Orbital Retinoblastoma

17

Santosh G. Honavar

Contents

17.1 Introduction

The systemic prognosis of retinoblastoma has dramatically improved in the last few decades due to earlier diagnosis and better management protocols [1]. The 5-year survival rates of 88, 91, and 93 % have been reported from developed countries such as the United Kingdom [2], Japan [3], and the United States, respectively [1, 4]. However, the mortality is still high in the developing nations [5, 6]. Presentation for medical attention at advanced stage of disease due to compounding social and economic factors is believed to be the main cause of poor survival [3]. One of the major contributors to mortality is orbital retinoblastoma [7–9]. This chapter provides an update on the current concepts in the management of orbital retinoblastoma.

17.2 Incidence

Orbital retinoblastoma is rare in developed countries. Ellsworth observed a steady decline in the incidence of orbital retinoblastoma in his large series of 1,160 patients collected over 50 years [10]. The overall incidence was 8.2 % in the period 1925 to 1959 and 7.6 % between years 1959 and 1974 [10]. Later, authors from the same center reported that 6.3 % (11 of 175) of the patients presented with primary orbital retinoblastoma from 1980 to 1986 [11]. The histopathologic evidence of scleral invasion, extrascleral

S.G. Honavar, MD, FACS
Ocular Oncology Service, Centre for Sight,
Road No 2, Banjara Hills, Hyderabad 500034, India
e-mail: santosh.honavar@gmail.com

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extension, and optic nerve infiltration, although variable, is about 2 % [12].

Orbital retinoblastoma is relatively more common in the developing countries. In a recent large multicenter study from Mexico, 18 % of 500 patients presented with an orbital retinoblastoma [13]. A Taiwanese group reported that 36 % (42 of 116) of their patients manifested with orbital retinoblastoma [14]. The incidence is higher (40 %, 19 of 43) in Nepal, with proptosis being the most common clinical manifestation of retinoblastoma [15].

17.3 Clinical Manifestations

There are several clinical presentations of orbital retinoblastoma.

17.3.1 Primary Orbital Retinoblastoma

Primary orbital retinoblastoma refers to clinical or radiologically detected orbital extension of an intraocular retinoblastoma at the initial clinical presentation, with or without proptosis or a fungating mass (Fig. 17.1). Silent proptosis without significant orbital and periocular inflammation in a patient with manifest intraocular tumor is the characteristic presentation. Proptosis with inflammation generally indicates reactive sterile orbital cellulitis secondary to intraocular tumor necrosis. The other manifestations include a palpable orbital mass or an eyelid swelling. Exuberant fungating orbital mass, a dramatic manifestation of orbital retinoblastoma, is rarely seen. Such patients need orbital imaging, preferably with magnetic resonance imaging techniques.

17.3.2 Secondary Orbital Retinoblastoma

Orbital recurrence following uncomplicated enucleation for intraocular retinoblastoma is termed secondary orbital retinoblastoma (Fig. 17.2). This may present as an orbital mass several weeks to years after the primary surgery. Unexplained displacement, bulge, or extrusion of a previously well-fitting conformer or a prosthesis, a displacement of the implant, or a palpable orbital mass would be suggestive of an orbital recurrence. A vascular conjunctival nodule may also be a feature of orbital retinoblastoma.

17.3.3 Accidental Orbital Retinoblastoma

Inadvertent perforation during enucleation, fine needle aspiration biopsy, or intraocular surgery in an eye with unsuspected intraocular retinoblastoma should be considered as accidental orbital retinoblastoma and managed as such (Fig. 17.3).

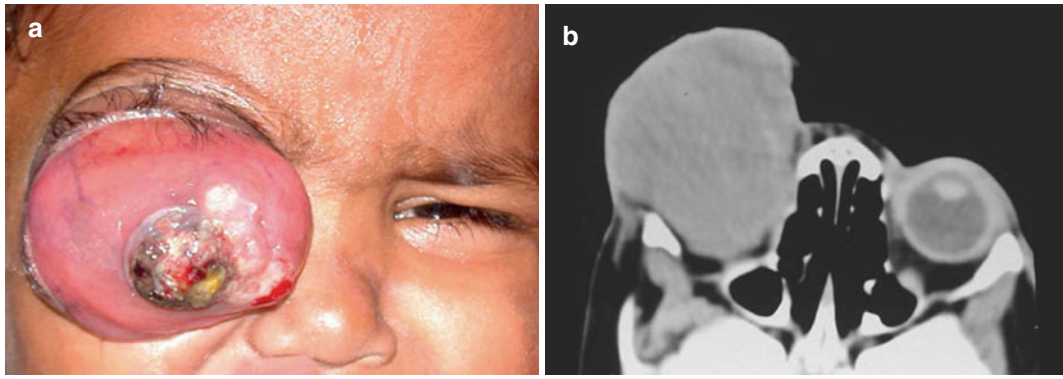

Fig. 17.1 Primary orbital retinoblastoma. Orbital extension of an intraocular retinoblastoma at the initial clinical presentation, manifesting as massive proptosis (**a**). Computed tomography scan confirmed an orbital mass (**b**)

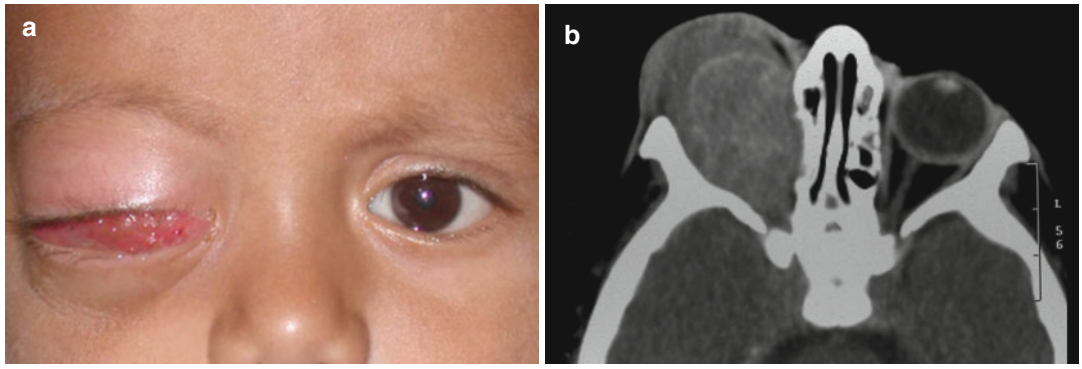

Fig. 17.2 Secondary orbital retinoblastoma. Orbital recurrence of retinoblastoma 6 months following enucleation for intraocular retinoblastoma in the right eye (**a**). Computed tomography scan showing an orbital mass (**b**)

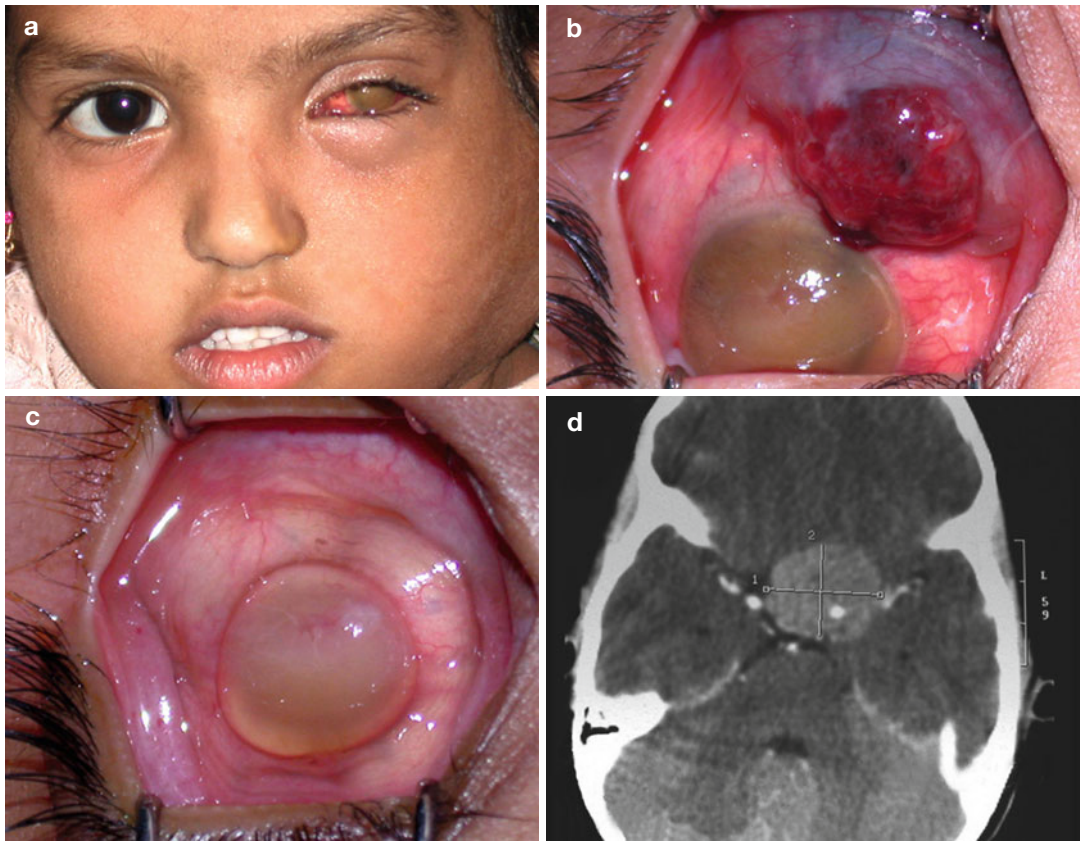

Fig. 17.3 Accidental orbital retinoblastoma. Cervical lymphadenopathy 6 months following hyphema drainage in an eye with unsuspected retinoblastoma (**a**). Note vascular conjunctival mass (**b**). Although the conjunctival mass resolved with high-dose chemotherapy (**c**), the child succumbed to intracranial metastasis (**d**)

17.3.4 Overt Orbital Retinoblastoma

Previously unrecognized extrascleral or optic nerve extension discovered during enucleation qualifies as overt orbital retinoblastoma (Fig. 17.4). A pale pink to cherry red episcleral nodule, generally in a juxtapapillary location or at the site of vortex veins, may be visualized during enucleation. An enlarged and inelastic optic nerve with or without nodular and adherent optic

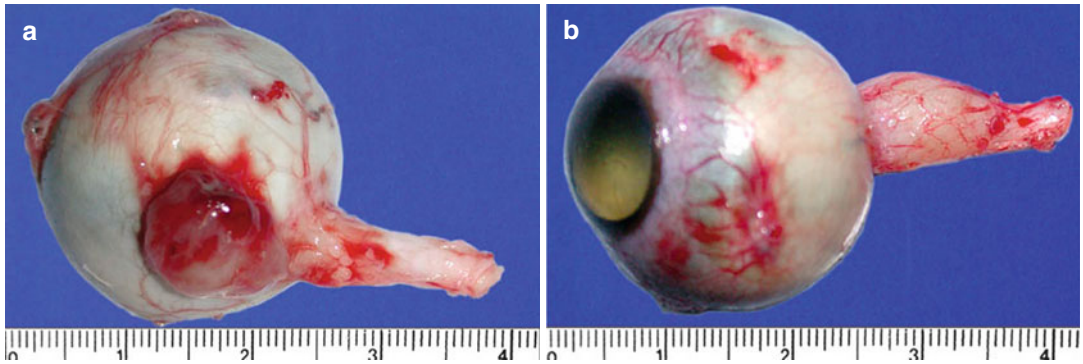

Fig. 17.4 Overt orbital retinoblastoma. Previously unrecognized extrascleral mass (**a**) and optic nerve extension (**b**) discovered during enucleation

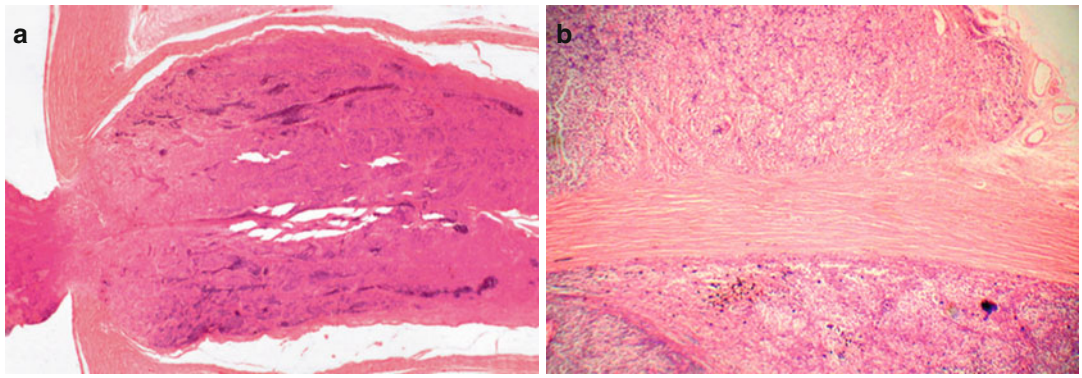

Fig. 17.5 Microscopic orbital retinoblastoma. Histopathologic evaluation of an eye enucleated for intraocular retinoblastoma. Invasion of the optic nerve to the level of transection (**a**) and extrascleral extension (**b**)

nerve sheath are clinical indicators of optic nerve extension of retinoblastoma that can be recognized on careful inspection of the eye following enucleation.

17.3.5 Microscopic Orbital Retinoblastoma

In several instances, orbital extension of retinoblastoma may not be clinically evident and may only be microscopic. Detection of full-thickness scleral infiltration, extrascleral extension, and invasion of the optic nerve on histopathologic evaluation of an eye enucleated for intraocular retinoblastoma are unequivocal features of orbital retinoblastoma (Fig. 17.5). Tumor cells in choroidal and scleral emissaria and optic nerve sheath indicate possible orbital extension mandating further serial sections and detailed histopathologic analysis.

17.4 Diagnostic Evaluation

A thorough clinical evaluation paying attention to the subtle signs of orbital retinoblastoma is necessary. Magnetic resonance imaging preferably or computed tomography scan of the orbit and brain in axial and coronal orientation with 2-mm slice thickness helps confirm the presence of orbital retinoblastoma and determine its extent. Systemic evaluation, including a detailed physical examination, palpation of the regional lymph nodes, and fine needle aspiration biopsy of the enlarged lymph nodes, imaging of the orbit and brain, chest

x-ray, ultrasonography of the abdomen, bone marrow biopsy, and cerebrospinal fluid cytology are necessary to stage the disease. Technetium-99 bone scan and positron-emission tomography coupled with computed tomography (PET-CT) may be useful modalities for early detection of subclinical systemic metastases [16, 17]. Orbital biopsy is rarely required and should be considered specifically when a child presents with an orbital mass following enucleation or evisceration where the primary histopathology is unavailable.

17.5 Management

17.5.1 Primary Orbital Retinoblastoma

Primary orbital retinoblastoma has been managed in the past with orbital exenteration, chemotherapy, or external beam radiotherapy exclusively or in sequential combination, with variable results [18–23]. It is well known that local treatments have a limited effect on the course of orbital retinoblastoma. Orbital exenteration alone is unlikely to achieve complete surgical clearance and preclude secondary relapses and systemic metastasis; external beam radiotherapy will not affect systemic micrometastasis; and chemotherapy alone may not eradicate residual orbital disease [21, 22]. Therefore, multimodal therapy with a judicious, customized, and sequential combination of neoadjuvant and adjuvant chemotherapy, surgery, and EBRT is considered to be more effective. In a case series of five children, Goble and associates demonstrated long-term survival with local surgical excision, orbital radiotherapy, and systemic chemotherapy [21].

We have developed a treatment protocol (Table 17.1) consisting of triple-drug (vincristine, etoposide, and carboplatin) high-dose neoadjuvant chemotherapy (3–6 cycles) followed by surgery (enucleation, extended enucleation, or orbital exenteration as appropriate after determining the extent of residual orbital tumor by CT scan), orbital radiotherapy, and adjuvant chemotherapy (Table 17.2) [24, 25]. In all, 12 cycles of chemotherapy are administered.

Table 17.1 Suggested protocol for management of primary orbital retinoblastoma

Baseline investigations		
Computed tomography scan or magnetic resonance imaging		
Bone marrow biopsy		
Cerebrospinal fluid cytology		
Treatment		
Initial chemotherapy		High-dose three-drug chemotherapy for 3–6 cycles (every 3 weeks)
Surgery	Enucleation	Assessment of orbital tumor by imaging after completion of third cycle
		After completion of third cycle if the orbital tumor is resolved
		Additional 3 cycles of chemotherapy
		After completion of sixth cycle if the orbital tumor is resolved
	Exenteration	After completion of sixth cycle if the orbital tumor is present
External beam radiation		45–50 Gy (fractionated) to the orbit
Subsequent chemotherapy		Continuation high-dose chemotherapy for 12 cycles
Follow-up investigations		
Imaging at 12, 18, 24, and 36 months		
Bone marrow biopsy and cerebrospinal fluid cytology at 6, 12, 18, 24, and 36 months		

Table 17.2 Chemotherapy drugs, dose (milligram per kilogram body weight), and schedule for treatment of orbital retinoblastoma

	Standard dose		High dose	
Drugs	Day 1	Day 2	Day 1	Day 2
Vincristine	0.05		0.025	
Etoposide	5.0	5.0	12.0	12.0
Carboplatin	18.6		28.0	

17.5.2 Secondary Orbital Retinoblastoma

Our treatment protocol outlined for primary orbital retinoblastoma currently under evaluation for secondary orbital retinoblastoma and early results have been very encouraging. Surgical

intervention in such cases may be limited to excision of the residual orbital mass or an orbital exenteration depending on the extent of the residual tumor after the initial 3–6 cycles of high-dose neoadjuvant chemotherapy. Surgery is not necessary if the orbital tumor completely resolves following neoadjuvant chemotherapy. Treatment is completed with orbital EBRT and chemotherapy for a total of 12 cycles.

17.5.3 Accidental Orbital Retinoblastoma

The surgeon should be careful not to accidentally perforate the eye during enucleation for retinoblastoma. Many surgeons prefer to avoid traction sutures applied at the insertion of extraocular muscles to minimize the risk of accidental perforation. Instead, hemostat applied to medial or lateral rectus muscle stump or cryoprobe applied at the limbus provides adequate traction. Eyes manifesting tumor necrosis with aseptic orbital cellulitis pose specific risk for accidental perforation. Surgery in such eyes is best performed when the inflammation is resolved. A brief course of preoperative oral and topical steroids helps control inflammation. If inadvertent perforation does occur during enucleation, further steps of surgery should be performed carefully, with minimal manipulation, under good illumination and magnification, and preferably by a senior surgeon. If the perforation is small, orbital contamination can be limited by sealing the perforation site with a patch of Tenons glued into position with cyanoacrylate glue. Larger perforations can be handled by isolating the area with dry absorbent cotton, suturing the perforation if possible and sealing the suture site with a glued-on Tenon's patch. Extensive perforations can be managed by isolating the area with dry absorbent cotton and suction evacuation of tumor tissue prolapsing through the wound using a powered suction, followed by wound suturing and glued-on Tenon's patch. In all these situations, enucleation is completed as planned with minimal manipulation. Integrated orbital implants are best avoided, and a polymethyl methacrylate or silicone implant is preferred in such cases, since there would be an impending need for adjuvant radiotherapy.

If a patient has undergone inadvertent intraocular surgery, the immediate management depends on the nature of the intraocular surgery, the approach used, the possibility of orbital contamination with tumor cells, and the severity of retinoblastoma. There is scope to institute chemoreduction or perform intra-arterial chemotherapy as appropriate to try and salvage the eye if the retinoblastoma is less advanced, the eye is salvageable, and the extent of the intraocular surgery is limited. If the tumor is advanced, with no scope for eye salvage, then the treatment strategy depends on the nature of the intraocular surgery. For example, if a patient has undergone only a fine needle aspiration biopsy from the clear corneal approach, only a standard enucleation is indicated; no special treatment would be necessary. If fine needle aspiration biopsy has been performed by the pars plana route, then only an enucleation with en bloc excision of the conjunctiva around the site of perforation and triple freeze-thaw cryotherapy to the edges of the residual conjunctiva would be considered optimal. No special treatment is necessary in a patient who has undergone a cataract surgery by the clear corneal approach with preservation of the posterior capsule. However, en bloc enucleation with cryotherapy to the edges of the residual conjunctiva is mandated in a patient who has undergone a scleral tunnel approach to cataract surgery and where the posterior capsule has not been preserved. A similar strategy is adopted if a patient has undergone a 23-gauge or 25-gauge sutureless pars plana vitrectomy where conjunctiva has not been extensively dissected.

All eyes that have undergone an extensive intraocular surgical procedure such as a three-port conventional pars plana vitrectomy for unsuspected retinoblastoma should be considered for prompt enucleation [25]. The conjunctiva overlying the ports with about 4-mm clear margin should be included en bloc with enucleation. Random orbital biopsy may be also obtained, but there are no data to support its utility. If immediate enucleation is not logistically possible, then the vitrectomy ports or the surgical

incision should be subjected to triple freeze-thaw cryotherapy and enucleation should be performed at the earliest opportunity. It may also be acceptable if high-dose neoadjuvant chemotherapy is provided for 3–6 cycles before performing enucleation.

Histopathologic evaluation of the eyes with accidental perforation or inadvertent intraocular surgery may include specific analysis of the sites of sclerotomy ports or the cataract wound for tumor cells.

All patients with accidental orbital retinoblastoma after histopathologic confirmation of the extent of contamination (tumor cells in the needle track/surgical site, tumor cells in the conjunctiva) and the presence of high-risk features undergo baseline systemic evaluation to rule out metastasis. Orbital external beam radiotherapy and 6–12 cycles of standard or high-dose chemotherapy are recommended depending on the histopathology report, the nature and extent of intraocular surgery or perforation, and the extent of orbital contamination by the tumor [26].

17.5.4 Overt Orbital Retinoblastoma

If an extraocular extension is macroscopically visualized during enucleation, special precaution is taken to excise it completely along with the eyeball, preferably along with the layer of Tenon's capsule kept intact in the involved area [24]. Moreover, steps should be taken to obtain about >15-mm-long optic nerve stump in all cases of advanced retinoblastoma [24]. In case the optic nerve is thickened and inelastic and is suspected to be involved and the optic nerve stump is small (<10 mm), it may be best to explore the orbit and attempt to obtain an additional length of the optic nerve. This difficult maneuver is made easier by hemostasis, good magnification, and direct illumination. Placement of a biointegrated implant such as hydroxypapatite or porous polyethylene is generally avoided if orbital extension is present [24]. Although most implants structurally tolerate radiotherapy well, implant vascularization may be diminished by radiotherapy, thus increasing the risk of implant exposure.

All patients with overt orbital retinoblastoma after histopathologic confirmation undergo baseline systemic evaluation to rule out metastasis. Orbital external beam radiotherapy (fractionated 45–50 Gy) and 12 cycles of high-dose chemotherapy are recommended.

17.5.5 Microscopic Orbital Retinoblastoma

The management protocol for patients with microscopic extension of retinoblastoma up to the level of optic nerve transection, scleral infiltration, and extrascleral extension detected on histopathologic evaluation of the enucleated specimen includes orbital external beam radiotherapy (fractionated 45–50 Gy) and 12 cycles of high-dose chemotherapy [12, 26].

17.6 Prognosis

Orbital retinoblastoma has traditionally carried a poor prognosis with mortality rates ranging from 25 to 100 % [19–21, 27]. The presence of orbital invasion was associated with a 10–27 times higher risk of systemic metastasis as compared to cases without orbital invasion [5]. In 30 carefully selected cases of orbital retinoblastoma without intracranial extension and systemic metastasis, where we followed the management protocol as described above, there was an excellent outcome. Orbital retinoblastoma was primary in 16 (54 %), secondary in four (13 %), accidental in seven (23 %), overt in two (7 %), and microscopic in one (3 %). In patients with primary orbital retinoblastoma, 15 of the 16 involved eyes became phthisical and the orbital component of the tumor completely resolved after 3–6 cycles of high-dose neoadjuvant chemotherapy. No clinically apparent orbital tumor was found in these patients during enucleation. Only one patient had residual orbital tumor and needed orbital exenteration. All the patients with primary orbital retinoblastoma completed the treatment protocol of orbital external beam radiotherapy and 12 cycles of chemotherapy. Two patients with secondary orbital

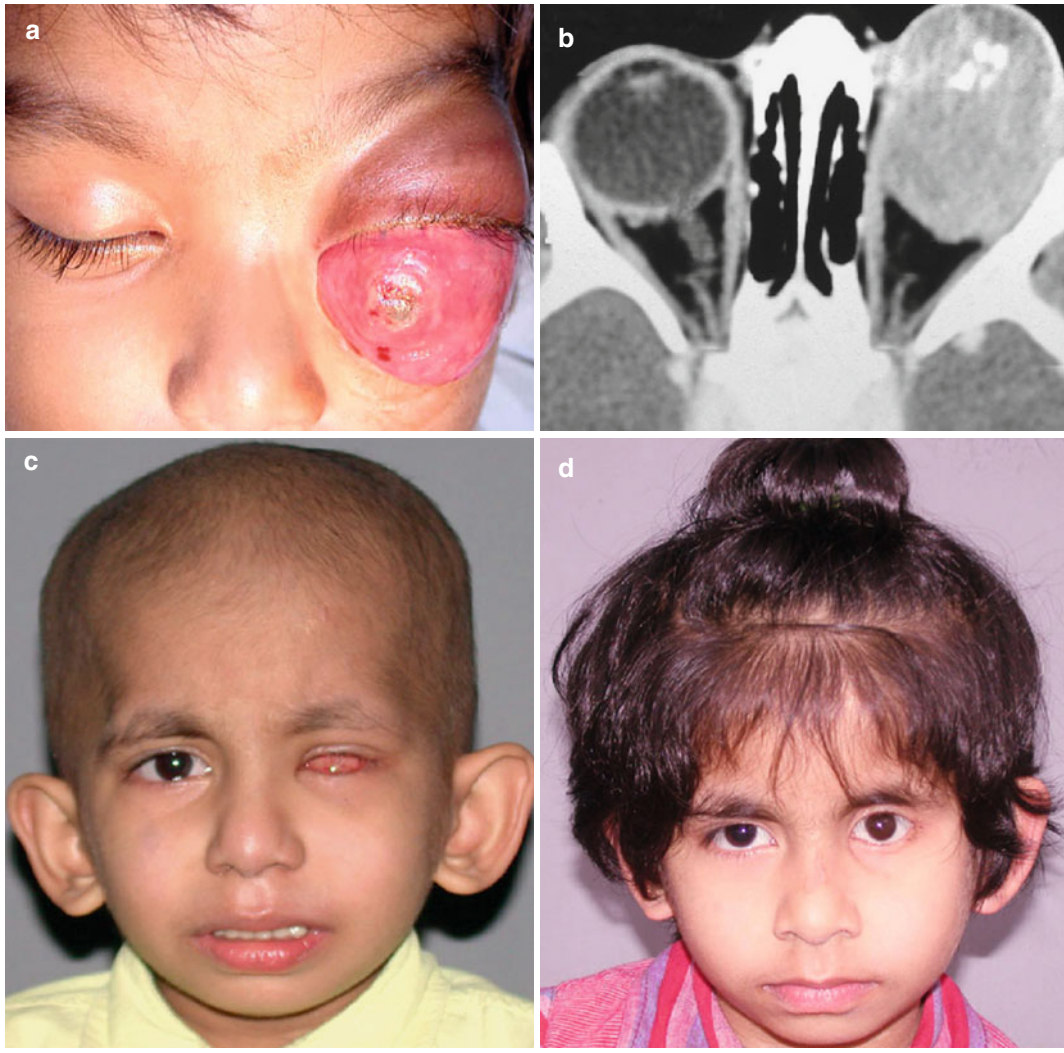

Fig. 17.6 Outcome in a case of primary orbital retinoblastoma. A 2-year-old child with primary orbital retinoblastoma in the left eye (**a**). Computed tomography scan showing massive orbital tumor (**b**). Following 3 cycles of neoadjuvant chemotherapy, enucleation, orbital external beam radiotherapy, and additional 9 cycles of chemotherapy, the orbital tumor is completely resolved (**c**). Three years later, the child is free of local and systemic recurrence and has an acceptable cosmetic appearance (**d**)

retinoblastoma resolved completely with neoadjuvant chemotherapy alone, while two needed orbital exenteration for residual tumor. All four received orbital external beam radiotherapy and 12 cycles of chemotherapy. Systemic metastasis occurred in two patients (both with primary orbital retinoblastoma with optic nerve infiltration up to the orbital apex) at a mean follow-up of 60 months, while 28 (93.4 %) were tumor-free and achieved acceptable cosmetic outcome (Fig. 17.6) [25]. In addition to our observations, several authors have reported improved survival when surgery (usually exenteration) was combined with chemotherapy [10, 18, 22, 27]. A recent large series reported poor treatment compliance (68 %) and reduced overall survival (40 %) in orbital retinoblastoma [28]. Compared to the previously reported survival, our current multimodal protocol has provided excellent survival in a limited number of selected patients [24, 25].

17.7 Prognostic Factors

The identification of frequency and significance of high-risk histopathologic factors that can reliably predict orbital recurrence of retinoblastoma and subsequent systemic metastasis is vital for patient selection for adjuvant therapy (Chap. 16) [5, 9, 12]. It is generally agreed that invasion of the optic nerve to transection, scleral infiltration, and extrascleral extension are the risk factors that are predictive of orbital recurrence [5, 9]. The role of adjuvant therapy in minimizing the risk of systemic metastasis and improving ultimate survival in patients with various histopathologic risk factors is discussed elsewhere (Chap. 11) [24].

Conclusions

Orbital retinoblastoma encompasses the spectrum of orbital invasion at primary presentation (primary), orbital recurrence following enucleation (secondary), inadvertent perforation or intraocular surgery in an eye with unsuspected retinoblastoma (accidental), intraoperative discovery of extraocular or optic nerve extension (overt) and scleral, extrascleral, and optic nerve transection involvement with tumor cells on histopathology (microscopic). The current preferred management for primary and secondary orbital retinoblastoma is multimodal with a combination of initial high-dose neoadjuvant chemotherapy, surgery, external beam radiotherapy, and prolonged (adjuvant) chemotherapy for 12 cycles in all. For accidental, overt, and microscopic retinoblastoma, each clinical situation is unique with a gross variation in tumor load, and hence, optimal customization of multimodal approach can help improve prognosis while limiting the side effects of treatment.

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