Retinoblastoma: Focal Therapy – Laser Treatment, Cryotherapy, and Brachytherapy

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10.1 Introduction

In the management of intraocular retinoblastoma, the term "focal therapy" refers to focal modalities such as laser treatment, cryotherapy, and brachytherapy. They can be used as primary treatment for small tumors or in conjunction with intravenous chemotherapy for larger tumors (i.e., chemoreduction). Focal therapies have the inherent advantage of eradicating focal areas of tumor formation in the retina without any risk of regional or systemic side effects. In this chapter, general guidelines on the use of focal therapies are provided to assist an ophthalmic surgeon who is relatively new to the treatment of retinoblastoma. This chapter might also be of help to those ophthalmologists who would like to compare their current approach with principles and techniques used by other surgeons.

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10.2 Terminology

10.2.1 Focal Treatment

The term "focal therapy" in the management of retinoblastoma refers to the use of laser treatment, cryotherapy, and brachytherapy (Table 10.1). External beam radiotherapy (EBR) of retinoblastoma (local therapy rather than focal therapy) is discussed elsewhere (Chap. 14).

10.2.2 Focal Primary Treatment

Primary treatment refers to focal treatment employed as the sole therapy for a retinoblastoma lesion, typically for very small tumors (group A).

10.2.3 Chemoreduction

The term "chemoreduction" is used to describe the induction of tumor shrinkage with primary intravenous chemotherapy, followed by subsequent consolidation treatment with focal therapies, and less commonly with EBR.

10.2.4 Consolidation Treatment

In most centers, focal treatment is utilized most frequently following primary intravenous chemotherapy (i.e., chemoreduction) for group B–D tumors. The term "consolidation," as used in oncology, is a therapy that is used in tandem with primary therapy to "mop up" or eliminate the tumor cells that were resistant to, or were not inactivated by, the primary therapy. In most other childhood tumors, consolidation involves switching treatment modalities entirely or at least changing to different agents and/or doses of the primary modality. In the case of intraocular retinoblastoma, focal consolidation consists of direct laser photocoagulation, thermotherapy, cryotherapy, or brachytherapy.

Table 10.1 Local treatment of retinoblastoma

Treatment	Indication	Complications
Photocoagulation	Primary treatment, consolidation treatment, and for tumor recurrence	Tumor seeding into vitreous, retinal fibrosis and traction, retinal vascular occlusion
	Tumors not more than 3 mm in diameter, with no evidence of seeding, and located posterior to the equator	
Thermotherapy	Primary treatment, consolidation treatment, and for tumor recurrence	Iris atrophy, focal cataracts, tumor seeding into vitreous, retinal fibrosis and traction, retinal vascular occlusion
	Tumors not more than 3 mm in diameter, with no evidence of seeding, and located posterior to the equator	
Thermochemotherapy	Consolidation treatment	Iris atrophy, focal cataracts, tumor seeding into vitreous, transient retinal detachment, diffuse choroidal atrophy
	Tumors not more than 12 mm in diameter with no evidence of seeding, and located posterior to the equator	
Cryotherapy	Primary treatment, consolidation treatment, and for tumor recurrence	Large area of retinal atrophy, transient retinal detachment, retinal hole, retinal detachment
	Tumors not more than 3 mm in diameter with no evidence of seeding, and located anterior to the equator. "Cutting cryo" for posterior tumors	
Brachytherapy	Primary treatment, residual tumor following photocoagulation/thermotherapy/ thermochemotherap/cryotherapy, and for tumor recurrence	Radiation retinopathy, radiation optic neuropathy
	Tumor less than 15 mm in diameter	
	Presence of diffuse vitreous seeding is contraindication	

10.2.5 Photocoagulation

Described by Meyer-Swickerath in 1949, photocoagulation involves heating of the tumor to temperatures above 65 °C [1].

10.2.6 Hyperthermia

Hyperthermia implies raising the tumor temperature to 42–45 °C. Hyperthermia can be induced by laser, microwave, ultrasound, a localized current field, or ferromagnetic thermoseeds.

10.2.7 Thermotherapy

During the thermotherapy, the tumor is heated to a temperature of 45–60 °C. Oosterhuis and coworkers in 1994 introduced thermotherapy for choroidal melanomas using an infrared diode laser through the pupil (transpupillary thermotherapy [TTT]) [2]. Increased depth of tumor necrosis was achieved with TTT as compared with photocoagulation. Unlike hyperthermia, the cytotoxic effects of TTT are irreversible. Transpupillary thermotherapy can be achieved in retinoblastoma tumors using the 810 nm diode laser if the continuous mode is used to treat each spot for 45–60 s.

10.3 Focal Primary Treatment

Group A eyes with small intraretinal lesions away from critical structures are ideal candidates for focal primary therapy such as direct laser photocoagulation or cryotherapy. Larger focal tumors may be candidates for brachytherapy, and the indication for plaque radiotherapy is discussed below. Tumor foci that have not been treated with systemic chemotherapy may be more fragile and sensitive to intense energy density from the laser. For this reason, small spot size, high power, and prolonged burn duration, all of which contribute to increased power density, should be used with caution to avoid sudden mechanical tumor disruption and dissemination.

10.4 Focal Consolidation Treatment

10.4.1 Photocoagulation with Argon Green Laser (532 nm)

10.4.1.1 Background

The argon 532 nm (green) laser is particularly useful for very small retinoblastoma tumors (1.5 mm or less) or for focal consolidation after at least one cycle of systemic chemotherapy. As with other uses of retinal photocoagulation, focal consolidation should not be attempted if the retina containing the lesion is detached. We have found that the argon laser midrange visible (532 nm) wavelength is more readily absorbed in the nonpigmented retinoblastoma tissue than the longer wavelength infrared 810 nm diode laser, which becomes a factor in thick tumors or those occurring over calcified scars. The margins of the treated zone when using the argon laser are also easier to control than with the diode laser. Its main disadvantage when compared to the diode laser is the small spot size. Care must be taken to increase the power density judiciously within the small spot to avoid tumor dissemination or hemorrhages. Tumor disruption may occur in a small spot if the power out of the laser exceeds 700–800 mw for more than 0.3–0.4 s.

10.4.1.2 Technique

The 532 nm green laser is available as a tabletop solid state laser with an indirect laser delivery system that works best for transpupillary laser applications under general anesthesia. The desirable end point for the ophthalmologist is a gentle white spot generated at the boundary between normal retina and tumor edge (Fig. 10.1). The power is initially set between 250 and 350 mw for 0.3–0.5 s. Laser burns are initially placed at the edge of the lesion, half-on and half-off the tumor. The power and/or burn duration is slowly increased until a clear reaction is achieved. Punctate hemorrhage within the treatment spot is a sign that the power density is near the maximum tolerated levels.

Once the appropriate power level is set, the edge of the tumor is treated with overlapping burns to establish the perimeter of the lesion.

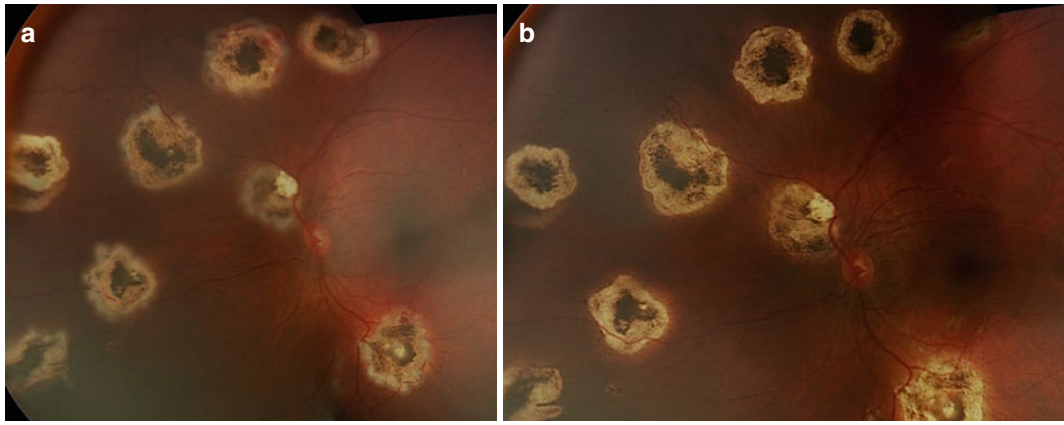

Fig. 10.1 Image taken immediately after the third consolidation laser photocoagulation (**a**). Each lesion was covered with laser burns. Note the distinct gentle white burn at the lesion edge. There is differential energy uptake. Three weeks later, all lesions are all flat with no clinical evidence of active disease (**b**)

Subsequently the entire lesion should be treated with burns having the same overlap. In the central thicker portions of the tumor, a visible whitening reaction following treatment may not be present. However, neither the power nor the burn duration should be increased once the parameters have been established.

10.4.1.3 Frequency of Treatment

Typically the treatment is repeated every 3–4 weeks, immediately before the next cycle of chemotherapy. A 2–4 week interval can be adopted if the course of intravenous chemotherapy has been completed. Edge tumor recurrence may appear if the laser consolidation process was insufficient, typically within the first 6 months after the last laser session (rarely up to 2 years) (Fig. 10.2).

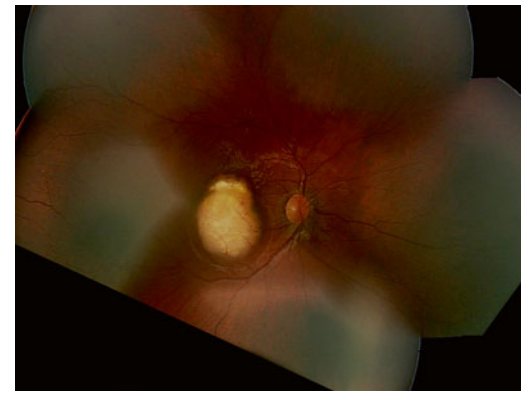

Fig. 10.2 Edge regrowth 8 weeks after the last laser treatment that almost covers the original flat chorioretinal scar. This child missed one follow-up EUA

10.4.1.4 Mechanism of Action

When photocoagulation is used on retinoblastoma lesions and the patient subsequently receives planned systemic chemotherapy (e.g., carboplatin) within 24 h, two tumor-destroying mechanisms may come into play. The first and the most important is direct tumor cell destruction generated by temperatures in excess of 65–70 °C within the treatment spot. The second mechanism occurs in the "donut" or ring of tissue extending for several millimeters outside the laser spot. Heat radiating out from the central spot increases the temperature to the thermotherapy range between 45 and 60 °C. In this region, there is a synergism with the carboplatin, assuming an adequate level of carboplatin is achieved in the tumor. To take advantage of the latter mechanism, we typically perform laser treatment within 24 h of the next cycle of intravenous chemotherapy.

10.4.1.5 Recommendations

In Los Angeles, our treatment protocol requires that each lesion be treated completely with laser on at least three occasions, 2–4 weeks apart. In our experience, even a flat chorioretinal scar achieved after one laser session cannot be considered sterilized. Larger lesions should be lasered at sequential examinations (minimum of three sessions) until the regressed tumor is either flat

(type IV scar) or completely calcified (type I). Fleshy type II regression should be lasered until you achieve a type I/IV scar or until you begin to notice retinal contraction. Small areas of type II regression may be left untreated immediately adjacent to the optic nerve or fovea, although the risk for tumor recurrence is always higher with type II vs. type I (or type IV) scars.

10.4.2 Photocoagulation with Diode Laser (810 nm)

10.4.2.1 Background

The 810 nm diode laser is most effective when there is intact RPE beneath the tumor. Through a 28D lens, the indirect ophthalmoscope delivery system offers a spot size of 0.35 mm (small spot) and 1.4 mm (large spot). We typically use the large spot indirect system, which provides improved safety and convenience for treating larger tumors versus the argon laser. Safety comes from the reduced likelihood of concentrated power intensity in a small spot creating tumor dissemination. The larger spot size as compared with argon saves treatment time, thus conferring convenience. It is also our impression that the depth of treatment with the diode laser is greater than the argon laser. However, it is more difficult to control the size of the burn with the diode laser, and care is warranted near the optic nerve and fovea.

10.4.2.2 Technique

The delivery technique is similar to that with argon green laser photocoagulation. The entire tumor is treated with overlap of the spots similar to that described above for the argon 532 nm laser. The initial power settings with the diode laser, especially when the large spot is used, are somewhat higher than for the argon laser. We generally select an initial setting of 300 mw for peripheral and macular lesions undergoing primary therapy and 400–500 mw for large tumors undergoing chemoreduction. If there is little color change induced at the initial power settings for these larger tumors, it is possible to increase the power up to 800 mw, provided that the surgeon is carefully monitoring for complications. The power settings will vary for each patient and for each tumor because of the degree of pigmentation underlying the lesion(s). As with the argon laser, both the power and burn duration can be increased incrementally until the appropriate end point is reached. We typically leave the duration of the treatment on the longest setting (9,000 ms) and set the interval to 50 ms; with these parameters the laser is essentially being used in continuous mode and the surgeon can control the duration of each spot treatment with the foot pedal. Using the diode laser in this manner allows the surgeon to use the diode laser for photocoagulation (1–10 s) or possibly thermotherapy (30–50 s).

10.4.2.3 Frequency of Treatment

The treatment is repeated every 3–4 weeks immediately before the next cycle of chemotherapy. A 2–4 week interval can be adopted if the course of intravenous chemotherapy has been completed.

10.4.2.4 Mechanism of Action

The most commonly employed effect is the direct heat-mediated tumor cell kill through photocoagulation. When longer spot duration is utilized (30–50 s), thermotherapy can be employed. The diode laser is most effective when intact RPE is present beneath the tumor to be treated. If the RPE has been destroyed, it is believed that most of the 810 nm wavelength energy passes into the orbit without being absorbed by the retinoblastoma (see discussion under TTT below).

10.4.2.5 Recommendation

If only one laser has to be chosen for use in delivering local therapy to retinoblastoma, the argon green laser is probably the most versatile.

10.4.3 Transpupillary Thermotherapy (TTT)

Transpupillary thermotherapy describes a laser system that couples large spot size (2–3 mm) and long burn duration (1 min) with low power settings, applied to achieve the end point of gentle whitening in the treatment spot. Initially described for choroidal melanoma, the infrared diode laser (810 nm) has been shown to be effective in killing melanoma cells because pigmentation in the tumor

allows absorption of the laser energy [2]. However, the long-term efficacy of this approach for treating small choroidal melanomas is under question. Transpupillary thermotherapy is difficult to adapt to the treatment of retinoblastoma because of the inherent lack of pigmentation in the tumor. Initially, intact RPE will absorb the laser energy and generate heat to affect the tumor. However, once the RPE is no longer intact under the retinoblastoma, relatively little of the delivered energy will be absorbed [3, 4]. However, a modified TTT regimen can be used for retinoblastoma by employing the large spot 810 nm diode laser in a continuous mode and using burn durations of 30–50 s. The effect of thermotherapy may be enhanced by using indocyanine green (ICG), a chromophore with an absorption peak of 805 nm, which coincides with the diode laser emission of 810 nm [5].

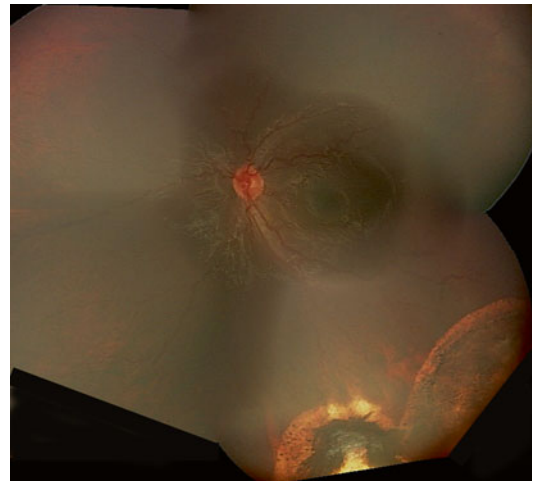

Fig. 10.3 Two cryotherapy scars in the inferotemporal periphery. Note the extensive destruction of peripheral retina

10.5 Transscleral Cryotherapy

10.5.1 Background

The indications for cryotherapy are similar to those for laser thermotherapy (i.e., small tumors) except that it is more suitable for anterior tumors [6]. Approximately 90–95 % of carefully selected tumors can be treated successfully with cryotherapy [7]. Overall, small tumors less than 3 mm in diameter, below 2 mm in height, and anterior to the equator are ideal candidates for cryotherapy. Larger tumors can occasionally be treated with cryotherapy alone, but the recurrence rate and risk of complications are higher. For group B tumors, it is usually better to utilize another modality such as intravenous chemotherapy to shrink the tumor so that it is amenable to local therapy. For tumors with localized vitreous seeding at the apex of the lesion (within 1–2 mm), cryotherapy can be utilized as primary therapy, although patients should be followed carefully because of the significant risk of recurrence and spread of the vitreous seeds.

10.5.2 Technique

The cryotherapy machine should be tested to ensure proper functioning and adequate ice ball formation at the tip. The cryoprobe tip position is verified by indirect ophthalmoscopy using the standard techniques of scleral indentation. Once the tip is centered directly under the tumor, freezing is begun. The ice ball used to freeze a tumor should cover the apex for 2 mm for adequate coverage and to incorporate all of the vitreous near the lesion that may contain the local tumor cell clumps or "seeds." The lateral spread of the ice ball should be monitored as well as the apex of the tumor to minimize the treatment of the uninvolved retina. Double or triple freeze-thaw cycles of cryotherapy are generally applied. The number of sites treated with cryotherapy at one setting should be limited to two or three because of the risk of creating a secondary serous or rhegmatogenous retinal detachment with more extensive treatment. It should also be kept in mind that cryotherapy tends to destroy a relatively large amount of peripheral retina (Fig. 10.3). Complications of cryotherapy can include retinal breaks that lead to rhegmatogenous retinal detachment, particularly in tumors located in the superior quadrants and those that have preexisting areas of calcification [8]. Cryotherapy is contraindicated for the treatment of more than one quadrant of disease at the ora serrata. For tumors located posterior to the equator, a small conjunctival incision in the fornix located between the rectus muscles may be necessary to advance the

curved cryoprobe posteriorly ("cutdown" cryotherapy). Careful monitoring of the probe position is required when performing posterior cryotherapy to avoid inadvertent treatment of the macula or optic nerve. Following the completion of cryotherapy, it is recommended that a subconjunctival injection of marcaine and dexamethasone be given for pain control and episcleral scarring, respectively.

10.5.3 Mechanism of Action

Cryotherapy is a local destructive modality that kills tumor cells mechanically via ice crystal disruption of the cell membranes.

10.5.4 Frequency of Treatment

The treatment is repeated every 3–4 weeks. A flat chorioretinal scar is the desired end point.

10.5.5 Recommendations

Cryotherapy is suitable for the anteriorly located group A tumors. Excessive cryotherapy should be avoided to minimize risk of complications.

10.6 Brachytherapy

10.6.1 Background

Brachytherapy (after Greek "brachy," for short distance) refers to implantation of radioactive material within or close to the tumor. Moore first used brachytherapy for uveal melanoma in 1930 by inserting radon-222 seeds into the tumor [9]. This technique was later modified by Stallard when he introduced cobalt-60 radioactive plaques sutured to the episcleral surface [10, 11]. Iodine-125 and ruthenium-106 isotopes are the most common source of radiation currently used in brachytherapy for retinoblastoma [12, 13]. In the United States, iodine-125 is the preferred radioactive source for ocular brachytherapy [14]. In Europe, ruthenium 106 is commonly used as a radioactive source for episcleral brachytherapy [15]. Ruthenium offers some advantages over iodine as a source of radiation to be used in brachytherapy for retinoblastoma. Ruthenium has a longer half-life of 6 months compared to iodine [16]. Other less frequently used radionuclides used for episcleral brachytherapy are palladium-103, gold (aurum)-198, iridium-192, and strontium-90. Improved calculation of dose distribution for clinical planning has ushered in the routine use of ruthenium for retinoblastoma and choroidal melanoma at the University of South California and Children's Hospital Los Angeles [17].

10.6.2 Technique

The principles of brachytherapy and plaque design are beyond the scope of this chapter. A standard apical dose of 40–45 Gy is usually prescribed for retinoblastoma, which is significantly lower than the dose used for choroidal melanoma [18]. The dose rate for retinoblastoma is typically 1,000 cGy per day, and the plaque is removed in a second operation 2–3 days later. Unfortunately, most children require sedation and hospitalization during the treatment to prevent dislodging of the plaque. The surgical technique of plaque application is similar to that used for uveal melanoma.

10.6.3 Mechanism of Action

Tissue absorption of ionizing radiation causes DNA damage, loss of reproductive capacity, and cell death. Retinoblastoma with a large proportion of dividing cells is more radiosensitive than uveal melanoma. Because of the dose gradient in episcleral plaque radiotherapy, the most severe effects are seen at the tumor base, where the dose of radiation is the highest. Astrahan and colleagues recently described a simple concept of shielding each ^{125}I source by creating deeper slots in the gold carrier, thereby increasing individual source collimation [17]. Their "slotted" plaque reduces delivered scleral dose by as much as 50 % without reducing the dose to the apex.

10.6.4 Frequency of Treatment

Plaque radiotherapy is usually applied only once. The treatment effects are noticeable within 4 weeks. The tumor typically regresses completely with only residual calcification. Failure of a lesion to respond to brachytherapy may indicate that it was a "presumed" early retinocytoma.

10.6.5 Recommendations

Brachytherapy should not be considered for routine focal consolidation because of a very high risk of aggressive radiation retinopathy in eyes that have received chemotherapy and/or external beam radiation (Fig. 10.4). Instead it is useful for either the primary treatment of an isolated group B tumor, or anterior to the equator, or for the treatment of edge recurrences that are too large or extensive for laser or cryotherapy alone (Fig. 10.5). Unlike external beam radiotherapy, radiation exposure is limited to the ocular structures, and there is no increased risk of second non-ocular cancers or orbital hypoplasia. The ideal candidate for a radioactive plaque is a patient with a focal tumor (8 mm or less in thickness), without vitreous or subretinal seeds and more than 2 disk diameters away from the macula or optic nerve. Tumors with localized seeding (<3 mm from the tumor margin) can be treated with brachytherapy although the recurrence rate is higher. A large retinoblastoma tumor in the posterior pole treated with brachytherapy is likely to have a poor visual outcome, although in most cases the tumor has already destroyed central vision.

10.6.6 Efficacy

When used as the primary modality in eyes with retinoblastoma patients, Shields and colleagues reported a tumor recurrence rate of only 12 % at 1 year of follow-up and an overall tumor control rate of 79 % at 5 years [18]. Schueler and colleagues in Germany reported a 5-year tumor control rate of 94.4 % and a 5-year eye preservation rate of 86.5 % using ruthenium plaques, with a very high radiation dose to the tumor apex (>100 Gy) [16]. Brachytherapy is also effective as a salvage technique in eyes that have failed other types of therapy including external beam radiation, photocoagulation, or cryotherapy, as long as the seeding is absent or limited. Used as salvage therapy for eyes that have failed other treatment methods, Abramson reported an overall success rate for brachytherapy of 50 %, utilizing cobalt plaques [19]. Merchant and colleagues recently reported a salvage rate of 60 % in eyes that had failed chemotherapy or external beam radiotherapy [20]. Risks for tumor recurrence following brachytherapy include the presence of tumor seeds in the vitreous and subretinal space, large tumor size, prior failure of external beam radiation, lower dose of radiation (<38 Gy), and increasing patient age [16, 18, 20].

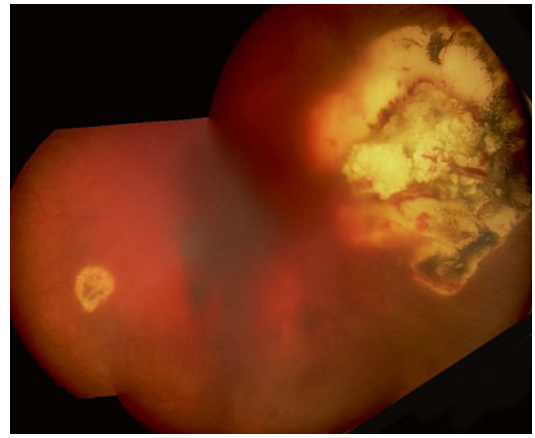

Fig. 10.4 Radiation retinopathy in the nasal periphery following primary brachytherapy. Recurrent vitreous seeding required external beam radiation therapy. This vitreous hemorrhage began about 6 months after completion of the external beam radiation therapy

10.6.7 Complications

Although the radiation dose for retinoblastoma is lower than the doses typically used for uveal melanoma, ocular complications should be anticipated. In their series of 208 tumors managed with plaque radiotherapy, Shields et al. reported retinopathy in 27 % of eyes, papillopathy in 26 %,

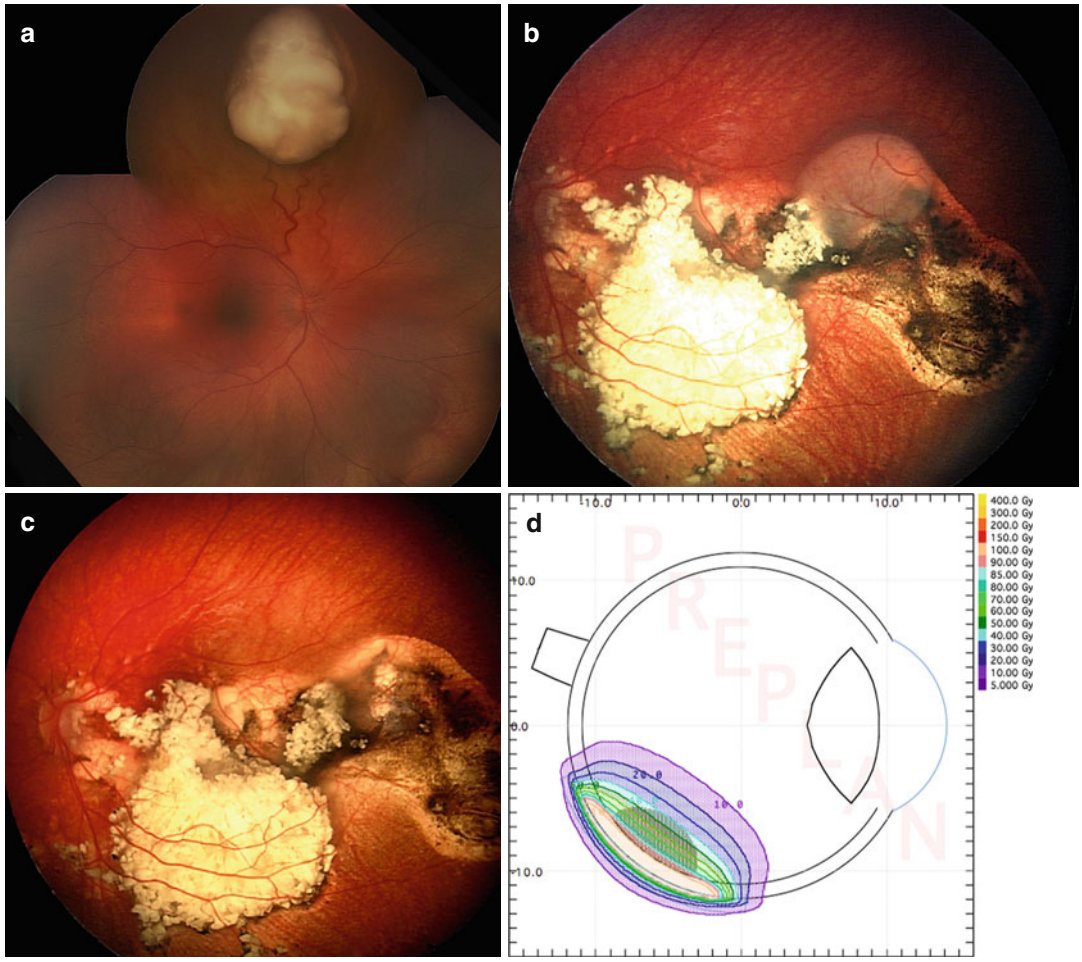

Fig. 10.5 A group C eye with solitary peripheral tumor that is a candidate for brachytherapy (**a**). A 12-month-old child with bilateral retinoblastoma treated with chemoreduction and consolidation treatment. Note tumor recurrence within the chorioretinal scar of previous cryotherapy in the left eye (**b**). There was tumor regression within 4 weeks of brachytherapy (**c**). A 16 mm round ruthenium-106 plaque (apical dose 38.70 Gy; total duration 32 h) was used for plaque radiotherapy (**d**)

cataract in 31 %, and glaucoma in 11 % of treated eyes [18]. Schueler reported a high incidence of intraocular hemorrhage of 29.1 % in their series of patients treated with ruthenium-106 plaques, with almost half of these patients developing vitreous hemorrhage [16]. The authors did not comment on the possible cause for this high rate of intraocular hemorrhage in their series, although the radiation doses used in this study may have contributed (mean 138 Gy to tumor apex). It has also been recognized that eyes that have previously received external beam radiation are at higher risk for these ocular complications, and the total dose to critical structures such as the optic nerve should be carefully monitored.

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