Chapter 8
Laser Treatment in Intraocular Tumors

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There are following intra ocular tumors:

Malignant tumors: choroidal melanoma, iris/irido-ciliary melanoma, retinoblastoma, metastatic tumor.

Benign tumors: iris nevus, choroidal hemangioma, retinal capillary hemangioma, vasoproliferative tumors, astrocytoma, iris melanocytoma (Table 8.1).

Some of the more important conditions that lend themselves to this modality of management are discussed below.

Uveal melanoma.

Laser photocoagulation. Death rate associated with uveal melanoma decreased in last decades from 60–80% to 25–30% [1, 2]. It's connected with improvement of early diagnostic and development of new possibilities of organ preservation treatment.

Currently there are two main directions in the therapy of patients with uveal melanomas–enucleation and organ preservation treatment. Enucleation was the main and alone treatment and the most reliable. However, analysis of long-term outcome showed that enucleation doesn't prevent development of metastatic lesions. Also it may leads to promotion of spreading of melanoma cells [3–8].

Photocoagulation as a means of treatment of of the choroidal melanoma was introduced by Meyer-Schwickerath in 1952 [9]. The technique aimed at surrounding the tumor with a scar which both limited its spread and deprived it of its blood supply. Subsequently the tumor itself was ablated by direct treatment.

Currently laser photocoagulation as monotherapy is used for limited indications. There are: small, pigmented and postequatorial uveal melanomas [2, 10–14]. Indicated for laser photocoagulation are: 3 mm or smaller in height and less 4 DD in diameter [13–15].

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Table 8.1 Laser treatment options in intra ocular tumors

Type of tumor	Parameters of tumor for laser treatment	LPC	TTT	PDT	Combination with radiation
Choroidal melanoma		Up to 3.0 mm height, pigmented	Up to 4.0 mm height	Up to 4.0 mm height	Up to 6.0-12 mm height
Iris/irido-ciliary melanoma		+	+	No role	+
Metastatic tumors	Lesions up to 3 mm basal diameter and 2 mm height	+	+	No role	+
Retinoblastoma	Lesions up to 3 mm basal diameter and 2 mm height Cryo/TTT acceptable options Forms important part of consolidation after chemotherapy	+	+	No role	+
Choroidal hemangioma	Progressing	No role	+	+	No role
Retinal capillary hemangioma	Progressing	+, including feeder vessel closure	No role	+	
Vaso proliferative tumors		Thermal laser can be used. Combination with anti-VEGF	No role	No role	Brachytherapy needed on occasion
Astrocytoma		Rarely laser used	No role	No role	No role
Iris nevus		No role	No role	No role	No role
Iris melanocytoma		No role	No role	No role	No role

LPC: laser photocoagulation, TTT: transpupillar thermotherapy, PDT: photodynamic therapy. +: application is possible

Additional conditions are–maximal mydriasis and transparency of optic medias.

It may be used lasers with different wave lengths—532, 577, 810, 1064 nm (31, 105). Laser energy is absorbed by pigment epithelium cells of the retina and melanin in the choroid with following transformation into heat energy. This heat leads to denaturation of proteins of melanoma cell and their necrosis.

Operation has two stages. The first is formation of a restrictive barrier. Laser burns are applied 500−1500 mcm far from a visible border of a tumor. Diameter of a laser

burn is 50−500 mcm, exposition 0.5−1.0 s., power 100−700 mW. Laser lesion must be confluent, III stage by L'Esperance, but not damaging retinal vessels [16].

The second stage−coagulation of a tumor starts 3−4 weeks later when scar is formed. Parameters of laser are following: diameter of a laser burn is 200−1000 mcm, exposition 0.5−2.0 s., power 200−850 mW [17]. Laser lesion must be III−IV stage by L'Esperance. Laser power may widely vary because of an optic medias and pigmentation of melanoma. Laser burns are applied from a periphery of a tumor toward a central part as roof tiles. Starting power on the periphery of the tumor is much less then on central part.

Possible complications of laser photocoagulation are: retinal hemorrhages, occlusion of retinal vessels, optic disc swelling, exudative retinal detachment, vitritis and uveitis, choroidal neovascularisation, cystoids macular edema, IOP elevation, cataract.

A number of researchers [11, 18] showed promise of using laser with a wavelength 1.06 μm, capable of penetrating deep in tumor tissues and carrying sufficiently large thermal energy. Moreover, by changing the spatial and temporal characteristics of laser radiation and treatment tactics at the same time, it is possible to destroy a tumor with thickness of up to 4 mm [19].

Local radiotherapy had a significant impact on the enhancement of organ-preserving treatment for patients with uveal melanomae. Thus, according to a number of researchers [18, 20, 21], application of beta-therapy with the use of radioactive Sr-90 makes it possible to destroy the tumor with thickness of up to 5 mm while using Ru-106 allowed to achieve positive result with thickness tumors of up to 7 mm [18]. More impressive results have been obtained using gamma radiation for local treatment of uveal melanoma. Char D. H. and Grizzard W. S. [22, 23] succeeded to destroy a 12mm tumor by irradiating helium ions. The positive experience of using light energy and the application of beta-therapy in the treatment of patients with uveal melanoma, as well as the results of studying their biological effect on tumor cells, made it possible to substantiate the expediency of their combined use to obtain a potentiated positive therapeutic effect [24].

Conducted at the Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine analysis of the results of combined organ-preserving treatment (photocoagulation and application beta-therapy) in 560 patients with uveal melanomas with a tumor thickness of 2 to 12 mm showed in 27% of cases complete resorption of the tumor, in 35.9%—partial resorption, in 17.8 %—stabilization of malignant growth, and in 19.3% of cases—recurrence of tumor growth. In this group of patients, mortality from metastases after 5 years was 13.2% [12], while after enucleation it was 35.5% [8, 25].

Terentyeva et al. [12, 18] treated patients with uveal melanoma using combined photocoagulation and beta therapy (Ru−106). They have shown that this combined treatment allows the management of intraocular tumors with a thickness of more than 7 mm.

Transpupillar thermotherapy (TTT). Originally described by Oosterhuis, TTT was suggested for the treatment of small tumors near the optic disk or fovea [26]. TTT is performed by diode laser with wave length 810 nm. Infrared radiation penetrates

into melanoma tissue much deeper then visible laser with wave length—514, 532, 577 nm or even red radiation. So, it may heat melanomas with bigger height [27]. Histological examination of uveal melanomas after TTT shows necrosis 3.9 mm in depth [26].

TTT may be used as monotherapy or in combination with radiation therapy or/and surgery removal of a tumor [26, 28–30].

As monotherapy TTT is performed for melanomas with height 3.5−5.0 mm and diameter of basement less 12 mm (Figs. 8.1 and 8.2) [26, 31]. Parameters are following: diameter of laser beam 1−3 mm, exposition 60−90 s., power—200−900 mW, number of treatments 1−6 with interval 1−6 months [32–36]. Treatment includes exposition of tissues 200−1500 mcm from visible edge of melanoma [28, 37].

TTT starts from low power increasing it till mild graying of surface of tumor at the end of exposition. If surface starts graying at the beginning of exposition power must be decreased by 100 mW [28, 38]. In case of melanoma with height more than 4−5 mm may be used combination with brachytherapy [26, 30].

Effectiveness of TTT as monotherapy of melanomas with height less 3.5 is more than 90% [34, 36, 37]. However, Stoffelns B.M. used TTT of uveal melanomas with height up to 4.5 mm and diameter up to 12 mm [39, 31].

Possible complications of TTT are: retinal hemorrhages, occlusion of retinal vessels, traction of the retina, optic disc swelling, exudative retinal detachment, vitritis, choroidal neovascularisation, cystoid macular edema [33, 37, 40, 41].

Photodynamic therapy (PDT) with verteporphin. Cellular injury from PDT is mediated by singlet oxygen. The main advantage of PDT is the selectivity of the treatment and minimal disruption of tissues. PDT is a two steps treatment. The first step is intravenous injection of photosensitiser verteporphin with dosage 6 mg for square meter of a body surface of a patient. During the second step the photosensitizer verteporfin is activated by non-thermal red laser to obtain closure of neovascular structures. Parameters of laser are following: wave length 689 nm, diameter of laser beam 1−7 mm, exposition 83 s., energy–standard dose of 50 J/cm^2, irradiance of 600 mW/cm^2, number of treatments 1−6 with interval 3 months [42].

Preclinical and clinical studies indicated that PDT is a safe, selective, and effective treatment for choroidal neovascularization in age-related macular degeneration. No significant damage to the neurosensory retina was found, which explains why PDT does not cause loss of visual acuity and may be used in a larger population than laser photocoagulation [43].

Although treatment of small pigmented or amelanotic posterior choroidal melanoma with PDT effectively preserves visual acuity (Figs. 8.3 and 8.4). Roelofs K.A. et al. showed 5-year treatment-success calculated by Kaplan-Meier analysis was only 38.4%. Recurrences after PDT tend to occur along the tumor edges, often with minimal increase in thickness. Given the substantial risk of treatment failure, primary PDT with vertepofrin is recommended in exceptional cases of choroidal melanoma, for which other treatments with greater tumor control are not a feasible option [44, 45]. Possible complications of PDT are: retinal and subretinal hemorrhages, exudative retinal detachment and occlusion of retinal and choroidal vessels.

The existing methods of organ-preserving treatment of uveal melanomas and the evaluation of the effectiveness of their use allow us to draw the following conclusions:

Traditional enucleation for uveal melanoma, especially for small and medium-sized tumors, is being replaced by organ-preserving treatment techniques, which, in addition to saving the eye, significantly improve the prognosis for the patient's life. An essential point of organ-preserving treatment is that in 41−52% of cases it is possible to preserve visual functions, which is very important in the presence of a tumor in a single eye.

The effectiveness of treatment of intraocular melanomas depends on a size, cellular structure, pigmentation and localization of the tumor.

Choroidal hemangioma.

Choroidal haemangiomas are a benign vascular tumour of the choroid, which can be either circumscribed or diffuse. Circumscribed choroidal haemangiomas have no systemic association while diffuse choroidal haemangiomas are often associated with Sturge-Weber syndrome. The presentation of a choroidal haemangioma is dependent on its location, with diffuse haemangiomas more likely to cause retinal detachment [46]. Many however are asymptomatic and found incidentally. Treatment is indicated if a patient's vision is affected or threatened due to exudative retinal detachment, macular oedema or the lesions proximity to the fovea. Haemangiomas that involve the macula often cause reduced vision, metamorphopsia and progressive hypermetropia [47].

Diffuse choroidal haemangiomas have been treated with many modalities including radiotherapy, anti-vascular endothelial growth factor (VEGF), TTT, PDT and laser photocoagulation. PDT is an ideal treatment option as it selectively destroys tumour vasculature while sparing the overlying retina. PDT [48–53].

Treatment of Circumscribed Choroidal Hemangioma

Laser photocoagulation has been an effective treatment modality for hemangioma for many years. Shields and coworkers [51] reported 62% resolution of subretinal fluid and 71% stability of vision with argon laser photocoagulation. The main complication of laser photocoagulation is the expansion of RPE atrophy and coexistent scotoma. Other reported complications include preretinal membrane, choroidal neovascular membrane, vascular occlusion and retinal bleeding. Diode laser photocoagulation has been shown to be equally efficacious with probably lower absorption by the retinal pigment epithelium [48]. Currently, laser photocoagulation is rarely used to treat hemangiomas as this has been largely replace by photodynamic therapy.

In various studies the visual acuity improvement or stabilization after PDT for choroidal hemangioma ranges from 73 to 100% [52]. Blasi and co-workers reported the five year outcome of 25 patients treated with PDT for circumscribed hemangioma and found that visual acuity improved by two lines in 76% of patients with complete resolution of macular exudation in all cases and no complications

were observed [53]. Shields CL and co-workers nearly 50 patients treated with PDT, 95% of patients required only one session with complete resolution of the tumor and fluid. A second session was needed in 5% to resolve persistent or recurrent subretinal fluid. Long-term recurrence of subretinal fluid is uncommon [54].

The use of TTT is limited to extrafoveal tumors. Treatment with TTT successfully causes tumor regression in many patients (42%, partial 50%) complete but carries a risk of cystoid macular edema, preretinal fibrosis, focal iris atrophy and retinal vascular occlusion [46].

Treatment of Diffuse Choroidal Hemangioma

The management of diffuse choroidal hemangioma can be challenging. In addition to choroidal hemangioma, patients with Sturge-Weber syndrome also have congenital glaucoma in 70% of patients. The mechanism of raised intraocular pressure is angle anomaly and raised episcleral pressure. Treatment options for diffuse choroidal

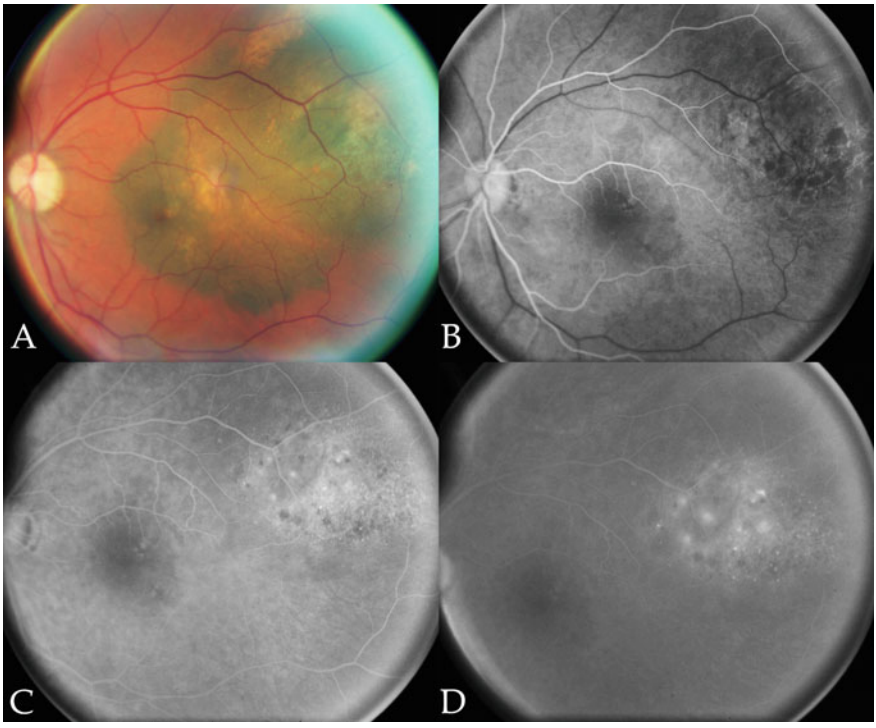

Fig. 8.1 Choroidal melanoma arose from benign nevus **A** Color fundus photograph shows dark nevus in the macula area and melanoma is located temporal to the nevus. **B–D** Fluorescein angiogram shows hyperfluorescence with diffuse leakage from melanoma

hemangioma include observation, amblyopic therapy, laser photocoagulation, irradiation, photodynamic therapy, retinal detachment surgery or even enucleation in advanced cases with neovascular glaucoma [55].

Multispot photodynamic therapy has been used successfully in patients with diffuse hemangioma. Reported cases in the literature document resolution of subretinal fluid, decrease in thickness of the tumor and improvement in visual acuity [56, 57].

Retinoblastoma (RB).

In the treatment of RB, laser (thermal/TTT) is used as primary modality of treatment only for very small tumors [58]. In most cases, however, it is used as an adjunct. Tumors are regressed with chemotherapy and then subjected to laser treatment to achieve total destruction. Tumors of up to 3 mm basal diameter and height of about 2 mm are amenable for laser treatment. The laser is applied around the tumor to cut off the blood supply. Direct treatment of the tumor can also be done although there are

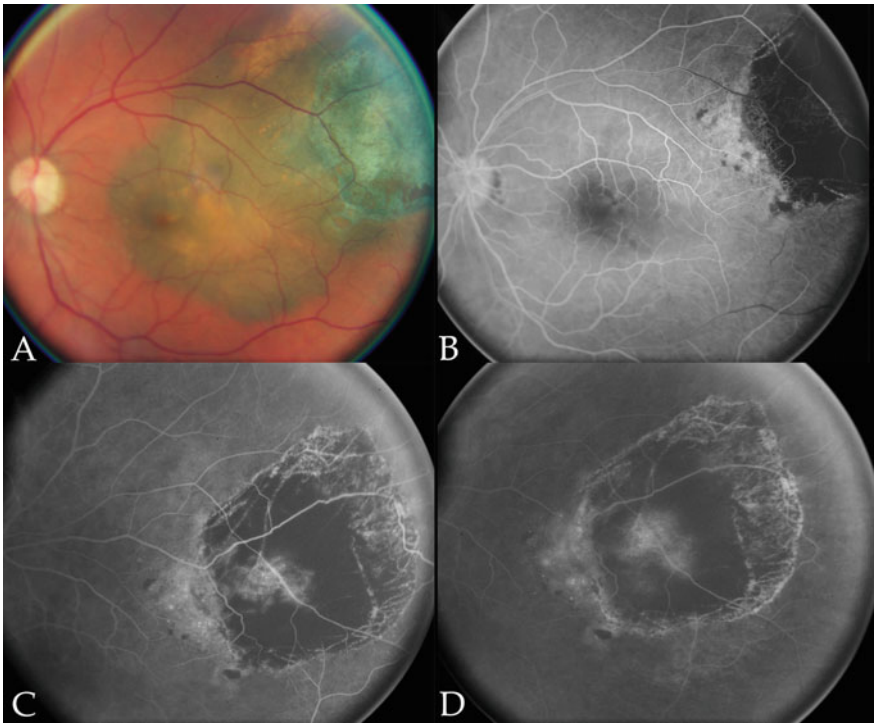

Fig. 8.2 Fundus images of a patient treated with TTT for choroidal melanoma arose from benign nevus **A** Color fundus photograph shows gray scar instead of the melanoma located temporal to the nevus. **B–D** Fluorescein angiogram shows hypofluorescence at the site of melanoma

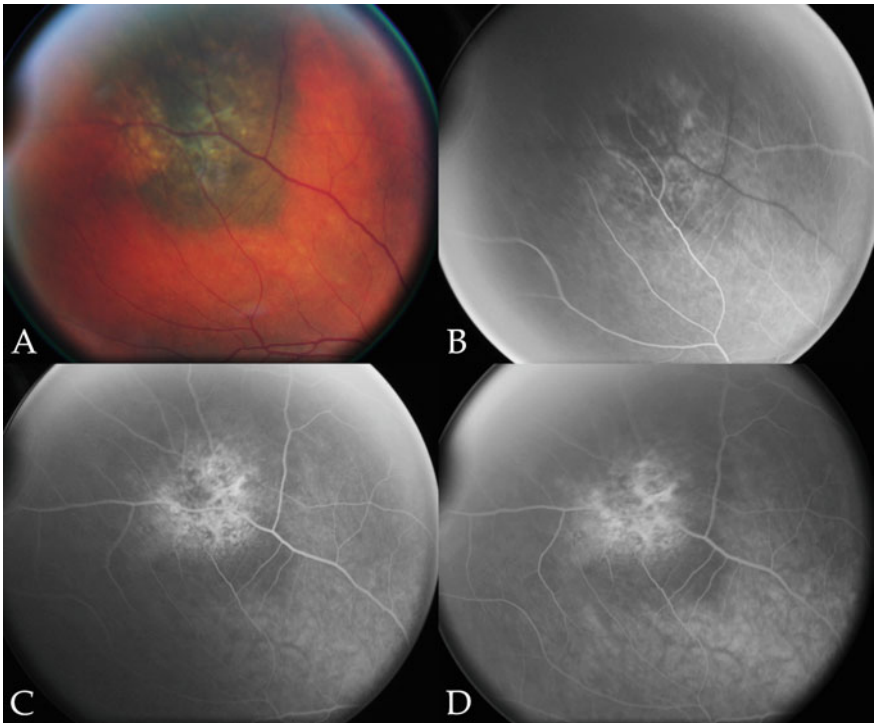

Fig. 8.3 Small pigmented choroidal melanoma **A** Color fundus photograph shows melanoma is located at the mid periphery. **B–D** Fluorescein angiogram shows hyperfluorescence with diffuse leakage from melanoma

concerns about the vitreous dissemination of tumor cells. Direct treatment of RB can be more safely done with TTT rather than by thermal photocoagulation. With TTT, the end point of each burn is the development of mild opalescence in the tumor. One can combine the treatment surrounding the tumor with thermal coagulation followed by TTT of the tumor itself.

Tumors bordering the macula are best allowed to shrink with chemotherapy till it is safe to destroy the residue without compromising the fovea. However, it may not always be possible to preserve the fovea-especially where the epicenter of the tumor lies in the foveal location, and it shrinks toward and not away from fovea [59].

Shields et al. have shown a success of 85.6% in achieving complete tumor regression. The risk factors for tumor recurrence were male sex, inability to produce a color change in the tumor with TTT and tumors being treated after chemo reduction [60].

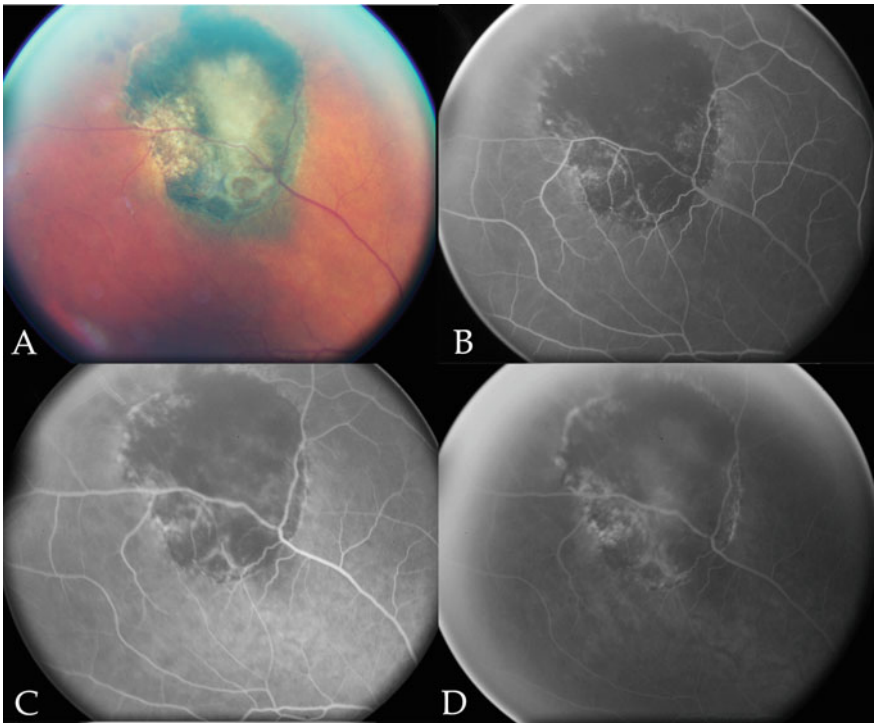

Fig. 8.4 Fundus images of a patient treated with PDT for choroidal melanoma **A** Color fundus photograph shows gray scar and hyperpigmentaton instead of the melanoma located at the mid periphery. **B–D** Fluorescein angiogram shows hypofluorescence at the site of melanoma

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