Ocular Tumors

H. V. Nema
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Editors

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Foreword

It is my privilege to write the foreword for *Ocular Tumors.*

Professor Nema has more than 50 years of experience in education and is well recognized as a prolific author and editor of ophthalmic textbooks. *Ocular Tumors* represents a contribution of leading experts in the field of ocular oncology from the major centers in India.

The book provides a broad spectrum introduction to not only intraocular tumors in adults and children but also tumors of the eyelid, conjunctiva, and the orbit. With high-quality illustrations, *Ocular Tumors* is certain to attract wide readership from India and abroad.

I congratulate all the authors for working collectively to represent their knowledge and experience in this masterfully edited book.

Arun D. Singh
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Preface

Literature on ocular tumors in the past six decades has undergone a sea change. Recent developments in the diagnosis and management of ocular tumors have greatly changed the prognosis and visual outcome.

Ocular tumors are seen in both pediatric and elderly age groups. Retinoblastoma is a common tumor of childhood. Delayed diagnosis of retinoblastoma can cause morbidity and mortality. In the past, the gold standard of treatment for retinoblastoma was enucleation to save the life of the child. Recent diagnostic techniques and treatment strategies such as brachytherapy and intra-arterial, intravitreal, and intracameral chemotherapy have dramatically improved the survival rate. Considering the importance of retinoblastoma in this region, three chapters have been devoted to this topic.

Malignant melanoma of choroid is the most common primary intraocular malignancy of adults. A number of risk factors for the development of choroidal melanoma and its metastasis are known. Genetic alteration in uveal melanoma slows the risk of metastasis and helps in determining its prognosis. Many benign lesions of choroid may cause a diagnostic dilemma as they clinical resemble choroidal malignant melanoma. Pitfalls in the diagnosis of choroidal malignant melanoma are critically discussed by Shanmugam and Sagar.

To adequately cover the subject, chapters on Intraocular Lymphoma, Vasoproliferative Retinal Tumor, Orbital Tumors, Leukemia and Eye, Choroidal Metastasis, and Phacomatoses have been included in this book. Chapters on Tumors of Conjunctiva and Eyelid Tumors are liberally illustrated for the benefit of readers.

The contributing authors of the book were selected on the basis of their expertise in the area covered. Some of the authors have been trained at Wills Eye Hospital, Philadelphia, Pennsylvania, USA, while almost all primary contributors head the Department of Ocular Oncology in their respective institutes.

We hope this book will help practicing ophthalmologists, fellows, and residents in ophthalmology and radiology in early diagnosis and effective management of ocular tumors in order to provide appropriate care and better quality of life to the patients.

Indore, Madhya Pradesh, India — H. V. Nema
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We are indebted to all the authors for their timely and valuable scientific contributions and to Prof AD Singh for writing the Foreword of the book.

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About the Editors and Contributors

About the Editors

H. V. Nema has postgraduated from GR Medical College, Gwalior, India. He did his fellowship at the University of Manchester, England. He is a former professor and head, Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. He had been teaching ophthalmology to the undergraduate and postgraduate students at the Aligarh Muslim University, Aligarh and Banaras Hindu University, Varanasi for more than 30 years. Dr Nema has a distinguished academic career and is known for teaching, research, and publications. He had served as a consultant editor and advisory editor to the *Indian Journal of Ophthalmology*, *Afro-Asian Journal of Ophthalmology*, and *Indian Journal of Optometry*. He has many publications in national and international journals and authored and edited 24 books. Dr Nema has delivered guest lectures in many universities. He has served as an honorary general secretary and president of UP State Ophthalmological Society and was conferred Life Time Achievement Award by the society.

Nitin Nema is a professor of ophthalmology at Sri Aurobindo Medical College and PG Institute, Indore, India. He is an experienced vitreoretinal surgeon. After his postgraduation from the Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, India, he did his fellowship at Aravind Eye Hospital and PG Institute, Madurai, India. Additionally, he gained clinical and research experience from the University of Illinois at Chicago and the University of Wisconsin, Madison. He was awarded a fellowship by the All India Ophthalmological Society to work on a research project on uveitis at Sankara Nethralaya, Chennai, India. He was also awarded Dr Mohanlal Gold Medal for the best paper by the UP State Ophthalmological Society. He has published and presented many research papers, co-authored the *Textbook of Ophthalmology*, *Anatomy of the Eye and Adnexa*, and *Manual of Ophthalmology*, and co-edited 19 books.

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Abbreviations

A

ACC	Adenoid cystic carcinoma
AIDS	Acquired immuno deficiency syndrome
AJCC	American Joint Commission on Cancer
ALL	Acute lymphoid leukemia
AMD	Age-related macular degeneration
AML	Acute myeloid leukemia
AOX	Adult-onset xanthogranuloma
A-scan	Amplitude scan
ASCR	Autologous stem cell rescue
ASOCT	Anterior segment optical coherence tomography
AVM	Arterio-venous malformation

B

BAP1	BRCA1-associated protein 1
BCC	Basal cell carcinoma
BDUMP	Bilateral diffuse uveal melanocytic proliferation

C

CAM	Complexion-associated melanosis
CD	Cluster differentiation
CDK4	Cyclin-dependent kinase 4
CECT	Contrast-enhanced computed tomography
CIN	Conjunctival intraepithelial neoplasia
CLL	Chronic lymphoid leukemia
CML	Chronic myeloid leukemia
CO_2	Carbon dioxide
COMS	Collaborative Ocular Melanoma Study

COST Conjunctival stromal tumors
CSF Cerebrospinal fluid

D

DNA Deoxyribonucleic acid
DNS Dysplastic nevus syndrome
DLBCL Diffuse large B-cell lymphoma

E

EBRT External beam radiotherapy
EDI-OCT Enhanced depth imaging optical coherence tomography
EGFR Epidermal growth factor receptor
EIF1AX Eukaryotic translation initiation factor 1A, X linked
EMPSGC Endocrine mucin-producing sweat gland carcinoma
ERM Epiretinal membrane

F

FA Fluorescein angiography
FDA Food and Drug Administration
FISH Fluorescence in situ hybridization
FNA Fine needle aspiration biopsy
5-FU 5-Fluorouracil

G

GE Guanine nucleotide exchange factor
GEP Gene expression profiling
GFAP Glial fibrillary acid protein
GIST Gastrointestinal stromal tumor
GNA11 Guanine nucleotide-binding protein subunit alpha-11
GNAQ Guanine nucleotide-binding protein subunit alpha-Q
Gy Gray

H

HBID Hereditary benign intraepithelial dyskeratosis
HDM2 Human double minute 2
HIF Hypoxia-inducible factor

HIV Human immunodeficiency virus
HPV Human papilloma virus

I

IAC Intra-arterial chemotherapy
ICGA Indocyanine green angiography
ICRB International Classification of Retinoblastoma
IFN α2b Interferon alpha 2b
IGF1R Insulin-like growth factor 1 receptor
IgH/L Immunoglobulin heavy/light chain
IJCN Inflamed juvenile conjunctival nevus
IL Interleukin
IMRT Intensity-modulated radiotherapy
IOL Intraocular lymphoma
ISSVA International Society for the Study of Vascular Anomalies
IVitC Intravitreal chemotherapy

L

LAMB syndro Lentigines, atrial myxoma, mucocutaneous myxomas, and blue nevi syndrome
LOH Loss of heterozygosity
LUMPO Liverpool Uveal Melanoma Prognosticator Online

M

MALT Mucosa-associated lymphoid tissue
MAPK Miogen-activated protein kinase
MBAIT Melanocytic-BAP1-mutated atypical intradermal tumor
MITF Microphthalmia-associated transcription factor
MLPA Multiplex ligation-dependent probe amplification
MMC Mitomycin C
MRI Magnetic resonance imaging
MS Myeloid sarcoma
MSA Microsatellite analysis
MTS Muir–Torre syndrome

N

NCS Neurocutaneous syndrome
NGX Necrobiotic xanthogranuloma
NHL Non-Hodgkin's lymphoma

O

OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
OSSN	Ocular surface squamous neoplasia

P

PAM	Primary acquired melanosis
PCNSL	Primary central nervous system lymphoma
PCR	Polymerase chain reaction
PCV	Polypoidal choroidal vasculopathy
PDT	Photodynamic therapy
PED	Pigment epithelial detachment
PEHCR	Peripheral exudative hemorrhagic chorioretinal degeneration
PET-CT	Positron emission tomography combined with computed tomography
PI3K	Phosphoinositide-3-kinase
PIOL	Primary intraocular lymphoma
PNET	Primitive neuro-ectodermal tumor
PPV	Pars plana vitrectomy
pRB Rb	Tumor suppressor protein
PRiMeU	Prediction of Risk of Metastasis in Uveal Melanoma
PUL	Primary uveal lymphoma
PVRL	Primary vitreoretinal lymphoma
PWS	Port-wine stain

R

RB	Retinoblastoma
RNA	Ribonucleic acid
RPE	Retinal pigment epithelium

S

SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SFRT	Stereotactic fractionated radiotherapy
SCC	Squamous cell carcinoma
SLET	Simple limbal epithelial transplant
SNP	Single-nucleotide polymorphism
SOAI	Selective ophthalmic artery infusion
SWS	Sturge–Weber syndrome

T

TCR	T-cell receptor
TNM	Tumor node metastasis
TRD	Tractional retinal detachment
TTT	Transpupillary thermotherapy

U

UL	Uveal lymphoma
USG	Ultrasonography
UV	Ultraviolet

V

VH	Vitreous hemorrhage
VHL	van Hippel–Lindau
VM	Venous malformation
VPRT	Vasoproliferative retinal tumor
VRL	Vitreoretinal lymphoma

W

WHO	World Health Organization

Overview of Ophthalmic Tumors

1

Lingam Gopal, Gangadhara Sundar, and Su Xinyi

1.1 What Constitutes Ophthalmic Oncology?

Ophthalmic oncology is one of the advanced and multidisciplinary ophthalmic subspecialties that involves the diagnosis and management of intraocular, ocular surface, and ocular adnexal (orbit, eyelid, and lacrimal system) tumors. Most tumors arise primarily from the site (one of the sites mentioned above) where they are found. Not infrequently, they can also metastasize from known or unknown primary malignancy elsewhere or spread by contiguity from adjacent sites such as paranasal sinuses, nasopharynx, or intracranial cavity. On occasions, the ophthalmologist may be the first to diagnose a systemic malignancy that has metastasized to the eye or orbit, causing ophthalmic symptoms before causing symptoms related to the primary malignancy.

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1.2 Who Are the Personnel Involved in the Management?

An ideal practice of Ophthalmic Oncology involves close collaboration between many specialists, both within ophthalmology and beyond. Apart from the ophthalmologist, other specialists involved include, the diagnostic and interventional radiologist, radiation oncologist along with radiation physicist, pediatric and adult oncologist, ocular pathologist, geneticist, ocular prosthetician and anaplastologist, etc. Each one serves a distinct and important role with the ophthalmologist playing the lead role. Depending on background training of the ophthalmic oncologist, additional help may be needed from other ophthalmic subspecialists such as corneal surgeon, vitreoretinal surgeon, oculoplastic and orbital surgeon, etc.

Considering the complexity of the issues and numerous advances in various fields like chemotherapy, targeted therapy, tele- and brachytherapy, etc., one often needs the help of super specialists within each of the above-mentioned specialties. For example: a pediatric rather than an adult oncologist would be appropriate to advise, administer, and monitor the chemotherapy for retinoblastoma. Likewise, a general pathologist may not be best equipped to interpret a vitreous biopsy done for suspected intra ocular lymphoma. One needs a pathologist with special interest in ophthalmic pathology—not just with histopathologic techniques but also immunohistochemical techniques and even molecular genetic studies to come to reliable conclusions. Similarly, one needs an interventional radiologist who has experience in children to be able to cannulate the ophthalmic artery in a small child.

Given the rapid expansion in knowledge and application of numerous techniques for organ/vision salvage, therefore, ideally, an ophthalmic oncologist should be fellowship trained—either a vitreoretinal surgeon (intraocular tumors) or an oculoplastic surgeon (ocular surface and ocular adnexal tumors), and not just a general ophthalmologist attempting to manage everything including tumors of the eye.

1.3 What Are the Commonest Tumors One Comes Across?

The incidence and prevalence of most ocular and adnexal tumors are generally constant in most ethnic groups worldwide and geographically as well. However, there are specific tumors that are more common in certain ethnic and geographical situations, which one should be aware of. While metastatic tumors in the choroid are said to be the commonest intra ocular tumors seen [1], retinoblastoma still remains the commonest intra ocular tumor that an ophthalmologist is called upon to manage—a tumor that threatens vision and life of a child. In the Asian population, choroidal melanoma is not as common as in the Caucasian population [2], but is still seen reasonably frequently—hence often misdiagnosed and mismanaged. On the contrary, both ocular surface neoplasms and sebaceous gland carcinomas of the eyelid are much more common in Asians compared to the Caucasian population [3]. Likewise, a combination of fair complexion and increased sun exposure has led to a

Table 1.1 Some common pediatric and adult ophthalmic neoplasms

	Pediatric	Adult
Intraocular		
Benign	Astrocytomas, choroidal osteoma	Choroidal nevus, choroidal hemangioma, retinal capillary hemangioma
Malignant	Retinoblastoma, medulloepithelioma	Metastasis, uveal melanoma, intraocular lymphoma
Ocular surface		
Benign	Conjunctival nevi	Nevi
Malignant		Ocular surface squamous neoplasia (OSSN), conjunctival melanoma
Ocular adnexal		
Benign	Eyelid: Xanthogranulomas, infantile hemangioma Orbit: Dermoid, neurofibroma	Eyelids: nevi, dermal adnexal tumors Orbit: solitary venous malformation (cavernous hemangioma), schwannoma, hemangiopericytoma, pleomorphic adenoma, osteoma, etc.
Malignant	Orbit: Rhabdomyosarcoma, neuroblastoma (metastatic), orbital retinoblastoma	Eyelid: basal cell carcinoma, squamous cell carcinoma, sebaceous gland carcinoma, melanoma Orbit: lymphoma, metastasis, adenoid cystic and adenocarcinoma of the lacrimal gland

significant increase in basal cell carcinoma and melanoma in the Australian population [4]. Patients with xeroderma pigmentosa, have been shown to have an increased risk of all cutaneous and ocular surface neoplasms [5]. An overview of common and less common intraocular and ocular adnexal tumors is shown in Table 1.1.

1.3.1 Presentation

Traditionally neglect and delay in presentation has been the norm in developing countries like India so much so that the commonest presentation of retinoblastoma in the 1970s was orbital presentation with proptosis [6]. Fortunately, the awareness levels have improved significantly and currently eye salvage is possible in a higher percentage of cases.

Ocular and adnexal tumors affect all ages. However, each type of tumor has usually a distinct age range of presentation. While retinoblastomas occur in children in the age group of 2–5 years [7], choroidal melanomas tend to occur in the adult age group. However, one must be cognizant of exceptions and be alert to avoid misdiagnosis. Retinoblastoma can occur in relatively older children and on occasion in adults [8], while choroidal melanoma has been reported in young children as well [9].

1.4 What Changes Were Seen in the Investigational Approach?

While most ocular and adnexal tumors can be reliably suspected and diagnosed based on history and clinical examination alone, imaging of the eye and orbit are frequently employed to narrow down and further refine preoperative diagnosis. Advances in technology have provided us with high resolution images of the eye and orbit. Ocular surface lesions may be imaged with (ASOCT) which may help in staging the disease and guide surgical treatment. For intra ocular tumors, ultrasonography still remains an important ophthalmologist performed investigation. It is an excellent cost-effective and reliable tool useful in diagnosis and follow up for some tumors. Additional information can be obtained from fluorescein and indocyanine green angiography. In case of tumors in ciliary body area, ultrasound biomicroscopy is valuable. Swept source optical coherence tomography has been a good addendum to imaging shallow tumors of the choroid [10, 11].

Contrast enhanced computed tomography (CECT) remains the imaging of choice for most orbital and ocular adnexal tumors, partly because of good bone and soft tissue differentiation, easy readability and also its cost-benefit ratio. However, in certain situations such as soft tissue tumors, apical orbital or optic nerve/sheath lesions and in young children who may require repeated imaging, magnetic resonance imaging (MRI) is the preferred modality of imaging, considering the possibility for greater soft tissue detail. In children with retinoblastoma, the radiation exposure of CT scan can increase the risk of second tumors and hence MRI is preferred—especially if the patient is less than 2 years old and with suspected germ line mutation [12].

When primary malignancy of the eye or adnexa or suspected, a positron emission tomography combined with computed tomography (PET-CT) is often employed to detect systemic spread and thus stage the disease prior to management.

Documentation has become easier with wide-angle imaging provided by Retcam and Optos fundus cameras. These not only provide crucial documentation but permit accurate comparison between visits to assess regression or otherwise of the tumor and appropriately change the approach to management [13]. They also help communicate with the patient/relatives better.

1.5 What Changes Have Taken Place in the Management Approaches?

In the management of retinoblastoma, several paradigm shifts have taken place. Historically most globes were enucleated. Currently with a combination of chemotherapy and local aggressive treatment, the threshold for enucleation is raised significantly, with attempts made to salvage most eyes even in unilateral cases. Chemotherapy has acquired the role of primary treatment. While systemic administration is still the most common route of administration, intra-arterial and intravitreal routes of administration of these agents have enabled salvage of many more

eyes than before. External beam radiation which was the treatment of choice in the past has now become the last therapeutic option. While plaque therapy is nothing new, the greater access to this facility has enabled its application to several posterior segment, anterior segment as well as surface tumors- both as primary treatment (choroidal melanoma) as well as salvage treatment after chemotherapy (retinoblastoma).

Direct high intensity thermal laser photocoagulation of retinoblastoma tumors has been replaced by slow heating using transpupillary thermotherapy. Photodynamic therapy has been found useful in eyes with choroidal hemangioma (with verteporfin) and some cases of retinoblastoma (with Indocyanine green dye) [14].

Ocular surface and adnexal tumors (sebaceous gland carcinoma of the eyelid, adenoid cystic carcinoma (ACC) of the lacrimal gland) which were managed with orbital exenteration are being managed by more conservative techniques of chemoreduction, topical immunotherapy (OSSN) [15], followed by local excision and a combination of postoperative adjuvant radiotherapy and chemotherapy(ACC) with better globe, vision and life preservation.

Targeted systemic therapy with Rituximab, BRAF inhibitors, etc. (based on histological type and molecular genetics) is playing increasing role in conditions such as orbital lymphoma and some metastatic melanomas [16–18].

1.6 Redefining the Role of Genetics and Molecular Markers

Genetics is no longer restricted to broad genetic counseling based on the known inheritance patterns of the tumors. Specific molecules can serve as biomarkers for the diagnosis and prognostication of intraocular malignancies. In addition, some distinctive molecules closely related to the growth profiles of different tumors can serve as valuable indicators of prognosis and for survival analysis.

In uveal melanoma, patients with monosomy of chromosome 3 have poorer prognosis (i.e., due to metastatic disease) [19] likely due to mutations identified in BAP1 (BRCA associated protein 1) [20]. Genetic testing of the trans vitreal retinochoroidal vitrector biopsy sample provided accurate stratification of patients with high, intermediate and low risk, based on copy number variations of chromosomes 3 and 8 [21].

Primary intraocular lymphomas (PIOL) are mostly monoclonal B-cell lymphomas that stain positively for B-cell markers, such as CD19, CD20, and CD22. They show restricted expression of either kappa or lambda chain, express germinal center markers such as BCL6 and CD10 and secrete high amounts of IL-10 (an immunosuppressive cytokine) [22]. MYD88 mutations detection by polymerase chain reaction significantly improves the diagnostic yield of vitrectomy specimens [23].

Retinoblastoma develops in the embryonic retina following biallelic loss of *RB1*. However, there are a wide range of genetic and epigenetic changes that can affect *RB1* resulting in different clinical outcomes. In addition, other transformations, such as MYCN amplification, have been known to generate particularly aggressive tumors [24, 25].

Further, genetic studies on specific molecules and pathways could reveal more detailed features of intraocular tumors and provide hints or identifying pivotal molecules that can be targeted therapeutically.

1.6.1 Region Specific Issues

Despite the progress in many fronts in the understanding of the disease, availability of newer chemotherapeutic drugs, etc. there are several challenges one faces in a country like India with diversity in cultures, beliefs, financial capabilities, and geographic locations. Cost of treatment remains the most important factor that controls the final outcome of treatment. Crucial to the success of treatment in a condition like retinoblastoma is the rigidity with which follow up schedules are maintained and interventional treatment is administered—a goal not always attained because of social issues. Reluctance to subject a child to enucleation based on religious beliefs is still an issue to reckon with.

1.6.2 Proactive Approaches

Traditionally medicine has been reactive—investigating and treating only when the patient comes with symptoms or signs. There are several situations in ocular oncology however, where being proactive is desired and probably mandated. Top in this list is the need to screen siblings of a child with retinoblastoma periodically till the risk of occurrence is estimated to be very low. This recommendation is applicable even to yet to be born siblings. Detecting the intra ocular tumor while the child is in utero has enabled early delivery of the child and prompt institution of treatment thus salvaging the eyes [26].

In cases of angiomatosis retinae, the routine evaluation with MRI brain, abdominal ultrasound, etc. for other known associated tumors in the body is a well-known practice.

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Retinoblastoma

2

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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 transpupillary thermotherapy (TTT), cryotherapy and laser photocoagulation, 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 treatment modality. Periocular and intravitreal chemotherapy have specific indications in the management of retinoblastoma. Intra-arterial chemotherapy has emerged as a promising alternative for advanced and refractory retinoblastoma, both as a primary and secondary therapy. Recent advances in genetics of retinoblastoma have also helped in improving the overall clinical management of this malignancy.

2.1 Epidemiology of Retinoblastoma

The incidence of retinoblastoma is 1 in every 15,000–18,000 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 5000–8000 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.

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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.

2.2 Clinical Features

Leukocoria (white pupil) is the most common sign of retinoblastoma, and strabismus is the second most important presenting sign. In majority of cases, the parents notice the white reflex first and seek the opinion of a pediatrician. This makes the pediatricians an important bridge between the retinoblastoma families and the treating ophthalmologist, making it extremely crucial that they have a basic knowledge of retinoblastoma (Table 2.1). 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 are positive for germline mutation, whereas only 10–15% patients with unilateral retinoblastoma carry a germline mutation.

A child with a suspicious retinoblastoma is best examined under anesthesia for a detailed fundus evaluation (Table 2.2). 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, 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 toward it (endophytic) [1].

In the exophytic growth pattern, the tumor causes diffuse retinal detachment (Fig. 2.1a). It is most often associated with numerous small subretinal seeds. In contrast, an endophytic retinoblastoma progressively fills the vitreous cavity, and causes vitreous seeding (Fig. 2.1b). 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 flat retinal infiltration, and is acalcific. It is generally seen in older children, and the incidence is less than 2%. Diffuse anterior retinoblastoma, a recent 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].

Table 2.1 Presenting signs in retinoblastoma

Leukocoria
Strabismus
Poor vision
Red painful eye
Vitreous hemorrhage
Phthisis bulbi
Sterile orbital cellulitis
Proptosis

Table 2.2 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 eyes5 • 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)

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 are other clinical presentations seen in patients with advanced tumor (Fig. 2.1c). Orbital cellulitis-like picture occurs when a large tumor undergoes necrosis and induces inflammation in and around the eye (Fig. 2.1d). 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.

2.3 Differential Diagnosis

The most important differential diagnosis is Coats' disease [3]. There are several other lesions that can simulate retinoblastoma and are known as pseudoretinoblastomas. The important differential diagnoses are listed in Table 2.3.