to do a complete vitrectomy when doing a vitreous biopsy although vitrectomy alone should never be used as a sole treatment method.

Emerging new treatment modalities

Stem cell therapy (SCT) has been particularly useful in refractory and recurrent systemic CNS lymphoma. SCT has been shown not only to induce remission in refractory cases but also increases overall survival rate.

Role of Ibrutinib: Ibrutinib, a chemotherapeutic agent originally used for chronic myeloid leukemia, has shown promising results in systemic lymphoma. Its particularly invaluable as ibrutinib has been shown to cross both the blood retinal and blood brain barrier and is available as an oral agent. It’s role in PVRL will need further research.

SUMMARY

PVRL is a unique ocular condition where the role of an ophthalmologist in its diagnosis cannot be over emphasized. Keeping it as a differential whenever examining any elderly patient with recurrent uveitis will surely help in detecting it early. Most importantly taking second opinion from our colleagues whenever in doubt, rather than empirically starting steroids will also help to catch it early.

REFERENCES

1) Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma
Primary Intraocular Lymphoma


Vascular Tumors of the Retina and Choroid

Pradeep Sagar, P. Mahesh Shanmugam

Vascular tumors of the retina and choroid are rare intraocular tumors. Some are congenital and some are acquired. Some are associated with systemic syndromes and can be the first clinical sign of underlying systemic abnormality. All the vascular tumors of the retina and choroid are benign tumors and do not exhibit malignant potential. Some tumors are stable with minimal or no visual symptoms. But some tumors can lead to retinal detachment (RD) and neovascular glaucoma (NVG). The vascular tumors of the retina include retinal capillary hemangioblastomas (RCH), cavernous hemangioma of the retina and optic disc and vasoproliferative tumor of retina. Vascular tumors of the choroid comprise of diffuse and solitary choroidal hemangioma. In this chapter, we will discuss the clinical features, investigations, differential diagnosis and the management of these vascular tumors.

VASCULAR TUMORS OF THE RETINA

Retinal capillary hemangioblastoma

Introduction

Retinal capillary hemangioblastoma is a benign vascular tumor composed of endothelial cells, pericytes and foamy stromal cells. RCH may occur as an isolated lesion or as a part of von- Hippel Lindau (VHL) syndrome. The mean age at diagnosis is 18 years in patients with VHL and 36 years for sporadic cases. Approximately one-half of patients with VHL have bilateral tumors and one-third have multiple tumors. In a patient with solitary RCH, the risk of developing VHL is 45% if the patient is <10 years of age and decreases to 1% if the age at diagnosis is > 60 years. RCH can be associated with other systemic conditions such as Marshall-Stickler syndrome. RCH can be seen in the peripheral and mid-peripheral retina or in the juxta papillary region.
Clinical features

Symptoms

Peripheral RCH

- Can be asymptomatic: It is diagnosed during routine fundus evaluation or during screening of patients with VHL.
- Decrease in visual acuity or metamorphopsia: It can be due to subfoveal fluid accumulation, macular exudation or tractional RD.
- Floaters. They are seen rarely due to vitreous hemorrhage.
- Visual loss. Visual loss can occur due to combined tractional-rhegmatogenous RD involving the posterior pole.

Juxta papillary RCH:

- Usually asymptomatic.
- Decrease in visual acuity or metamorphopsia: Due to peri-papillary exudation and macular edema.

Signs

Peripheral RCH

Smaller RCHs appear as a yellow spot between a feeding arteriole and a draining venule.

Larger ones appear as orange-red circumscribed lesions with a dilated tortuous feeding arteriole and a draining venule (Figure 1). Presence of dilated pair of vessels in the posterior pole and macular exudation should prompt one to examine the periphery for the presence of RCH (Figure 2 and 3).

The most common retinal location of these tumors are in the superotemporal quadrant (42%) and in the midperiphery (58%).

Two forms of disease exist.

A. Exudative form: Exudation at the macular region is due to subretinal migration of lipid from the peripheral tumor. Untreated cases develop exudative RD (Figure 2).

B. Vitreo-retinal form: The proliferation of the epiretinal membrane causes tractional detachment of macula and decreased vision. Traction on the RCH can lead to “free-floating” tumor in
the vitreous, vitreous hemorrhage and combined traction-rhegmatogenous RD (Figure 4).

**Figure 1:** Fundus photograph of a small RCH (1A) seen as a yellow spot (within circle) between a feeding arteriole and a draining venule (arrows). Fundus photograph of a large RCH (1B). Tumor is orange red in colour.

**Figure 2:** Exudative form of RCH. A larger RCH is seen in the inferotemporal quadrant with extensive hard exudates at the fovea.

**Figure 3:** Fundus photograph of posterior pole (3A) showing dilated pair of vessels (arrow). Montage (3B) shows a RCH communicating with this pair of vessels.
Figure 4: Fundus photograph of vitreo-retinal form of RCH showing extensive fibrous proliferation (arrow). Multiple RCH (circles) are seen in the adjacent area.

**Juxtapapillary RCH**

Juxtapapillary RCH is ill-defined and involves an eccentric part of the optic disc. It differs from the peripheral RCH in that, a definite feeder arteriole or a draining venule is not usually seen. It can be classified as:

A. Exophytic: Exophytic tumor grows on the surface of the retina and resembles the peripheral RCH. It is well defined and is orange-red in color.

B. Endophytic, sessile: The sessile tumor grows within the retinal layers. The sessile and endophytic tumors do not show the characteristic fundus appearance and can be misdiagnosed as papillitis, unilateral papilledema, choroiditis, choroidal hemangioma or choroidal neovascularization. (Figure 5)

Both the exophytic and the endophytic form can be asymptomatic. Both can lead to peripapillary exudation and macular edema.

Figure 5: Fundus photograph of juxtapapillary RCHs. Exophytic form (5A) and endophytic form (5B).
Without treatment, most eyes with RCH progress to total RD, NVG and a painful blind eye.

Anterior hyaloid proliferation resulting in ciliary body traction and subsequent hypotony can result in phthisis bulbi.

**Investigations**

Clinical examination with slit-lamp biomicroscopy and indirect ophthalmoscopy can detect larger RCH. But smaller RCH can be missed on clinical examination and needs investigation.

**Fundus fluorescein angiography (FFA)**

Retinal capillary hemangioblastoma shows intense hyperfluorescence in the early phase and the tumors either leak profusely or stain without a significant leak in the late phases. The paired vessels are well delineated. (Figure 6)

![Figure 6: Fundus fluorescein angiography of RCH. Early phase (6A) shows hyperfluorescence and late phase (6B) shows leak.](image)

A fundus fluorescein angiogram may be necessary to identify early lesions that are not visible on clinical examination.

Wide field FFA is helpful in identification of more peripheral tumors compared to clinical examination and conventional FFA.8

**Optical coherence tomography (OCT)**

In some cases, OCT aids in the detection of small RCHs that appear as retinal thickening with mild shadowing of the underlying structures.9 It helps to differentiate exophytic and endophytic forms of the tumor.
Optical coherence tomography helps in demonstration of intra retinal and sub retinal fluid due to extravasation from the tumor (Figure 7).\textsuperscript{10} It helps in the detection of epimacular membrane and traction on macula. It also helps in monitoring progression and to plan surgical intervention (Figure 8).

It aids in the assessment of response to the treatment such as the resolution of intra retinal and sub retinal fluid.

**Figure 7:** OCT through RCH. Peripheral RCH (7A): Tumor is seen as a hyperreflective lesion with shadowing. Adjacent retina shows schisis of inner retina due to exudation. Juxtapapillary RCH (7B): Macular schisis due to exudation is seen.

**Figure 8:** Fundus photograph (8A) and OCT (8B) of the posterior pole of the same eye in figure 4. Extensive proliferation of the posterior hyaloid with partial detachment is seen on OCT. OCT shows preserved foveal architecture.

**Optical coherence tomography angiography (OCTA)**

OCTA allows visualization of the depth of the lesion in the retina in addition to its vascularity. These tumors appear to arise from the
superficial retinal capillary plexus and appear bright on OCTA due to their rich vascularity (Figure 9). Tumors that were indistinct on clinical examination were picked up by OCTA, similar to fluorescein angiography (FFA). Current limitations of OCTA such as small field of view and difficulty in imaging the retinal periphery limit its role as a screening tool. It helps in the assessment of response to therapy such as a decrease in vascular density in larger RCH. In cases of smaller tumors, scarring prevents identification of incomplete treatment but OCTA helps to identify vascular network in cases with residual disease.11-13

Figure 9: OCTA of RCH (9B). Tumor shows compact vascularity. Feeding and draining vessels can be identified. Reference color photograph (9A)

Ultrasonography (USG)

It is helpful in the assessment of retinal status if fundus is not visible.

Differential diagnosis

The peripheral RCH may be misdiagnosed as

- Coat’s disease: Exudation in Coat’s disease can mimic RCH. In Coat’s disease paired dilated vessels are not seen. Peripheral vascular telangiectasia is seen in Coat’s disease whereas orange-red mass with feeder vessels is seen in RCH.

- Racemose angioma: Dilated tortuous vessels seen in retinal angioma can be mistaken as feeder and draining vessels of RCH. But no tumor is seen between the arteriole and venule in racemose angioma in contrast to RCH (Figure 10).

- Vasoproliferative tumor of retina (VPTR): Pinkish yellow vascular mass in the retinal periphery seen in VPTR can mimic RCH. In VPTR the tumor is usually seen in the inferior retina. The feeder
vessels are minimally dilated. It is usually solitary whereas RCH associated with VHL is multiple.

- **Retinal cavernous hemangioma:** Feeder and draining vessels are seldom seen in cavernous hemangioma. It is composed of multiple grape-like clusters of aneurysmal dilatation.

- **Familial exudative vitreo-retinopathy (FEVR).** Sub retinal exudates can be seen in FEVR that can mimic RCH. But peripheral avascular retina is seen in FEVR. Feeder vessels, draining vessels and tumor is not seen in FEVR.

**Figure 10:** Color photograph of racemose angioma. The dilated and tortuous vessels communicate with each other without any intervening tumor in contrast to RCH.

*Juxta papillary RCH:*

The endophytic tumor can simulate papilledema, optic neuritis, peripapillary choroidal neovascular membrane and optic disc granuloma. OCT can identify the intra retinal location of RCH. The retinal pigment epithelium is intact in RCH.

**Treatment**

The choice of treatment is determined by the size, location and associated findings such as sub retinal fluid, retinal traction and the visual potential of the eye. Early treatment of RCH leads to better visual results (Figure 11).14
Observation: Careful observation in a compliant patient can be recommended if the RCH is very small (up to 500 microns) and is not associated with exudation or sub retinal fluid. Juxta papillary tumors can be observed as they tend to remain stable.

Laser photocoagulation: Peripheral RCH without RD are treated with laser photocoagulation. It is preferable to use green, yellow or blue-green wavelength to treat these lesions, as red or infrared lasers may not be absorbed well by the tumor (Figure 12 and 13).

- Tumors < 2 mm in diameter are treated with direct laser photocoagulation.
- For tumors 3-5 mm in diameter, it is preferable to try occlusion of the communicating vessels – the arteriole first, followed by the tumor and the venule. Treating the feeder vessel (artery) leads to a reduction in blood flow velocity and aids in the generation of heat within the tumor during laser. Larger RCH can be treated in multiple sessions. Complications such as hemorrhage from the tumor and secondary RD may occur after laser photocoagulation.

Cryotherapy: For tumors larger than 5 mm, it is preferable to use triple freeze thaw cryotherapy. Complications such as exudative RD and hemorrhage can occur after cryotherapy. Treatment of peripheral large tumors can result in vitreoretinal proliferation, resulting in traction or combined tractional-rhegmatogenous RD, vitreous hemorrhage and in some cases circumferential fibro vascular proliferation of the vitreous base. The development of fibro vascular proliferation is multifactorial. It is due to VEGF.
secretion by the tumor, altered vitreoretinal interface and an increase in inflammation.

**Figure 12:** Macular OCT of the same eye in figure 9. Pre-treatment image (12A) shows macular edema with subfoveal fluid. Resolution of subretinal fluid (12B) after laser photocoagulation of the tumor.

**Figure 13:** Pre-treatment FFA of small RCHs (13A). Tumors replaced by scarring after laser photocoagulation (13B).

- Plaque brachytherapy: Brachytherapy of peripheral large tumors is a viable option and offers the ability to treat tumors elevated from the retinal surface due to vitreous traction. A radiation dose of 1250-2500 cGy delivered to the apex of the tumor (500-800Gy scleral dose) results in regression of the tumor.\(^{16,17}\) Multiple large tumors in an eye can be treated in a single session by rotating the plaque to treat an untreated tumor once the desired dose of radiation has been delivered to one tumor. A low penetrance plaque such as ruthenium 106 is preferable in such situations to limit the overall radiation dose delivered to the eye (Figure 14).
Vascular Tumors of the Retina and Choroid

Figure 14. Fundus photograph of a patient with large RCH (14A). The tumor was treated with plaque brachytherapy. Complete regression of the tumor with sclerosis of feeding and draining vessels is evident (14B).

**Juxta papillary RCH**

- Photodynamic therapy (PDT): PDT is the preferred modality to treat Juxta papillary RCH. Standard fluence PDT can lead to regression of the tumor and resolution of the macular edema and detachment. However, it may be associated with a risk of retinal vascular occlusion and optic disc ischemia.\(^{18}\)

- Transpupillary thermotherapy (TTT): TTT can be employed to treat juxtapapillary RCH considering its relatively non-destructive characteristics. In a case report, three sessions of TTT resulted in improvement in the visual acuity and decrease in hard exudates.\(^{19}\)

If the tumors are associated with bullous RD, drainage of the subretinal fluid and cryotherapy may be necessary. Advanced vitreoretinal form of the disease with tractional or rhegmatogenous RD requires vitrectomy.\(^{20}\) There are multiple reports of tumor resection during vitrectomy.

Over time we have moved away from aggressive vitreoretinal surgical techniques to multimodal therapy to treat advanced disease with multiple large RCH with vitreoretinal complications. We employ brachytherapy to treat elevated or large tumors that could not be treated with cryotherapy or laser photocoagulation. Judicious vitrectomy to remove relevant vitreoretinal traction, such as that exerting traction on the posterior pole is employed. Scleral buckling is employed to support elevated RCH and peripheral vitreoretinal traction (rather than resort to resection of tumors or retinectomy). We are successful in stabilizing a subset of an advanced vitreoretinal form of VHL with this technique (Figure 15).
Vascular Tumors of the Retina and Choroid

Figure 15: Ultrasound image of the same eye in figure 14 after the development of retinal detachment with vitreous hemorrhage (15A and 15C). Patient underwent vitreo-retinal intervention with encerclage. Post-operative images (15B and 15D) showing attached retina. Break (within circle) can be seen posterior to the tumor.

**Other treatment options**

- Bevacizumab and ranibizumab have shown some beneficial effect on subretinal exudation and cystoid macular edema associated with juxtapapillary RCH and some peripheral retinal hemangioblastoma. Multiple injections are required and treatment is often combined with PDT and intravitreal or sub-tenon’s triamcinolone. The efficacy appears to be limited to the exudative component and does not bear any significance in decreasing the size of the lesions or the occurrence of newer ones. Anti-VEGF agents are useful to treat small lesions and as adjuncts in treating exudation associated with larger lesions.21,22

- Intravitreal dexamethasone and triamcinolone are shown to be helpful in decreasing the macular edema in combination with PDT.23,24

- Trans-retinal feeder vessel ligation combined with vitrectomy and photocoagulation has been reported in the literature and is performed infrequently by the authors.25 While a successful ligation of the feeder vessel could be achieved and the tumor appeared to regress on short-term follow-up, the tumor generated
new feeder vessels over time. Vitrectomy with excision of the tumor and extensive intraocular diathermy are other techniques that have been attempted to treat recalcitrant tumors. However, these extensive surgeries will not yield long-lasting results due to the severe vitreous base proliferation that occurs over time resulting in chronic hypotony.

- Proton beam irradiation and external beam radiotherapy are used as salvage therapy when other treatments fail.26

What’s new?

Submacular sclerosing capillary hemangioblastoma: It is a recently described entity. It is seen as a white yellow submacular lesion and it would be difficult to differentiate from other submacular lesions. It was confirmed based on the histopathological examination of the excised sample.27

Intra arterial bevacizumab: Catheterization of the ophthalmic artery and intra arterial injection of high dose bevacizumab monthly, for three months, was shown to be effective in stabilization of juxtapapillary RCH which was resistant to PDT.28

CAVERNOUS HEMANGIOMA OF THE RETINA

Introduction

Cavernous hemangioma of the retina is a rare vascular tumor and is more prevalent in females.29

The average age at presentation is 23 years. It is mostly unilateral with few reports of bilateral occurrences. Cavernous hemangioma of the retina is recognized as a phakomatoses with the involvement of the retina, skin and the central nervous system. It is inherited in an autosomal dominant pattern. Penetrance and expressivity are variable. The causative gene is localized to the locus 7q11-q22.30-32 Its pathogenesis is largely unknown. It can involve the optic disc, macula or peripheral retina.

Clinical features

Symptoms

- Peripheral tumors are asymptomatic. It can be diagnosed during
routine fundus evaluation.

- **Blurred vision or metamorphopsia:** Peripapillary and macular lesions and tumor complications such as intra-retinal hemorrhage at the macula, macular distortion due to the epiretinal membrane.
- **Poor vision:** Amblyopia in children may lead to poor vision.\(^{33,34}\)
- **Visual loss:** Rarely vitreous hemorrhage can result in visual loss.

**Signs**

Cavernous hemangioma appears as a cluster of dark red saccules with associated fibroglial proliferation within the inner retinal layers or on the surface of the optic disc (Figure 16).

![Figure 16: Fundus photograph of cavernous hemangioma of optic disc. (Image courtesy: Dr. Madhukumar and Dr. Surabhi Ruia)](image)

The lesions are variable in size and location and frequently follow the course of a major retinal vein.

No feeder arteriole or draining venule is usually seen though some authors have noted twin vessels to be associated with this tumor.\(^{35}\)

They are usually non-progressive. A few may enlarge and lead to vitreous hemorrhage.

Epiretinal membranes and fibroglial proliferation may result in foveal ectopia.\(^{34}\)

Massive growth of the tumor up to the iris root with concomitant vitreous hemorrhage and hyphema is reported.\(^{5}\)

We reported a case of cavernous hemangioma of the optic disc with recurrent sub retinal hemorrhage in a patient with immune thrombocytopenia purpura.\(^{36}\)
Diagnosis

The diagnosis is mainly based on clinical appearance. Ancillary testing would be required in atypical cases.

*Fundus fluorescein angiography:*

Fundus fluorescein angiographic appearance of cavernous hemangioma is quite characteristic (Figure 17). Cavernous hemangioma has a sluggish circulation. It leads to the separation of the blood cells from the plasma that settles down inferiorly within the saccule. Fluorescein enters the saccule slowly and fills the supernatant plasma, giving an appearance of ‘fluorescein cap’. 37

![Figure 17: Early (17A) and late (17B) phase FFA images of cavernous hemangioma of optic disc. Late phase image shows typical ‘fluorescein caps’ (arrows). (Image courtesy: Dr. Madhukumar and Dr. Surabhi Ruia)](image)

*Optical coherence tomography:*

On cross sectional OCT, vesicular lesions with hyper reflective margins are seen corresponding to the saccules. Hyper reflective material is seen within the vesicle in the dependent part due to the separation of plasma and red blood cells. 38 OCT helps in detection of epimacular membrane and traction on macula. It also helps in monitoring progression and plan surgical intervention (Figure 18).

*Optical coherence tomography angiography:*

In a few reports, flow signal is detected within the saccular dilatation with the presence of branching vessels extending into the lesion. 39,40 In one case report, it was seen as irregular saccular dilatation of the venous system. 41 In another report, the saccular dilatation was not seen on OCTA. It is postulated to be due to the slow flow within the saccules. 38
Figure 18: Nasal cavernous hemangioma with epimacular membrane. OCT through the macula confirms the absence of macular traction.

Differential diagnosis

The fundus appearance and FFA are quite classical. Rarely the cluster of saccules can be confused with a cluster of aneurysms seen in:

- Adult onset Coat’s disease: In adult onset coat’s disease multiple discrete aneurysms and hard exudates are seen, which is not seen in cavernous hemangioma.
- Leber’s miliary aneurysm.

Treatment

Cavernous hemangioma of the retina is usually stable and can be observed.

Some cases can develop vitreous hemorrhage. In such cases, cryotherapy, laser photocoagulation, low energy plaque and vitrectomy to clear the vitreous hemorrhage may be employed.

Vitrectomy may be considered for relieving macular traction secondary to epimacular membranes. Associated retinal changes such as cystoid macular edema may, however, limit visual recovery.
We treated a patient with recurrent sub retinal and vitreous hemorrhage secondary to a cavernous hemangioma of the optic disc with standard photodynamic therapy (PDT) after the resolution of hemorrhage. The cavernous hemangioma regressed after PDT (Figure 19).36

Figure 19: Color photograph (19A), FFA (19C), indocyanine green angiography (19B) of cavernous hemangioma of disc showing subretinal and vitreous hemorrhage. Complete resolution of the tumor with gliosis after photodynamic therapy (19D).

VASOPROLIFERATIVE TUMOR OF THE RETINA

Introduction

Vasoproliferative tumor (VPT) of the retina is a rare intraocular tumor. It can be primary or secondary. Primary VPT is more common than secondary tumor. In a large case series of 103 patients, 74% of cases were primary.43 But in contrast to western literature, in a series of 120 cases of VPT from the Indian population, only 40% of the cases were primary.44 In another series of 19 eyes with VPT from the Indian population, only 32% of the cases were primary.45 VPT can be solitary, multiple or diffuse. Most of the primary tumors are solitary (about 87%), whereas only half of the secondary tumors are solitary. Secondary tumors tend to be multiple and diffuse. Secondary tumors are seen in cases with underlying ocular conditions. The ocular diseases reported to be associated with VPT include retinitis pigmentosa, intermediate
uveitis, toxocarasis, toxoplasma retinitis, retinochoroidal coloboma, Coat’s disease, polypoidal choroidal vasculopathy, retinal vasculitis, traumatic chorioretinopathy, familial exudative vitreoretinopathy, regressed retinoblastoma treated with external beam radiotherapy, regressed melanoma, proliferative diabetic retinopathy treated with laser photocoagulation, X-lined retinoschisis related RD, Eales’ disease and open globe injury post scleral tear repair. Other reported associations include Waardenburg’s syndrome, bilateral occurrence in monozygotic twins, neurofibromatosis type I, hypertension.

VPT is mostly a pseudotumor. It is due to the reactive proliferation of blood vessels in response to retinal inflammation, injury or ischemia. The blood vessels proliferate in a loose glial matrix and form a vascular mass. Over time reactive gliosis exceeds the vascular component. So the pinkish yellow tumor turns into a yellow white tumor in the late stage. On histopathology, glial cells interlaced with a fine capillary network are seen. Dilated, hyalinized, partially occluded blood vessels, exudates, macrophages and foreign-body giant cells can be seen.

A staging system for VPT has been proposed

**Stage 1**
- 1a: VPT with focal exudates (<5 mm from the lesion)
- 1b: VPT with diffuse exudates (>5 mm from the lesion)

**Stage 2**
- 2a: VPT with remote exudates not involving the fovea
- 2b: VPT with remote exudates involving the fovea

**Stage 3**
- 3a: VPT with epiretinal membrane not involving the fovea
- 3b: VPT with epiretinal membrane involving the fovea

**Stage 4**
- 4a: VPT with RD not involving the fovea
- 4b: VPT with RD involving the fovea

**Stage 5**
- 5a: VPT with complications with visual potential (vitreous hemorrhage, neovascularization of the iris, secondary glaucoma)
5b: VPT with complications with no visual potential or painful blind eye

**Clinical features**

**Symptoms**
Blurred vision: can occur due to macular edema and pre macular fibrosis.

Visual loss: Can occur due to sub retinal exudation, hemorrhage, tractional RD and vitreous hemorrhage.

**Signs**
In western literature, the mean age of presentation is in the third to fourth decade of life. In a series of 120 cases of VPT from the Indian population, the mean age at presentation for primary VPT was 48 years. In secondary tumors, the bimodal age distribution was seen, beyond the sixth decade and in the first-second decade of life. Men and women are equally affected.

VPT appears as a pinkish-yellow vascular mass commonly located anterior to the equator typically located in the inferior retina. Older tumors can appear yellow white in color (Figure 20).

![Figure 20: Vasoproliferative tumor of retina. Color photograph of posterior pole showing extensive subretinal exudates (20A). Yellowish white tumor with surface vascularity is seen in the inferior quadrant (20B). FFA (20C and 20D) showing extensive leak from the tumor.](image-url)
Vascular Tumors of the Retina and Choroid

Vascular Tumors of the Retina and Choroid

VPT has normal caliber feeder vessels and is seen entering the posterior aspect of the tumor. The feeder vessels are not dilated and tortuous as in RCH.

_Tumors may be surrounded by pigment hyperplasia._

Sub retinal exudation is common and extensive in VPT and is seen in approximately 80% of cases.

Macular edema, epimacular membrane, exudative and tractional RD, vitreous hemorrhage and neovascular glaucoma are other reported complications of VPT.

Signs related to the underlying ocular condition can also be seen.

**Investigations**

**Fundus fluorescein angiography**

The tumors are commonly located in the retinal periphery. If it is visible on angiography, tumors demonstrate early phase hyper fluorescence (due to rapid filling) and diffuse leak in late phase (Figure 20).

Wide field angiography: It is helpful in imaging the peripheral tumors.

**Ultrasonography**

Vasoproliferative tumor is seen as a solid mass elevated from the retinal surface. Internal reflectivity can be low, medium or high and there is no distinct pattern. It can detect exudative RD.

**Optical coherence tomography**

Optical coherence tomography is helpful in the detection of macular edema and epiretinal membrane. If the tumor is captured, irregular thickening of the retina on the surface of the tumor is seen.

**Treatment**

Observation: Considering its peripheral location, smaller tumors with limited exudation can be observed.

Larger tumors and tumors associated with visual loss due to exudation, macular pucker, vitreous hemorrhage, RD need treatment. The treatment options include:
**Triple freeze thaw cryotherapy**

Trans conjunctival triple freeze thaw cryotherapy is the most commonly used modality to treat the peripheral tumors. It is found to be successful in a few case series (Figure 21).\textsuperscript{43}

![Figure 21: Vasoproliferative tumor of retina with subretinal exudates (21A) and macular edema (21E). The tumor was treated with triple freeze thaw cryotherapy and intravitreal ozurdex was administered. Decrease in subretinal exudates (21B) and macular edema (21F) is seen. Reduction in tumor vascularity is seen (21D).](image)

**Laser photocoagulation and trans pupillary thermotherapy**

Confluent laser spots are applied directly over the tumor surface. It is found to be successful in smaller tumors.\textsuperscript{43}

**Plaque brachytherapy**

Iodine I-125 and ruthenium-106 brachytherapy are reported to be useful in the treatment of VPTR.\textsuperscript{54,55,56} In a series of 30 eyes with mean tumor thickness of 3.7 mm (range: 2.5-6.3 mm) treated with I-125 plaque, tumor regression was seen in 97% of the eyes, complete resolution of retina detachment was seen in 65% of the eyes and visual acuity improvement or stabilisation was seen in 77% of eyes.\textsuperscript{54}

In a series of 35 patients with a mean tumor thickness of 2.8 mm treated with Ru-106 plaque, tumor activity was controlled in 88.6% of the cases. A slight reduction in visual acuity was noted.\textsuperscript{55}
Epiretinal gliosis, transient vitreous haemorrhage and cataract were seen.

**Photodynamic therapy (PDT)**

Few case series with different protocols of PDT are used in the treatment of VPT. In a series of three eyes with VPT treated with intravenous injection of 6 mg/m² body surface area of verteporfin and a dose of 100 J/cm² at 689 nm delivered in 166 seconds, reduction in the size of the tumor and resolution of macular hard exudates were seen in all the cases.\(^5\) In another report of VPT treated with the dose of 100 J/cm² delivered over 83 seconds, involution of tumor and improvement in visual acuity was seen.\(^5\)

**Anti-VEGF agents**

Immunohistochemistry of a resected VPT shows strong immunoreactivity to VEGF.\(^5\) So bevacizumab is used as a treatment option in a few small case series. In a series of 9 eyes with VPT treated with one injection of 1.25mg bevacizumab, 2 small tumors regressed completely, but additional therapy was required for the large tumors. Improvement in visual acuity and central retinal thickness were noted.\(^5\)

In a series of 6 eyes treated with bevacizumab, a temporary reduction in tumor thickness was seen in 3 eyes. But there was no statistically significant change in visual acuity or tumor thickness in the long term.\(^6\)

Based on the available evidence, bevacizumab can be used as an adjunct to decrease macular edema and neovascularisation in VPT along with an additional treatment modality.

**Indocyanine green (ICG) mediated photothrombosis**

In this technique, 1mg/kg of ICG is administered intravenously. Thirty minutes later, multiple, confluent, 810 nm diode laser spots are applied over the surface of the tumor. ICG dye in the tumor vessels absorbs the laser energy and leads to thrombosis of tumor vessels. In a case report of one VPT treated with 2 sessions of ICG mediated photothrombosis, complete resolution of the tumor was noted.\(^6\)
**Systemic infliximab**

Infliximab is an anti-tumor necrosis factor monoclonal antibody. In a single case report, when infliximab was administered to treat a patient with collagen vascular disease, incidental regression of bilateral VPT was seen. But there is no evidence to prove its efficacy in the treatment of VPT.

**Vitrectomy**

Vitrectomy is indicated in cases with macular pucker, tractional RD, vitreous hemorrhage. After vitrectomy the tumor is treated with cryotherapy or laser photocoagulation.

Some surgeons consider resection of the tumor. In a comparative study of 17 eyes, the tumor was resected in 8 eyes and was conservatively treated in 9 eyes. In the group with conservative treatment, 33% of the cases had tumor activity. Visual acuity improvement was better in the tumor resection group than the conservative group.

**Enucleation**

May be required in cases with NVG.

There are no established criteria to guide treatment. To summarise:

- Smaller tumors with the absence of overlying sub retinal fluid can be managed with laser photocoagulation or transpupillary thermotherapy.
- Larger lesions with overlying sub retinal fluid can be treated with cryotherapy.
- Thicker tumors (>2.5mm thick) need plaque brachytherapy.
- Intravitreal triamcinolone or dexamethasone implant can be used to treat macular edema and exudation.
- Anti-VEGF agents can be used to treat neovascularisation and macular edema.
- Vitrectomy is indicated to treat secondary complications.
- Photodynamic therapy and ICG mediated photothrombosis have shown promising results in treating larger tumors.
CIRCUMSCRIBED CHOROIDAL HEMANGIOMA

Introduction

Circumscribed choroidal hemangiomas (CCH) are relatively rare vascular hamartomas usually diagnosed in the second and fourth decade of life.\textsuperscript{66} The tumor is commonly unilateral and unifocal. Three cases of bilateral CCH are reported so far in the literature.\textsuperscript{67-69} It is usually sporadic and is not associated with systemic conditions. CCH is classified into three types: capillary, cavernous and mixed forms.\textsuperscript{66} The capillary form is rare and is composed of small blood vessels with inconspicuous endothelial cells separated by loose connective tissue. The cavernous form is more common and consists of large, thin-walled blood-filled vascular channels lined by a flat endothelium and separated by thin intervascular septa.\textsuperscript{66} The mixed type is common and is composed of both the capillary and cavernous form.\textsuperscript{66}

Clinical features

Symptoms

Asymptomatic in majority of the cases.

Poor vision due to induced hypermetropia and amblyopia in subfoveal tumors.

Blurred vision and metamorphopsia can occur due to accumulation of subfoveal fluid.

Vision loss can occur due to exudative RD. Rarely complicated cataract and neovascular glaucoma can develop in cases with long standing RD.

Signs

Circumscribed choroidal hemangioma is seen as a solitary, round or oval mass. The surface is usually smooth. The tumor is orange red in color.\textsuperscript{70-72} In long standing cases, reactive gliosis over the tumor can be seen (Figure 22). The tumor is usually located posterior to the equator with most in the macular or peripapillary region.\textsuperscript{70} The tumor size may range from 3-18 mm in diameter and 1-7 mm in thickness.\textsuperscript{71}

In some cases, extensive cystic changes are seen in the outer retinal layers overlying the tumor and may coalesce to form retinoschisis. The RPE overlying the tumor may show fibrous or osseous metaplasia.
The pigmented rim seen clinically is caused by irregularly compressed choroidal melanocytes at the margin of the hemangioma.

**Investigations**

**Ultrasonography**

Circumscribed choroidal hemangioma is seen as a heterogenous mass with high surface and internal reflectivity on A-scan (Figure 23). Acoustic shadow is usually not seen. Occasionally dense fibrosis or osseous metaplasia can lead to high reflectivity and shadowing. Associated RD can be identified.  

**Figure 22:** Solitary choroidal hemangioma. Orange red tumor is seen superonasal to optic disc with subretinal fluid at the macula (22A). Subretinal gliosis over the surface of the tumor.

**Figure 23:** Ultrasonography of choroidal hemangioma. Elevated heterogenous mass is seen on B scan. A scan shows high surface and internal reflectivity. RD is seen in the B scan (23B).
Fundus fluorescein angiography (Figure 24)
The large choroidal vessels fill rapidly in the early phase and are seen as irregular linear hyperfluorescence in the choroidal or the arterial phases. In the venous phase, there is an increase in the hyperfluorescence. In the late phases, pooling of dye is seen in the area corresponding to RD.

Indocyanine green angiography
Indocyanine green characteristics are pathognomonic and are the most important investigative modality in doubtful cases. Once ICG dye is injected, within 30 seconds, the intrinsic vascular pattern of the tumor is apparent. It is followed by a rapid increase in hyperfluorescence that reaches a peak around 3 to 4 min. In the late phases, a “washout” effect with a reduction of the initial hyperfluorescence compared to surrounding normal choroid is observed secondary to the rapid outflow of dye from the tumor.

Autofluorescence
Choroidal hemangioma shows little intrinsic autofluorescence. Overlying lipofuscin and fresh subretinal fluid (SRF) shows
hyperautofluorescence. Retinal pigment epithelial (RPE) atrophy shows hypoautofluorescence.\textsuperscript{73}

**Optical coherence tomography (Figure 25)**

On OCT, smooth dome shape elevation of the retinochoroidal complex is seen corresponding to the anterior surface of the tumor. Increase in the caliber of medium and large choroidal vessels is seen within the tumor without the compression of the overlying choriocapillaris. OCT helps in identification of the overlying retinal changes such as the presence of subretinal fluid, intraretinal fluid, photoreceptor loss. OCT helps in the assessment of response to therapy, such as the resolution of subretinal fluid. OCT also helps in identifying signs of chronicity and assessment of visual prognosis.\textsuperscript{74-76}

**Figure 25:** OCT through the tumor. Convex elevation of the RPE bruch complex corresponding to the tumor. Sparing of choriocapillaries is noted. Subretinal fluid is seen under the macula (25B).

**Optical coherence tomography angiography (Figure 24)**

Optical coherence tomography angiography of CCH shows choroidal vessels with intervening signal void areas. Dark signals in OCTA can be either due to masking by retinal pigment epithelium or limited laser light penetration. Irregularly arranged choroidal vessels are seen in both superficial and deeper sections of the choroid. OCTA can identify a decrease in the vascular density, post treatment.\textsuperscript{77,78,13}
Magnetic resonance imaging (Figure 26)
On magnetic resonance imaging (MRI), CCH is hyperintense to the vitreous in T1-weighted images and isointense to the vitreous in T2-weighted images. The tumor shows intense enhancement on gadolinium.

![MRI of choroidal hemangioma. T1 weighted MRI showing elevated lesion with hyper intensity in the right eye. Overlying retinal detachment is seen.](image)

Differential diagnosis

Amelanotic choroidal melanoma
A typical CCH is orange red in color, in contrast to choroidal melanoma. Ultrasonography shows acoustic hollowing, choroidal excavation and low internal reflectivity in choroidal melanoma in contrast to high internal reflectivity in CCH. Late phase washout is usually seen on ICG in CCH but is not seen in melanoma.

Choroidal metastasis
Choroidal metastasis is usually seen in elderly individuals in contrast to CCH, which is seen in middle age. Choroidal metastasis is dull creamy yellow in color, but metastasis from renal cell carcinoma, thyroid and carcinoid tumors can be bright orange or pink in color. Metastasis is usually multifocal and bilateral in contrast to CCH which is usually unifocal and bilateral.
Nodular scleritis

Posterior nodular scleritis can mimic intraocular mass, but it is usually seen as choroidal elevation and is associated with inflammatory signs and choroidal folds. But in some cases, inflammatory signs are not evident.

Treatment

The management of choroidal hemangioma depends on the presence or absence of exudative RD.

Asymptomatic cases can be observed periodically as CCH does not increase in size and remains quiescent for months or years.

Treatment is indicated in cases with visual symptoms. The treatment modalities include photodynamic therapy, plaque brachytherapy, transpupillary thermotherapy, laser photocoagulation, external beam radiation therapy, proton beam therapy and gamma knife stereotactic radiosurgery.

Photocoagulation

Laser photocoagulation does not help in tumor regression. But in some case series, it is known to be useful in the resolution of sub retinal fluid by inducing chorioretinal adhesion. But recurrence of the sub retinal fluid can be seen in up to 40% of cases. Additional treatments would be required in these cases. The treatment should be intense enough to produce a white reaction on the surface of the tumor. In cases of extensive RD, surgical drainage of SRF can be carried out to allow photocoagulation.

Transpupillary thermotherapy (TTT) (Figure 27)

In TTT, infrared laser (810 nm diode) is employed to raise the internal tumor temperature above 45°C but below 60°C. The chorioretinal scar observed after treatment is less pronounced in comparison to photocoagulation. Intravenous injection of ICG dye prior to TTT can augment the effect of TTT by inducing thrombosis of the intrinsic vascular network. TTT can result in cystoid macular edema (CME), epiretinal and sub retinal gliosis and retinal vascular occlusion, making TTT unsuitable for subfoveal and peripapillary tumors.
Photodynamic therapy (Figure 28)

Photodynamic therapy is the treatment of choice for CCH. PDT has the advantage of tumor destruction with lesser damage to the overlying retina and retinal vasculature. Selective occlusion of tumor vascular network is achieved and the neurosensory retina is almost unaffected. So the retinal function will remain intact. This property makes PDT the preferred treatment option for CCH involving the macula and the peripapillary area. With a single session of PDT, visual improvement or stabilization is reported in 73-100% of cases.

Standard PDT: Standard PDT involves the injection of 6 mg/m² of verteporfin over 10 minutes followed by treatment at 15 minutes for a duration of 83 seconds. Laser of 689 nm wavelength is used. In standard PDT the radiant intensity used is 50 J/cm² and the irradiance used is 600 mW/cm². It is preferable to wait for 4-6 months after PDT for resolution of SRF, before repeating the treatment as repeat PDT may result in RPE atrophy and vision loss. Various modifications of the standard PDT are employed in the treatment of CCH.

Bolus PDT: In contrast to infusion of verteporfin over 10 minutes,
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it is injected over 1 or 2 minutes followed by treatment at 5 minutes for a duration of 166 seconds. Radiant intensity used is 100 J/cm². Clinical regression and improvement in visual acuity are seen in both standard PDT and bolus PDT. Bolus PDT results in faster resolution of subretinal fluid. But the risk of RPE hyperplasia and a decrease in retinal sensitivity on microperimetry is more with bolus PDT.92

**Proton beam therapy**

Proton beam therapy uses charged particles. They have a highly localized and uniform dose distribution and has the advantage of causing less damage to the overlying structures. So proton beam therapy was one of the options to treat macular and juxtapapillary CCH prior to PDT.93 Tumor regression is seen after proton beam therapy. But the results of various case series in terms of optic neuropathy and maculopathy is contradictory. In one series, proton beam therapy was associated with a lesser risk of maculopathy and optic neuropathy93 where as in other series proton beam therapy did not prevent optic neuropathy and maculopathy compared to external beam radiation therapy.94
**Plaque brachytherapy (Figure 29)**

Plaque brachytherapy is employed in CCH with extensive subretinal fluid where PDT is not feasible and in juxtapapillary tumors not responding to PDT. The ionizing radiation causes a progressive, occlusive vasculitis secondary to destruction of the vascular endothelial cell and pericytes and results in regression of the tumor. Low-dose radiation delivering 20 Gy to the tumor apex is adequate. Visual loss due to radiation retinopathy and optic neuropathy may occur in up to 30% of patients despite the low dose. Tumor regression, resolution of subretinal fluid and regression of iris neovascularization is reported with Ru-106, I-125 and palladium-103 brachytherapy.

Figure 29: Choroidal hemangioma nasal to disc with subretinal fluid (29A, B). It was treated with brachytherapy. Decrease in height of the tumor with resolution of subretinal fluid after treatment (29C, D).

**External beam radiation therapy**

External bean radiation is mainly employed in the treatment of diffuse choroidal hemangioma. In a series of 3 patients of CCH treated with a maximal dose of 10 Gy, good anatomical and functional outcome was seen with no side effects in the follow-up period of 18-36 months.

**Anti-VEGF agents**

Single or multiple intravitreal bevacizumab injections with or without PDT or TTT is reported to resolve SRF associated with CCH.
Oral propranolol
Oral propranolol is found to be effective in partial or complete resolution of sub retinal fluid associated with CCH.\textsuperscript{101,102}

Larger, comparative prospective studies are required to define the role of anti-VEGF injections and oral propranolol in the treatment of CCH.

Gamma knife radiosurgery
Stereotactic radiosurgery involves focused delivery of radiation to the tumor with sub millimeter accuracy. It is shown to be effective in achieving tumor regression in multiple reports.\textsuperscript{103,104}

What’s new?

Optical density ratio
Optical density ratio (ODR) is a ratio of the light reflectivity of subretinal fluid with respect to vitreous in spectral domain OCT. ODR is low in CCH compared to choroidal melanoma and would differentiate the two tumors in doubtful cases.\textsuperscript{105}

DIFFUSE CHOROIDAL HEMANGIOMA

Introduction
Diffuse choroidal hemangioma (DCH) is a rare intraocular tumor commonly associated with Sturge Weber syndrome. Sturge-Weber syndrome is a neurocutaneous syndrome affecting the leptomeninges, facial skin in the ophthalmic and maxillary distributions of the trigeminal nerve (encephalotrigeminal angiomatosis). It is associated with leptomeningeal angioma, facial port-wine stain (PWS) and glaucoma in its complete form. Diffuse choroidal hemangioma is characterised by an intermixed proliferation of small and large blood vessels and is usually classified as a mixed hemangioma. Fibrous transformation of the proliferated retinal pigment epithelium is observed in over 50% of DCH in SWS.\textsuperscript{106,107}

Clinical features

Symptoms
The tumor is asymptomatic in a good percentage of cases. But the presence of PWS would prompt fundus evaluation and DCH can be detected in early life.
DCH can cause visual impairment due to hyperopia, amblyopia, exudative RD.

Episcleral hemangioma and glaucoma are other ocular manifestations of SWS and can be seen in cases with DCH.

**Signs**

A brilliant red reflex (tomato catsup fundus) is seen in the involved eye in contrast to the normal reflex in the opposite pupil (Figure 30 and 31).\(^{108}\)

A definite mass may not be seen and presence of DCH can be missed on examination. A diffuse red-orange discoloration of the choroid is seen in the area corresponding to the tumor. Cystoid degeneration in the overlying retina and hyperpigmentation is commonly seen. In comparison to circumscribed choroidal hemangioma, the diffuse choroidal hemangioma is frequently large and often extends anterior to the equator.

![Figure 30: Fundus photograph of right (30A) and left eye (30B) of a patient with port wine stain involving right side of face. Asymmetry of optic disc is evident. Subtle orange discoloration in the inferior half of macula.](image)

**Diagnosis**

**Ultrasonography (Figure 31)**

Ultrasonography demonstrates a markedly thickened choroid with medium to high internal reflectivity with or without an overlying RD.

**Fundus fluorescein angiography**

Fundus fluorescein angiography shows widespread areas of early phase hyperfluorescence with diffuse leakage.
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Magnetic resonance imaging
On magnetic resonance imaging, the tumor is hyperintense in T1 weighted images and isointense to the vitreous in T2 weighted images. The tumor shows a marked enhancement with gadolinium.

Optical coherence tomography (Figure 32)
Choroidal thickening is seen corresponding to the tumor. Subtle tumors can be identified and delineated on OCT.

Figure 31: Fundus photograph of an eye with diffuse choroidal hemangioma, showing orange red discoloration (31A). B scan (31B) and A scan (31C) images demonstrating a markedly thickened choroid (within circle) with medium to high internal reflectivity (within square) with an overlying retinal detachment (arrow).

Figure 32: OCT of diffuse choroidal hemangioma. OCT through subtle DCH showing thickening of choroid (32A). OCT showing choroidal thickening, intraretinal fluid and subretinal fluid.
Optical coherence tomography angiography (Figure 33)
Irregular vascular network distinct from the normal choroid can be seen on OCTA. The vascular network shows spaghetti appearance. Intervening dark areas are seen in between the irregular vessels.

![Figure 33: OCTA of subtle diffuse choroidal hemangioma. Part of OCTA to the left of the arrows show an irregular choroidal vascular pattern distinct from normal choroid. Normal choroid is seen on the right side.](image)

Differential diagnosis

Diffuse posterior scleritis
Exudative RD with thick choroid in posterior scleritis can mimic DCH. But posterior scleritis is associated with pain and other signs of inflammation. The RD in posterior scleritis can be multifocal rather than smooth bullous detachment in DCH. Ultrasonography shows subtenon collection in posterior scleritis.

Nanophthalmos and uveal effusion syndrome
Exudative RD with the presence of thick choroid on ultrasonography in nanophthalmos can mimic DCH. But the axial length is nanophthalmos is significantly shorter, where as it is normal in DCH. Nanophthalmos is usually bilateral whereas DCH is almost always unilateral.

Treatment
Asymptomatic DCH can be observed periodically. Symptomatic DCH is a difficult condition to manage.

Hyperopic refractive error can be addressed with refraction, corrective lenses and amblyopia therapy.¹⁰⁹
Photodynamic therapy: Photodynamic therapy is the preferred first line treatment for DCH with minimal subretinal fluid. A single spot over the thickest part of the tumor or multiple non-overlapping spots can be used. Single or multiple sessions of PDT results in resolution of exudative RD and regression of the tumor.\textsuperscript{110}

External beam radiation therapy: External beam radiation can be used to treat diffuse tumors that are too large for focal treatments or those associated with exudative RD that precludes visualisation of the tumor.\textsuperscript{111} A dose of 1250 to 2000 cGy in fractions can be used to treat the tumor. Radiation leads to resolution of the RD in most cases and can even control raised intraocular pressure in some cases (Figure 34).

**Figure 34:** Pre-treatment color photograph and OCT of diffuse choroidal hemangioma (34A and 34B). Flattening of choroid, decrease in subretinal fluid and intra retinal fluid (34D and 34E) is evident after external beam radiation (EBRT). Pre-treatment (34C) and post treatment (34F) ultrasound showing decrease in choroidal thickness.

Plaque brachytherapy: Plaque brachytherapy can also be employed to treat eyes with DCH. The plaque is centered on the thickest part of the tumor.\textsuperscript{112}

Propranolol: Propranolol, a nonselective β blocker in the dosage of 2 mg/kg/day has been reported to cause accelerated absorption of the exudative RD in some cases. Though the mechanism of action is unclear, it is assumed that propranolol may influence endothelial cell function, angiogenesis, apoptosis and may lead to the resolution of the retinal detachment.\textsuperscript{113}
Bevacizumab

A single intravitreal injection of bevacizumab resulted in sustained resolution of exudative RD in DCH over 20 months in a single case.\textsuperscript{114}

**Transpupillary thermotherapy:**

We treated diffuse choroidal hemangioma with bullous RD resistant to systemic propranolol and brachytherapy, with drainage of subretinal fluid and intra-operative transpupillary thermotherapy (TTT), resulting in resolution of the RD, regression of the tumor and control of associated glaucoma. In TTT, an infrared laser is employed to raise the internal tumor temperature above 450° but below 600°.\textsuperscript{115} The chorioretinal scar observed after treatment is less pronounced in comparison to photocoagulation.

Concomitant ICG can be used to augment the effect of TTT.\textsuperscript{116} Transpupillary thermotherapy can result in complications such as cystoid macular edema, preretinal fibrosis, and retinal vascular occlusion making TTT unsuitable for subfoveal and peripapillary tumors.\textsuperscript{117}

**CONCLUSION**

The vascular tumors of the retina and choroid exhibit distinct clinical appearance and clinical examination remains the main stay of diagnosis. In atypical cases, ancillary tests such as FFA, ICGA, ultrasonography can be helpful. OCT and OCTA are newer modalities and would help in diagnosis and monitoring. Though all the tumors are benign, they can affect the visual function due to exudation or traction secondary to the tumor. Treatment is indicated in symptomatic cases and many therapeutic modalities exist. Early and accurate diagnosis, identification of associated systemic disease is essential for effective management.

**References**


68. Perri P, Incorvaia C, Costagliola C, Parmeggiani F, Lamberti G, Paduano B. Bilateral circumscribed haemangioma of the choroid not associated with


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