# Intraocular Tumors

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*Editor*

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# Foreword by Brenda Gallie

Dr. Khetan has assembled strong leaders in ocular oncology, representing the multidisciplinary teams required for optimal care of intraocular tumors. The chapters show various approaches, with input from many geographic regions addressing the major intraocular tumors, that are biologically the same, no matter where the patients live.

Readers at all levels of expertise, ranging from general ophthalmologists and trainees to expert consultants, can find useful details in this book. The knowledge provided ranges from the very earliest history of these cancers to envisioning incorporation of personalized genomic knowledge into care, the future that is arriving quickly.

Several of the chapters describe the same elements, illustrating different approaches. Major differences are of interest, for example, the retinoblastoma prognosis to save an eye: different chapters cite systems that are significantly different, but generally they all recognize the difficulties this creates and welcome the newest, evidence-based, TNMH standard classification, developed by international collaboration and published in 2017 in the major Tumor, Node, Metastasis cancer staging manual. Incorporation of "H" for heritability shows the leadership of the field of ocular oncology in cancer in general; retinoblastoma is the first cancer in which heritability is recognized to influence outcome.

Against the historic background of the Cooperative Ocular Melanoma Study, which demonstrated that multicenter collaboration works, the current concern about accurately counseling the patient on prognosis emerges as a hot topic with many viewpoints that may best be resolved by good data and evidence.

Consistent in all chapters is support for collaborative research to generate a sound basis for treatment of ocular cancers! This book provides a good base to achieve high-quality evidence in support of the best care for our patients.

This book is not to be read from beginning to end. Rather, the reader can focus on finding details for their clinical or scientific issue at hand. Many chapters may be relevant, and frequently authors cross-reference so that the reviewer can also consider information in a different chapter.

Congratulations to Dr. Khetan! You have succeeded in leading a large multidisciplinary team, who have all contributed to produce a novel and useful book on intraocular tumors.

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# Foreword by Lingam Gopal

Subspecialization (or super specialization) is at the same time a boon and a bane. Very rapidly what was within the competence of a general ophthalmologist becomes the domain of the specialist (of course) with better quality of care being delivered. Ocular oncology has grown to be a distinct subspecialty in ophthalmology, courtesy some landmark developments in the management of common intraocular tumors. The developments in the field of imaging, chemotherapy, and genetics have been nothing short of being phenomenal. The force that drives these rapid strides is passion for the specialty and the ardent desire to make a difference.

Vikas Khetan has that passion. Ever since he became a vitreo-retinal fellow first, and then a fellow with the legendary Dr. Brenda Galle, this passion has been evident. In addition to making a difference to the way the specialty is practiced in his place of work, he strived to bring together like-minded people across the region to create forums for interaction.

It is this desire to disseminate knowledge that made him to bring together luminaries in the field and make them contribute to this textbook. This book does not pretend to be an all-encompassing encyclopedia of ocular oncology, but concentrates on the more common intraocular tumors. Retinoblastoma and choroidal melanoma take the center stage with detailed exposition of the diagnostic, genetic, and therapeutic aspects. General topics include imaging of ocular tumors (from ophthalmologist's and radiologist's perspective), pathology of intraocular tumors, management of the anophthalmic socket, and the art of counseling. Most of the chapters were written by internationally renowned ocular oncologists with decades of experience in the art and science of treating patients with intraocular tumors.

I am sure this textbook will be a good addendum to the practitioners of ocular oncology in delivering quality care, utilizing all available tools to control the tumors.

Singapore
September 2018

Lingam Gopal

# Preface

Ocular oncology is an emerging subspecialty in ophthalmology that is gradually making a place for itself. At the time of writing this text book, it is estimated that there are about 200–250 ocular oncologists all over the world. In India, until a few years ago there were only a handful of trained ocular oncologists; however, there is an encouraging trend and a lot of youngsters are now taking up this specialty. The world of ocular oncology is developing at a very rapid pace, and newer treatment modalities are emerging every other day.

The aim of the book is to provide the readers with a basic, yet detailed reference for a variety of intraocular tumors. Most of the chapters in the book are written by world experts. I hope it helps our readers in understanding the nuances of intraocular tumors.

I would like to offer my deepest thanks to the families and children who allowed us the privilege of participating in their care.

This work would not have been possible without the support of my family and friends. The time that I spent on this project was taken out the time from my spouse and child, and I am thankful to them for letting me do this.

I would also like to thank my parents and siblings for their constant and endless support.

I dedicate this book to the Founder of Sankara Nethralaya—Dr S S Badrinath. I sincerely hope that the world has many more visionaries like him.

Chennai, India — Vikas Khetan

# Acknowledgements

This book has been a wonderful journey, made possible by many beautiful people from around the globe, all coming together to make this happen.

I would like to thank all the contributors for their time, diligence and hard work in preparing the individual chapters and help enhance the knowledge with the readers.

I would like to especially thank my two mentors Drs Brenda Gallie and Lingam Gopal for their constant support and guidance in my career. I would also like to thank them for writing the forewords for this book.

A word of mention to my other mentor Dr Alex V Levin, who taught me the art of examining the patient as a whole.

I would also like to thank my family members for their understanding and support. It is the sacrifice of personal time that enable me to indulge in this book editing.

I am grateful to Springer Nature and their associates especially Mr Naren Aggarwal, Rakesh Kumar Jotheeswaran and Vignesh Manohar for their help with the book.

Last but not the least, I am grateful to Sankara Nethralaya and all the patients that I have cared for who have allowed me to share the information with the readers.

Wishing you happy reading…

# Contents

# About the Editor

**Vikas Khetan** is a specialist in vitreoretina, ocular oncology and ocular genetics. He is an alumnus of Sankara Nethralaya, Chennai, Hospital for SickKids, Toronto and Wills Eye Hospital, Philadelphia. He is a well-published author with articles in both national and international journals and has contributed chapters in many books. He is a well-known speaker at various conferences and a reviewer for many journals. He is currently the section editor of Ocular Genetics for *Indian Journal of Ophthalmology* and is also a section editor for *Nepalese Journal of Ophthalmology*.

He is the recipient of many awards including the prestigious JM Pahwa award at VRSI meeting, IJO Gold award for paper published in IJO for the year 2012 and IJO best reviewer award. He is also the recipient of many travel grants for various meetings like APAO, APVRS, etc. Last year he received the P Siva Reddy International award at the AIOS meeting. He also received SAO (SAARC Academy of Ophthalmology) excellence award at the SAO meeting in Kathmandu last year.

# 1 Retinoblastoma: Diagnosis, Classification and Management

Bhavna Chawla

## 1.1 Introduction

Retinoblastoma is the most common primary intraocular malignancy of childhood. It contributes to approximately 4% of all pediatric cancers. The incidence is around 1 in 18,000 live births [1]. The tumour was initially described as fungus haematodes in 1809 [2]. It was renamed as Retinoblastoma in 1926 by the American Ophthalmological Society after a general consensus was reached that the tumour originated from retinoblasts [3]. The retinoblastoma gene (RB1), encoded on chromosome 13q14, was the first described tumor suppressor gene. Constitutional loss of one RB1 allele causes cancer predisposition, and loss of the second allele in a developing retinal cell leads to retinoblastoma. Retinoblastoma can be sporadic or inherited. Older age and unilateral presentation is usually seen in sporadic tumours, whereas younger age and bilateral presentation is observed in inherited tumours. All cases of bilateral tumours are heritable and carry a germline mutation of the RB1 gene. They account for approximately one third of all the RB cases. Only a small proportion of unilateral retinoblastoma cases are heritable.

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## 1.2 Diagnosis

The average age for diagnosis of retinoblastoma is 18 months and 95% of children are diagnosed by the age of 5 years. Bilateral disease is diagnosed earlier then unilateral disease. Germline tumors can present as early as the first month while sporadic cases are diagnosed later, usually by 24 months of age [4].

A whitish pupillary reflex or leucocoria is the most common presenting symptom. Other signs include strabismus, poor vision and redness of the eye. In some instances, retinoblastoma may also present as buphthalmos, aseptic orbital cellulitis or phthisis bulbi. Proptosis and fungating orbital masses are signs of advanced disease, which may be accompanied by metastasis in the bone, bone marrow, lymph nodes, and central nervous system [5].

Figure 1.1 shows some of the clinical presentations of this tumour. Typically, the diagnosis of retinoblastoma is established by characteristic ophthalmic findings, often requiring general anaesthesia, and B-scan ultrasonography. A dilated fundus examination of both eyes with 360° scleral depression should be undertaken in all suspected cases. The tumour appears as an elevated mass in the fundus (Fig. 1.2). There may be multiple tumours in the same eye (Fig. 1.3). RetCAM is a wide angled fundus camera which helps to document the tumor and assess response to therapy. Other findings may be present such as the presence of vitreous and/or sub-retinal seeds, vitreous



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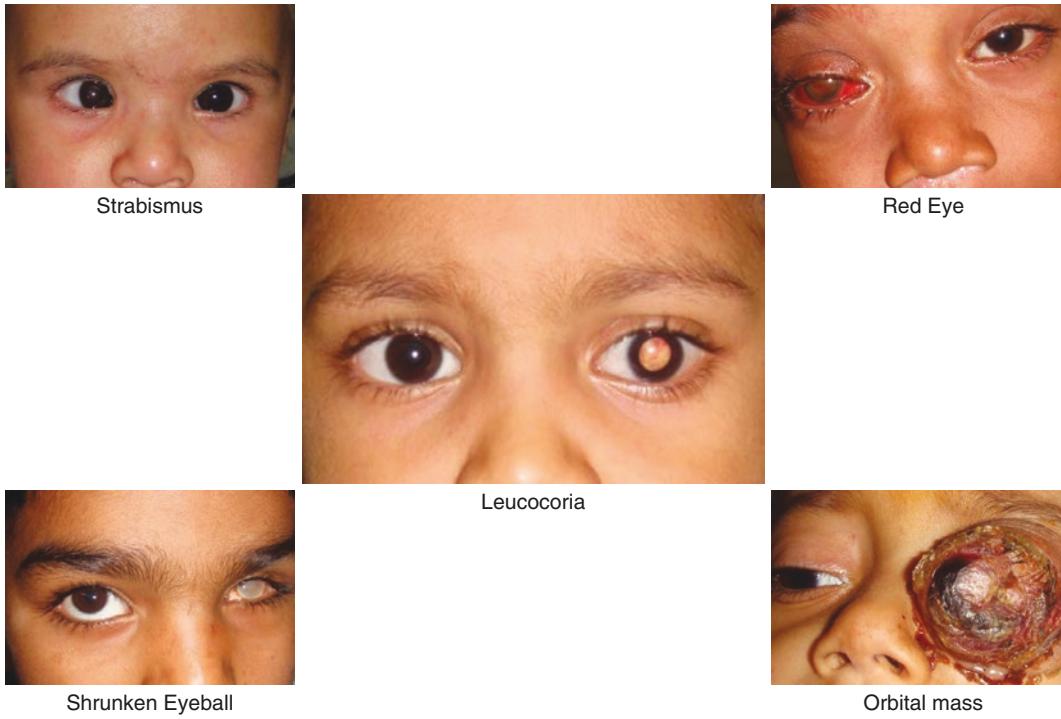


**Fig. 1.1** Various clinical presentations of retinoblastoma

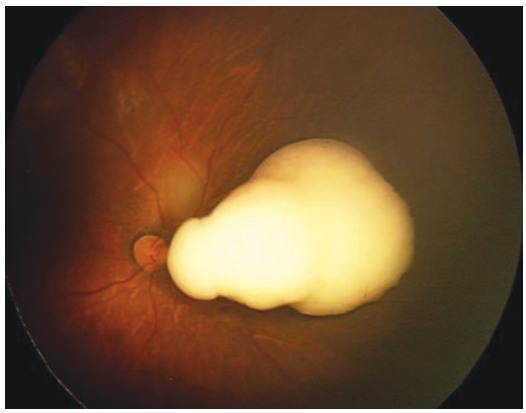

**Fig. 1.2** Fundus picture showing the elevated tumour

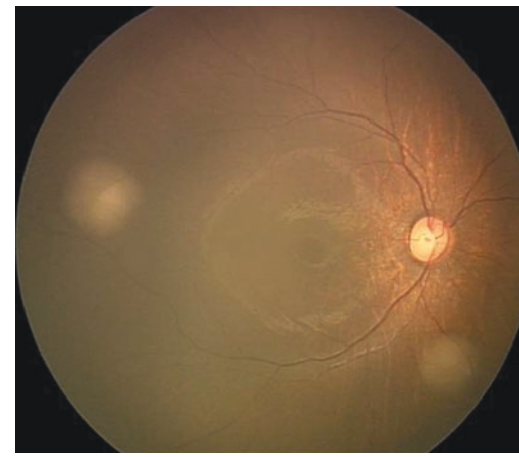

**Fig. 1.3** RetCAM image of the right eye showing two tumours

haemorrhage, sub-retinal fluid, retinal detachment etc. It is also important to evaluate the anterior segment and look for abnormal findings such as neovascularization of the iris, pseudohypopyon, cataract, ectropion uveae, hyphaema, iris seeding by tumor cells, buphthalmos or other abnormalities (Fig. 1.4). Measurement of intraocular pressure should be done. Some of these eyes may have elevated intraocular pressure, that could be due to neo-vascular glaucoma, anterior shift of the lens with resultant pupillary block and angle closure or the obstruction of the outflow of aqueous humour

**Fig. 1.4** Examination under anaesthesia

through the trabecular meshwork by the tumour cells [6].

Imaging plays an important role in confirming the diagnosis and in differentiating retinoblastoma from other simulating conditions. Imaging also helps in staging the disease and assessing the tumour response to treatment. When considering a diagnosis of retinoblastoma, there are several other diseases which need to be differentiated. These include congenital cataract, Coats' disease, persistent fetal vasculature, retinopathy of prematurity, retinal detachment, vitreous hemorrhage, Toxocariasis and coloboma and endogenous endophthalmitis. A misdiagnosis, although rare, can occur as some diseases, particularly end-stage conditions, may simulate retinoblastoma closely, resulting in a diagnostic dilemma [7, 8].

The various imaging modalities available include B scan ultrasonography, ultrasound biomicroscopy (UBM), fluorescein angiography (FA), optical coherence tomography (OCT), computed tomography (CT) scan and magnetic resonance imaging (MRI) [9]. Along with clinical examination, B-scan ultrasonography helps to establish the diagnosis in the majority of cases. On ultrasonography, retinoblastoma appears as an elevated mass in the posterior segment of the eye, with areas of high internal reflectivity due to calcification within the mass. It is also very useful in cases of diagnostic dilemma, to differentiate retinoblastoma from other common conditions that may present with leucocoria. Other advantages of ultrasound include its wide availability, simplicity of use by an ophthalmologist, no requirement for anaesthesia and lack of exposure to radiation. High-frequency UBM provides high-resolution in vivo imaging of the anterior segment in a non-

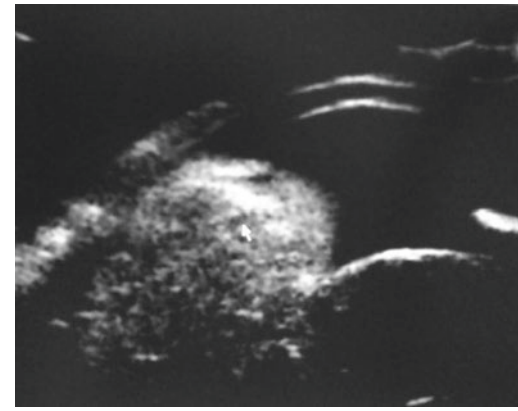

**Fig. 1.5** Ultrasound biomicroscopy for anterior segment invasion

invasive fashion. In addition to the tissues easily seen such as the cornea, iris, and sclera, structures hidden from clinical observation, like the ciliary body and angle, can be imaged and their morphology assessed (Fig. 1.5). Ultrasound bio-microscopy imaging has been shown to document anterior disease and contribute to the management of children affected with retinoblastoma [10, 11]. It is also used prior to intra-vitreal chemotherapy to look for tumour extension. Fluorescein angiography can be done for smaller tumors which show minimally dilated feeding vessels in the arterial phase, blotchy hyperfluorescence in the venous phase and late staining. Hand-held high-resolution spectral domain optical coherence tomography has been evaluated in retinoblastoma and found to be useful [12]. CT scan is most sensitive to detect calcification within the tumour (Fig. 1.6) and aids in identifying extraocular extension. However, it should be used sparingly due to the risk of exposure to ionizing radiation, especially in cases with germline mutation. It is usually reserved for cases that do not demonstrate calcification on ultrasound and/or cases of diagnostic dilemma with atypical presentation. Neuroimaging with contrast MRI is the imaging modality of choice in advanced cases with suspected extraocular extension for assessment of orbital, optic nerve and intracranial extension (Fig. 1.7). MRI has the advantage of superior soft tissue resolution as compared to CT scan and does not expose the child to radiation. There are several

studies on the diagnostic accuracy of MRI in predicting optic nerve invasion [13, 14]. Rarely, children with retinoblastoma have a pineal tumour (trilateral retinoblastoma)that may be found on imaging. MRI has also been helpful in tumor staging of patients who present with orbital cellulitis and in differentiating between inflammation of the coats and extra-ocular invasion [15]. Cerebrospinal fluid and bone marrow evaluation are not performed routinely and should only be undertaken if indicated clinically or by imaging studies.

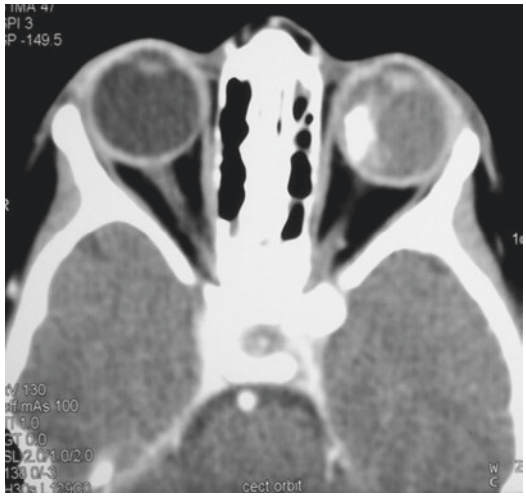

**Fig. 1.6** CT scan showing intralesional calcification in the left eye

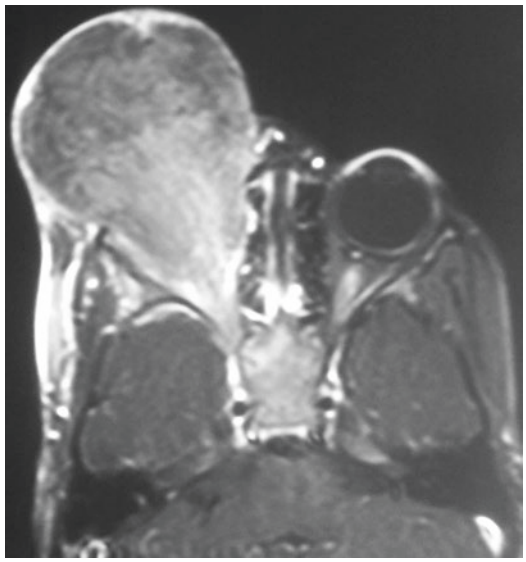

**Fig. 1.7** T1 weighted MR image showing extensive orbital invasion by the tumour

## 1.3 Classification and Staging

Retinoblastoma may be intra-ocular (Fig. 1.8) or extra-ocular at presentation.

Appropriate management requires correct staging of the tumour at the time of diagnosis. Hence, a knowledge of the classification systems for staging of retinoblastoma is essential.

In the 1960s, the primary treatment modalities for retinoblastoma were surgery and external beam radiotherapy (EBRT). It was during this period that Dr. Algernon Reese and Dr. Robert Ellsworth developed a classification system for intraocular retinoblastoma that had prognostic significance for maintenance of sight and control of local disease (Table 1.1) [16].

The Reese Ellsworth classification system had a few drawbacks. These included:

a. A worse ocular prognosis for peripheral, large and multi-focal tumours as they were presumed to be more aggressive in the EBRT era.

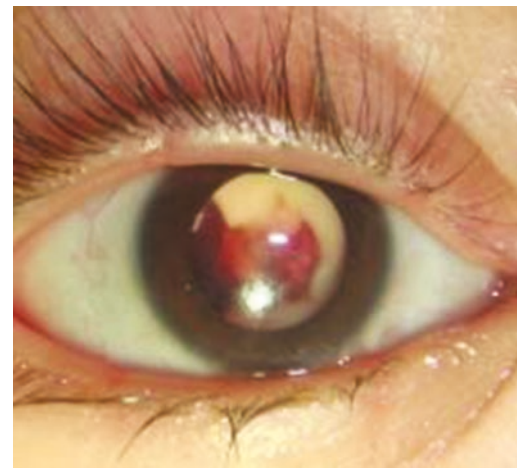

**Fig. 1.8** Intraocular tumour

**Table 1.1** Reese-Ellsworth classification for retinoblastoma

| Group | Likelihood of salvage | Features |
|---|---|---|
| I | Very favorable for maintenance of sight | a. Solitary tumor, <4 DD, at or behind the equator<br>b. Multiple tumors, none >4 DD, at or behind the equator |
| II | Favorable for maintenance of sight | a. Solitary tumor, 4–10 DD, at or behind the equator<br>b. Multiple tumors, 4–10 DD, behind the equator |
| III | Doubtful for maintenance of sight | a. Any lesion anterior to the equator<br>b. Solitary tumor, >10 DD, behind the equator |
| IV | Unfavorable for maintenance of sight | a. Multiple tumors, some >10 DD<br>b. Any lesion extending anteriorly to the ora serrata |
| V | Very unfavorable for maintenance of sight | a. Massive tumor involving more than one half of the retina<br>b. Vitreous seeding |

*DD* disc diameters

**Table 1.2** International Classification System for retinoblastoma [17]

| Group | Clinical features |
|---|---|
| A<br>Very low risk | All tumors are 3 mm or smaller, confined to the retina, and located at least 3 mm from the foveola and 1.5 mm from the optic nerve. |
| B<br>Low risk | Retinal tumors may be of any size or location not in Group A. No vitreous or subretinal seeding allowed. A small cuff of subretinal fluid extending no more than 5 mm from the base of the tumor is allowed. |
| C<br>Moderate risk | Eyes with only focal vitreous or subretinal seeding and discrete retinal tumors of any size and location. Vitreous or subretinal seeding may extend no more than 3 mm from tumor. Upto one quadrant of sub-retinal fluid may be present. |
| D<br>High risk | Eyes with diffuse vitreous or sub-retinal seeding and/or massive, non-discrete endophytic or exophytic disease. |
| E<br>Very high risk eyes | *Eyes with one or more of the following*<br>• Neo-vascular glaucoma<br>• Massive intraocular hemorrhage<br>• Aseptic orbital cellulites<br>• Phthisis or pre-phthisis<br>• Tumor anterior to anterior vitreous face<br>• Tumor touching the lens<br>• Diffuse infiltrating retinoblastoma |

b. No distinction was made between sub-retinal and vitreous seeds in the classification system and the presence of sub-retinal seeding was not addressed.

In the 1990s, systemic chemotherapy started becoming popular as a primary treatment for retinoblastoma. Therefore, a new classification system that could predict the results of chemotherapy with more accuracy was needed (Table 1.2). Thus, the International Classification System for intraocular retinoblastoma was introduced, and it was found to be a good predictor of chemoreduction success [17, 18].

Recently, the American Joint Committee on Cancer has formulated the 8th edition of retinoblastoma staging, with the view to define the extent of disease at the time of diagnosis and to predict eye survival, metastatic risk, and patient survival [19]. Unique to the 8th edition tumour node metastasis (TNM) staging for retinoblastoma, is the inclusion of germ line cancer predisposition, which incurs a high risk for new post-diagnosis tumors and second primary tumours such as osteosarcoma and cutaneous melanoma, thus affecting overall patient survival. It has introduced the stage category H to indicate the germ line status of RB1 gene (H1) inferred clinically by bilateral retinoblastoma, reti-

**Table 1.3** The International Retinoblastoma Staging System

| Stage | Description | |
|---|---|---|
| Stage 0 | Eye has not been enucleated | |
| | Conservative treatment | |
| Stage I | Eye enucleated, completely resected histologically | |
| Stage II | Eye enucleated, microscopic residual tumor in the form of | |
| | 1. Tumor invasion into extrascleral space | |
| | 2. Tumor invasion into the cut end of optic nerve | |
| Stage III | Regional extension | a. Overt orbital disease |
| | | b. Pre-auricular or cervical lymph node extension |
| Stage IV | Metastatic disease | a. Hematogenous metastasis |
| | | 1. Single lesion |
| | | 2. Multiple lesions |
| | | b. CNS extension |
| | | 1. Pre-chiasmatic lesion |
| | | 2. CNS mass |
| | | 3. Leptomeningeal and CSF disease |

noblastoma with an intracranial primitive neuroectodermal tumor (i.e., trilateral Rb), patient with family history of retinoblastoma, or molecular definition of a constitutional RB1 gene mutation. For extra-ocular retinoblastoma, the International Retinoblastoma Staging System proposed by Chantada et al. is used to stage the tumour (Table 1.3) [20]. The tumour is staged from Stage 0 to Stage IV, depending upon the extent of invasion, taking histopathology and imaging findings into account.

## 1.4 Management

The management of retinoblastoma depends on several factors such as age of the child, laterality and stage of the disease at presentation, and visual potential of the affected eye. The primary aim of treatment is survival of the child, with globe preservation and maintenance of vision being secondary goals. In the past, the tumour was associated with a high mortality but with the introduction of enucleation, the survival rate improved dramatically. While enucleation remains the standard of care for advanced intraocular tumours, conservative treatment which can result in globe salvage and preservation of useful vision is being successfully used for less advanced disease. These therapies include focal consolidation with trans-pupillary thermotherapy, laser photocoagulation and cryotherapy, systemic chemotherapy, radiation treatment with plaque brachytherapy or external beam radiotherapy, and local injections of chemotherapeutic agents through the sub-tenon or subconjunctival route, as an adjunct to systemic chemotherapy. In the following section, each of these treatment modalities will be discussed in detail.

## 1.5 Trans-pupillary Thermotherapy

Transpupillary thermotherapy (TTT) is used for local control of the tumour, alone or in conjunction with systemic chemotherapy. The procedure is usually carried out under general anaesthesia using an infra-red diode laser (810 nm) mounted on an indirect ophthalmoscope (Fig. 1.9). The laser is applied directly to the tumour under wide pupillary dilation. The target temperature ranges between 45 and 60 °C, which spares the retinal vessels from coagulation as it is below their coagulative threshold [21, 22]. A spot size of 1.2 mm and a mean power of 300–600 mW is used to cover the tumour. Initially, the power is started at 200 mW and increased or decreased at 5 mW increments until an adequate take is observed in the mass [21, 22]. Effective therapy usually requires multiple sessions at monthly intervals. Various mechanisms of action for TTT have been described which include a direct


**Fig. 1.9** Trans-pupillary thermotherapy

cytotoxic effect of heat on tumour cells, induction of apoptosis, heat-induced alteration of tumour microenvironment, modulation of drug resistance of tumour cells and increased uptake of carboplatin into tumour cells at temperatures above 44 °C [23, 24].

There are several studies on the role of TTT in retinoblastoma. Abramson et al. proposed that tumours <1.5 DD in base diameter can be treated with TTT alone [21]. Shields et al. treated 188 tumours (80 eyes) with TTT and reported complete regression in 161 (85.6%) tumours and recurrence in 27 (14.4%) tumours [22]. Complications reported included focal iris atrophy (36%) and peripheral focal lens opacity (24%).

## 1.6 Laser Photocoagulation

The purpose of argon laser photocoagulation (532 nm) is to coagulate all the blood supply to the tumour. Feeder vessels are obliterated at a mean power of 350 mW over a duration of 1–4 s. Only small and posterior tumours located away from the fovea and optic disc are managed by laser photocoagulation. Complications include retinal detachment, vascular occlusions, retinal traction, and preretinal fibrosis [25–27].

While TTT can be used for tumours adjacent to the fovea or optic nerve, laser photocoagulation can damage these vital areas. Thermotherapy causes a lower rise in temperature and its higher wavelength (810 nm) as compared to argon laser helps it to act directly on the retina so that the blood vessels are not damaged. On the contrary, during laser therapy (532 nm), the blood vessels are coagulated, leading to retinal ischemia [26, 27].

## 1.7 Cryotherapy

Cryotherapy alone may be used as primary therapy for small peripheral tumours located anterior to the equator. Cryotherapy induces the tumor tissue to freeze rapidly, and a temperature upto −90 °C causes intracellular ice crystal formation, protein denaturation, pH changes, and cell rupture, resulting in damage to the vascular endothelium with secondary thrombosis and infarction of the tumour tissue. Tumors are typically treated three times (triple freeze and thaw technique) per session trans-conjunctivally, with one or two sessions at monthly intervals [28, 29]. It is most effective for tumours <4 mm in basal diameter and 2 mm in thickness It can also be used as an adjunct to systemic chemotherapy and has synergistic effect when applied within 2–3 hours of intravenous chemotherapy. The complications are few and rarely serious, and include lid edema, transient conjunctival edema, serous retinal detachments and retinal tears. Vitreous hemorrhage can be observed in large or previously irradiated tumours [30, 31].

## 1.8 Systemic Chemotherapy

It was in the 1990s that systemic chemotherapy was used to treat intraocular retinoblastoma after observing good tumour control and ocular salvage rates of 30–70% when intravenous chemotherapy was given prior to EBRT [32]. The recognition of increased risk of second non-ocular cancers with EBRT further led to more extensive use of chemotherapy. Today, it is one of the most widely used treatment modalities for retinoblastoma.

The main objectives of chemotherapy for intraocular retinoblastoma are eye salvage and avoidance of enucleation or EBRT.

Systemic chemotherapy is indicated for large tumours that cannot be treated with local therapy alone, recurrent lesions, relapsed tumours, and as adjuvant therapy to enucleation surgery in cases with high risk histopathology features [33–35]. Systemic chemotherapy is also used as a part of multi-modal treatment for extra-ocular retinoblastoma. The various chemotherapeutic drugs used in treatment include carboplatin, etoposide, vincristine, methotrexate, cyclophosphamide, melphalan, doxorubicin, and triethylene melamine in various combinations. The most commonly used intravenous chemotherapy drugs are vincristine, etoposide, and carboplatin (VEC) [36]. Table 1.4 shows the standard dosage and schedule of drugs that are recommended for use. Cyclosporine has also been used to overcome the problem of drug resistance [37]. Other drug combinations such as two-drug therapy of vincristine and carboplatin have also been proposed so that the side effects of etoposide can be avoided [38].

Systemic chemotherapy combined with focal therapy has been the mainstay of globe-preserving treatment for less advanced disease [39]. The tumour size undergoes reduction following chemotherapy, and local therapies such as cryotherapy, laser photocoagulation, or TTT are used to eradicate the remaining disease. This combined treatment approach has been shown to be more efficacious for tumour control than chemotherapy alone. By employing combination therapy, Shields et al. reported tumour control rates of 100% for Group A, 93% for Group B, 90% for Group C, and 47% for Group D eyes [18]. In a recent study from our centre, systemic chemotherapy and focal consolidation was found to achieve outcomes that were comparable to those reported from the West [40]. Close monitoring by a paediatric oncologist is essential during therapy to look for any signs of drug toxicity. Although the VEC regimen is usually well tolerated, side effects include myelosuppression, neutropenia, infections, liver toxicity, and increased risk of second malignancy [41, 42]. Ototoxicity and nephrotoxicity may be rarely observed.

## 1.9 Local Chemotherapy

Although systemic chemotherapy in combination with focal therapy has achieved good outcomes, intravenous chemotherapy can lead to serious toxic side effects including myelosuppression and infection. As a result, newer treatment approaches have focused on localized delivery of chemotherapy to minimize the systemic side effects of intravenous chemotherapy. Routes of local chemotherapy delivery include subconjunctival or sub-tenon injections that are given as an adjunct to systemic chemotherapy. In recent years, targeted forms of drug delivery such as intra-arterial and intra-vitreal chemotherapy have shown promising results and gained popularity.

**Table 1.4** Intravenous chemotherapy for retinoblastoma [5]

| Drug | Dosage/route | Schedule | Side effect/remarks |
|---|---|---|---|
| Carboplatin<br>Platinum coordinator compound which cross-links DNA | 560 mg/m$^2$/day<br>18.6 mg/kg/day for children <3 years | Day 0 | Nephrotoxicity, ototoxicity, neurotoxicity, hypomagnesemia<br>Escalation of dose is done depending on stage of disease. |
| Etoposide<br>Inhibits DNA | 150 mg/m$^2$/day<br>5 mg/kg/day for children <3 years | Days 0 and 1 | Allergic reactions, hepatotoxicity, CNS toxicity, hypotension, AML, mucositis.<br>Escalation of dose is done depending on stage of disease. |
| Vincristine<br>Vinca alkaloid | 1.5 mg/m$^2$/day<br>(0.05 mg/kg/day for children <3 years) maximum dose 2 mg | Day 0 | Neurotoxicity, myelosuppression.<br>Avoid extravasation. |

### 1.9.1 Sub-conjunctival/Sub-tenon Chemotherapy

It has been observed that systemic chemotherapy alone may not be sufficient to treat Groups C and D eyes. Friedman et al. reported that only 53% of Reese Ellsworth Group V eyes could be controlled with chemotherapy alone [35]. Chan et al. and Villablanca et al. reported that approximately 40% of group C and 70% of group D eyes failed systemic chemotherapy alone [43, 44]. Therefore, local injections of chemotherapeutic agents have been used with varying degrees of success, usually as an adjuvant to systemic chemotherapy to avoid enucleation and external beam radiotherapy in these cases. Sub-conjunctival carboplatin has been noted to result in favourable outcomes in those tumours that progressed despite ablative therapy [45]. The trial proposed by the Children's Oncology Group (COG) involved the use of systemic chemotherapy with carboplatin, vincristine, and etoposide, along with subtenon carboplatin for group C and D eyes [46, 47]. The sub-tenon route, though slightly more invasive than the sub-conjunctival route, is associated with a decreased incidence of lid swelling and a rapid diffusion of drug. For Group C and D tumours, the use of 20 mg sub-tenon carboplatin along with chemo-reduction and focal consolidation has been recommended by the Children's Oncology Group [48]. Optic nerve ischaemic necrosis, reduced ocular motility due to fibrosis, orbital fat necrosis and pseudo-preseptal cellulitis are some of the reported side effects of treatment [49–51].

### 1.9.2 Super-Selective Intra-arterial Chemotherapy

In 2004, Japanese investigators described the technique of 'selective ophthalmic artery infusion' (SOAI), where a micro-balloon catheter was positioned by a trans-femoral artery approach at the cervical segment of the internal carotid artery, just distal to the orifice of the ophthalmic artery [52, 53]. Abramson and Gobin further modified the technique of SOAI into direct intra-arterial (Ophthalmic artery) infusion [54]. The technique, known as super-selective infusion, involved advancing a micro-catheter into the orifice of the ophthalmic artery through a trans-femoral artery approach (Fig. 1.10). In a Phase I/II clinical trial, Abramson et al. reported their

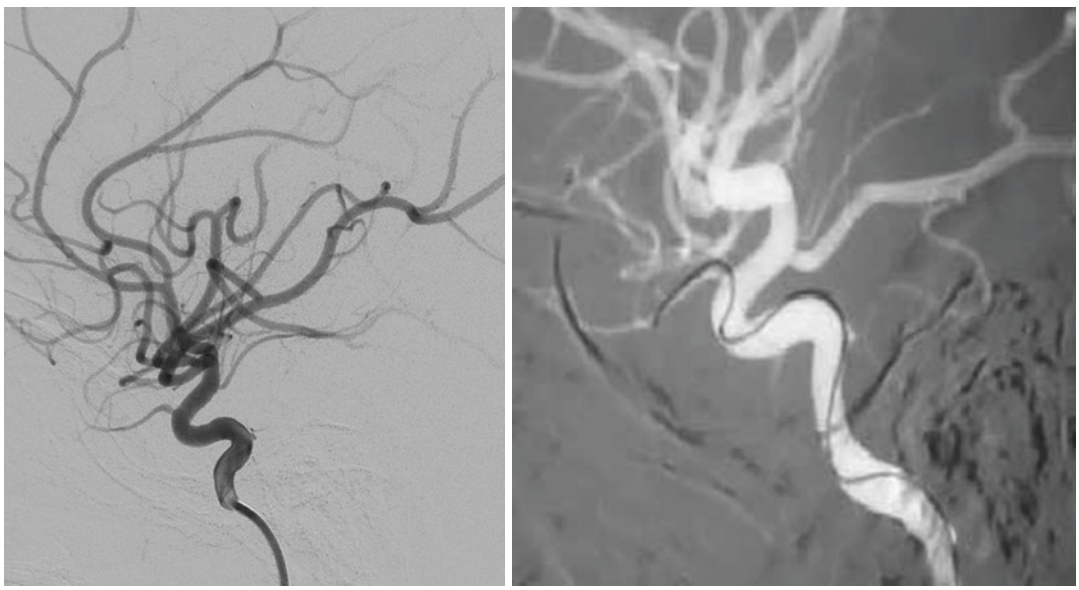

**Fig. 1.10** Intra-arterial chemotherapy

initial experience with intra-arterial ophthalmic artery chemotherapy using melphalan in 10 children with advanced retinoblastoma who were indicated for enucleation [54]. Since then, several investigators have reported their experience with selective intra-arterial chemotherapy [55, 56]. Intra-arterial chemotherapy has been reported to be associated with an overall success rate of 55–100% in salvaging the globe, in addition to the advantage of very low systemic toxicity. The most commonly used agent is melphalan; topotecan and carboplatin can be used in recalcitrant cases.

Based on the encouraging results in preliminary studies, Selective Intra-arterial Chemotherapy (SIAC) has also been used as a first line treatment in less advanced cases of intraocular retinoblastoma [57]. Although more widely used for refractory cases, SIAC has also been investigated in treatment naive eyes [58–60]. Chen et al. have studied the effect of IAC in infants less than 3 months of age [60]. Their study suggests that IAC as primary therapy is a feasible and promising treatment for retinoblastoma in infants less than 3 months of age [60]. Simultaneous bilateral ophthalmic artery chemosurgery for bilateral retinoblastoma (tandem therapy) has also been reported [61].

Although intra-arterial chemotherapy has the advantage of fewer systemic side effects as compared to intravenous chemotherapy, there are concerns about retinal toxicity of melphalan. Exposure to fluoroscopy related radiation and ophthalmic artery occlusion are other concerns. Michaels and co-workers reported the toxicities and outcome of 19 eyes in 17 patients with retinoblastoma receiving SIAC treatment between 2008 and 2013 [62]. From the 87 treatments, mild local reactions were common. Myelosuppression was more common after triple-agent SIAC than single-agent melphalan. Further, SIAC is not always a straightforward procedure, and it may require an alternative approach [63, 64]. Alternative routes of intra-arterial chemotherapy for intraocular retinoblastoma appeared in the short term as effective and safe as the traditional drug infusion through the ophthalmic artery.

### 1.9.3 Intra-vitreal Chemotherapy

Intravenous chemotherapy has poor penetration in the avascular vitreous cavity. Hence, vitreous seeds remain the biggest challenge in the management of intraocular retinoblastoma. Intravitreal chemotherapy (IViC) has overcome this problem and found to be effective in the treatment of vitreous seeds. Similar to intra-arterial chemotherapy, melphalan remains the drug of choice for IViC. The use of melphalan is based on in vitro studies by Inomata and Kaneko [65]. Among the 12 anti cancer drugs that were studied, melphalan was found to be the most effective against retinoblastoma [65].

Munier et al. have described the technique of IViC injections with melphalan drug in a dose of 20–30 μg/0.1 mL [66]. The injection is given 3–3.5 mm away from limbus. The globe is shaken after the injection for uniform distribution of drug in the vitreous. After withdrawing the needle, triple freeze-thaw cryotherapy application is done at the injection site to avoid needle-track seeding. The procedure can be repeated every 7–10 days until a complete response is achieved [66]. Complete response is established if the seeds (1) completely disappear (vitreous seeding regression type 0), or are converted into (2) refringent and/or calcified residues (vitreous seeding regression type I), (3) amorphous, often non-spherical, inactive residues (vitreous seeding regression type II), or (4) a combination of the last two (vitreous seeding regression type III) [66]. With this technique, Munier et al. reported vitreous seed regression rate of 84% in eyes that had already been treated with intravenous and/or intra-arterial chemotherapy [66]. A localised peripheral salt-and-pepper retinopathy at the injection site was the only complication observed [66]. Another study by Shields et al. showed 100% (11/11) success rate with 1–4 cycles of monthly IViC (melphalan 20–30 μg) at 2 year follow-up [67].

Some investigators have also used topotecan as intravitreal injection [68]. Topotecan has a longer half life; it is used in a concentration of 8–20 μg/0.04 mL. Ghassemi et al. studied the

effect of intravitreal topotecan (8–20 μg in 0.04 mL of balanced salt solution) combined with melphalan (40 μg in 0.04 mL of diluent) and found the combination to be safe and effective [68].

It is important to bear in mind that IViC is not a primary treatment modality but should be used as a salvage therapy in cases of recalcitrant and recurrent vitreous seeds.

Careful case selection and meticulous screening is very important. Contraindications for IViC include anterior segment or ciliary body invasion, group E retinoblastoma, presence of complete posterior vitreous detachment, diffuse vitreous seeds in all quadrants and total retinal detachment [69]. The risk of extra-ocular spread following IViC was evaluated by Smith et al. [70]. Of the 315 eyes of 304 patients who underwent 1300 injections, the proportion of patients with extra-ocular spread was found to be 0.003 [70]. Besides the risk of needle track seeding, the drug itself can have side effects on the retinal function. There have been some concerns about permanent melphalan induced retinal toxicity as evidenced by reduced ERG amplitude [69].

## 1.10 Radiotherapy

Radiation therapy has an established role in selected patients. It may be administered in the form of plaque brachytherapy or EBRT.

### 1.10.1 Plaque Brachytherapy

Plaque brachytherapy is mainly used as a secondary treatment option for recurrent and residual tumours after failure of systemic and focal therapies. The indications include unilateral solitary tumours <16 mm in base and <8 mm in thickness located anterior to the equator upto the ora serrata [71–74]. Larger tumours and those involving the macula are not suitable for plaque therapy. For tumours near the optic disc, special plaques with a notch are used. The most commonly used radioisotopes are Iodine ($I^{125}$) and Ruthenium ($Ru^{106}$) [75–77]. $I^{125}$ seeds are inserted into a gold carrier to protect the normal surrounding tissue from radiation effects. A dose of 40 Gy is provided to the apex of the tumour with the help of dosimetry planning. The plaque is kept in situ for a period of 2–4 days, until the desired radiation dose has been delivered.

Radiation therapy may be associated with side effects that include dryness of eye, madarosis, cataract, scleral necrosis, retinopathy, papillopathy, optic neuropathy, and strabismus [71–74]. Second malignancies are not associated with local therapy. Shields et al. found plaque brachytherapy to be particularly useful for tumours that failed treatment with other conservative modalities. They observed tumour control in 79% of cases at 5-year follow-up, with young patients without vitreous or subretinal seeding showing the best long-term control [74]. Plaque brachytherapy has come up not only as a secondary treatment modality for recurrent or resistant tumours but also as a primary treatment. The American Brachytherapy Society Ophthalmic Oncology Task Force (ABS-OOTF) recommends primary brachytherapy for unilateral anterior lesions less than 15 mm in base and upto 10 mm in thickness in the absence of vitreous seeding [78].

### 1.10.2 External Beam Radiotherapy

External beam radiotherapy (EBRT) was extensively used for treatment of retinoblastoma prior to the chemotherapy era. Due to concerns about radiation induced growth deformities and second malignancies, the popularity of EBRT declined [79, 80]. Although it has limited use in intraocular retinoblastoma these days, EBRT is used as adjuvant therapy in cases with residual microscopic disease after enucleation, and as part of multi-modal therapy for orbital retinoblastoma. Side effects of EBRT include dryness, foreign body sensation, cataract, radiation retinopathy and papillopathy. Systemic complications like secondary malignancies in cases with germline mutations have been attributed to radiotherapy. Orbital hypoplasia is another side effect of EBRT (Fig. 1.11).

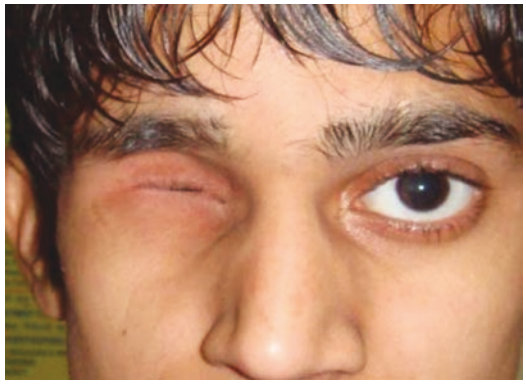

**Fig. 1.11** Late effects of radiation therapy

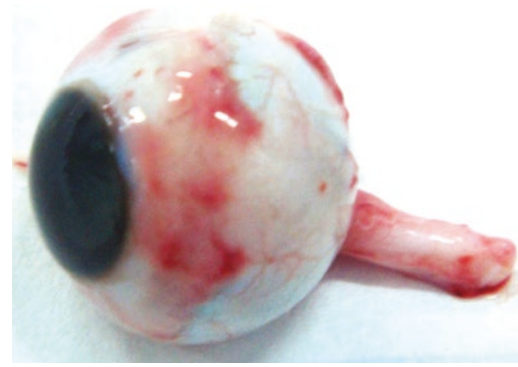

**Fig. 1.12** Enucleated eyeball

The advent of newer radiotherapy techniques has led to improved radiation delivery to the target with better sparing of normal tissue. Stereotactic conformal radiotherapy (SCR) uses highly accurate positioning to deliver treatment with small beams. A recent study has shown that SCR provides more homogeneous dose within the target volume and similar or lower doses to the surrounding normal tissues [81]. However, its efficacy over plaque therapy has not been proven. Proton beam therapy also provides a uniform dose coverage of the target and unlike photon beams, does not distribute energy beyond the target. As a result, the incidence of late effects of radiation are minimized [82]. However, proton therapy is expensive and is not widely available. Sethi et al. compared the risk of second malignancies in retinoblastoma survivors treated with photon and proton radiation therapy [82]. A significant difference was observed in the 10 year cumulative incidence of radiotherapy induced second malignancies between the proton and photon modalities ($p = 0.015$) [82].

## 1.11 Enucleation

Although one of the oldest modalities of treatment, enucleation remains the standard of care for advanced intraocular retinoblastoma with poor visual potential. Most often, Group E tumours are treated by enucleation. Unilateral Group D tumours may also be offered enucleation, especially if the potential for vision is poor. Due to late presentation, enucleation is one of the most commonly performed procedures in the developing world [83]. The surgery is done using minimal manipulation, and an optic nerve stump of 15 mm is recommended, to minimize the chances of residual disease at the resected end of the optic nerve. Gross inspection of the enucleated globe should be done to look for any suspicious area (Fig. 1.12). An adequate sized implant should be placed in the socket to restore the lost volume at the time of surgery. Careful microscopic examination of the enucleated specimen should be performed to look for presence of high risk histopathological features. These include tumour infiltration into the iris, ciliary body, anterior chamber, massive choroidal invasion, scleral invasion and post-laminar optic nerve invasion [84]. Cases with one or more high risk features should be treated with six cycles of intravenous chemotherapy (VEC) as prophylactic treatment against local recurrence/systemic metastasis [85]. Presence of tumour cells in the extra-scleral tissues or at the resected end of optic nerve is indicative of residual microscopic disease, which should be treated with adjuvant chemotherapy and radiotherapy. An ocular prosthesis (artificial eye) is usually fitted at six weeks after surgery and every effort should be made to achieve a good cosmetic outcome.

## 1.12 Extraocular Retinoblastoma

Although extraocular disease is rare in the West, it is not an unusual feature in the developing world, where it constitutes 20–50% of all cases [83, 86, 87]. Extra-ocular disease is associated with a 10–27 times higher risk of metastasis and therefore demands a more aggressive treatment approach [87]. Extra-ocular disease may be non-metastatic (confined to the orbit and regional lymph-nodes) or metastatic. Figure 1.13 shows a child with tumour involving the right eye and extensive orbital invasion.

Orbital exenteration, a mutilating and disfiguring surgery, was used to treat patients with overt orbital disease in earlier days. Studies have shown that a multi-modal approach that consists of neo-adjuvant chemotherapy, surgery, EBRT, and adjuvant chemotherapy is effective in managing local orbital extension [88–90]. Treatment is initiated with 3–6 cycles of systemic chemotherapy. This induces tumour regression and makes enucleation surgery possible. After enucleation, orbital irradiation is administered followed by adjuvant chemotherapy for a total of 12 cycles.

Chantada et al. reported a 5-year EFS rate of 84% in 15 patients with orbital or preauricular disease treated with chemotherapy that included vincristine, doxorubicin, and cyclophosphamide or vincristine, idarubicin, cyclophosphamide, carboplatin, and etoposide [89]. These patients also received EBRT of 4500 cGy administered to the optic chiasma for patients with orbital disease and to the involved nodes for those with pre-auricular lymphadenopathy.

Recently, a prospective randomized comparative study on 54 cases of Stage III Retinoblastoma (International Retinoblastoma Staging System) was published from our centre [91]. For chemotherapy, patients were randomized into two groups; one group was treated with high-dose triple-drug chemotherapy consisting of VEC and the other group with carboplatin and etoposide, alternating with cyclophosphamide, idarubicin, and vincristine (five drugs). The study showed more effective tumour control and a better safety profile with the VEC protocol [91]. Central nervous system (CNS) metastasis was the most common cause of relapse and death. None of the cases needed orbital exenteration. Patients with metastatic extraocular disease have a poor prognosis when treated with regimens of conventional doses of chemotherapy. Recently, there has been encouraging data to suggest that patients with distant metastatic disease may benefit from high-dose chemotherapy and EBRT in conjunction with bone marrow stem cell transplantation. Metastasis to the CNS can occur in advanced, untreated cases (Fig. 1.14). It is rare for a patient with metastatic CNS involvement to survive using the therapies described above. Second malignant neoplasms are a major concern for survival. Osteosarcoma is the commonest second malignancy; other second neoplasms include rhabdomyosarcoma and melanoma.

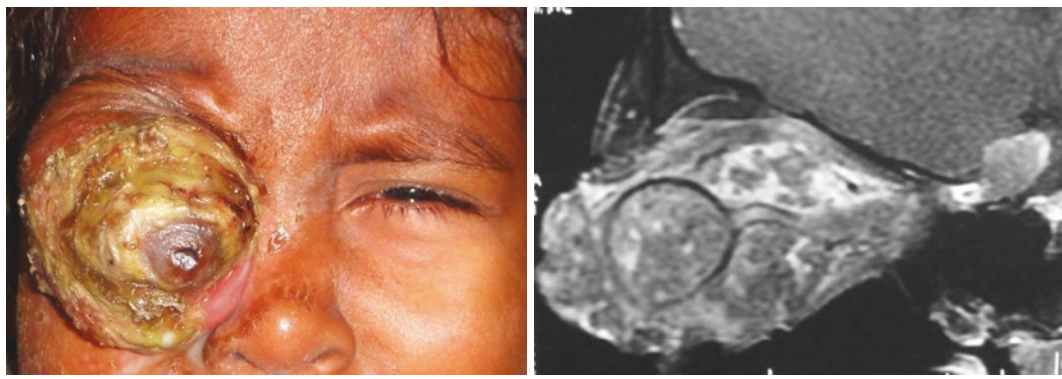

**Fig. 1.13** Orbital retinoblastoma

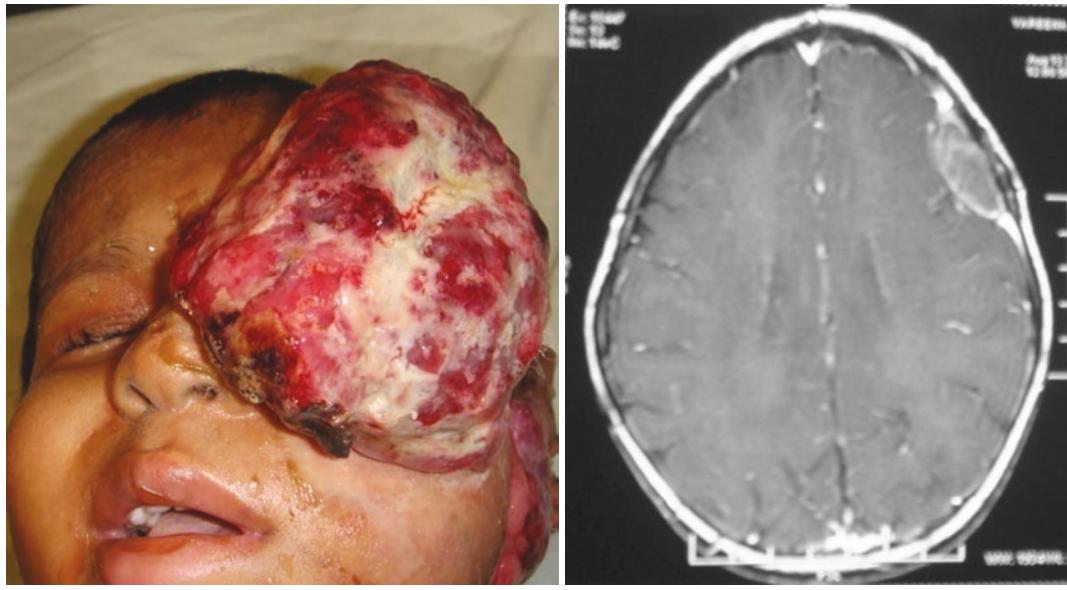

**Fig. 1.14** Metastatic retinoblastoma

## 1.13 Regression Patterns

Differentiation of tumour regression from an incomplete response or recurrence is critical for appropriate management. Upon regression, the tumour usually assumes a smaller size and attains some degree of calcification. While some tumours become completely calcified, others may have minimal or no calcification, making assessment of regression challenging (Table 1.5). Regression patterns following systemic chemo-reduction have been described [92].

**Table 1.5** Regression patterns in retinoblastoma following systemic chemotherapy

| Type | Regression pattern |
|---|---|
| Type 0 | No visible remnant |
| Type 1 | Completely calcified remnant |
| Type 2 | Completely noncalcified remnant |
| Type 3 | Partially calcified remnant |
| Type 4 | Atrophic chorioretinal flat scar |

## 1.14 Prenatal Diagnosis

Advances in technology have facilitated pre-natal diagnosis of retinoblastoma [93]. Prenatal diagnosis can facilitate anticipatory planning for the child and the family. Both imaging as well as genetic testing can be used for prenatal diagnosis. Investigators have used high resolution ultrasound at 37 weeks of gestation to detect a 2–3 mm elevated lesion in a foetus at risk of heritable retinoblastoma [93]. Soliman et al. compared the conventional postnatal screening of familial retinoblastoma with prenatal RB1 mutation dentification followed by planned early-term delivery [94]. They concluded that in case of a parent having retinoblastoma, prenatal molecular diagnosis with early-term delivery increased the chances of infants having no detectable tumours at birth, better vision outcomes, and less invasive therapy [94].

To summarize, significant advances have been made in the diagnosis and management of retinoblastoma [95]. A clear understanding of these is essential for achieving the best outcome.

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