2 Laser/Light Applications in Ophthalmology: Posterior Segment Applications

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Abstract

Among medical fields, ophthalmology has perhaps the richest history with regard to the widespread application of laser technologies. The first experimental use of laser in ophthalmology was that of the German ophthalmologist Gerd Meyer-Schwickerath, who began using the Beck arc in 1949 (Abramson. Acta Ophthalmol Suppl, 194:3–63, 1989; Neubauer and Ulbig. Ophthalmologica 221(2):95–102, 2007). By 1954, Meyer-Schwickerath had treated 41 patients with the xenon arc photocoagulator and by 1957, he reported that he was able to close 82 macular holes with this technology (Abramson. Acta Ophthalmol Suppl, 194:3–63, 1989). Working together with Littmann from the Carl Zeiss Company, he created a similar xenon arc photocoagulator which became available for widespread ophthalmic applications in the late 1960s and was used more frequently in the 1970s. Since then, lasers have been used with notable success for a wide variety of ophthalmic conditions including refractive error, glaucoma, lens-related conditions such as posterior capsular opacification, and retinal conditions including diabetic retinopathy and age-related macular degeneration.

Keywords

Ophthalmology · Laser therapy · Refractive error · Glaucoma · Posterior capsular opacification · Diabetic retinopathy · Age-related macular degeneration · Uveal melanoma · Retinoblastoma

- Lasers have a rich history in ophthalmology
- Lasers have been used to treat common diseases such as diabetic retinopathy and macular degeneration as well as rare conditions such as intraocular tumors

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K. Nouri (ed.), *Lasers in Dermatology and Medicine*, https://doi.org/10.1007/978-3-319-76220-3_2

- Several types of lasers are used in the posterior segment including argon, diode, and photodynamic therapy
- Lasers are commonly used in the clinic setting and operating room

Introduction and History

Among medical fields, ophthalmology has perhaps the richest history with regard to the widespread application of laser technologies. The first experimental use of laser in ophthalmology was that of the German ophthalmologist Gerd Meyer-Schwickerath, who began using the Beck arc in 1949 [1, 2]. By 1954, Meyer-Schwickerath had treated 41 patients with the xenon arc photocoagulator and by 1957, he reported that he was able to close 82 macular holes with this technology [1]. Working together with Littmann from the Carl Zeiss Company, he created a similar xenon arc photocoagulator which became available for widespread ophthalmic applications in the late 1960s and was used more frequently in the 1970s. Since then, lasers have been used with notable success for a wide variety of ophthalmic conditions including refractive error, glaucoma, lens-related conditions such as posterior capsular opacification, and retinal conditions including diabetic retinopathy and age-related macular degeneration.

This chapter will outline the past and current uses for laser in the posterior segment of the eye [1–58]. Anatomically speaking, the term posterior segment generally refers to the vitreous, retina, choroid, and posterior sclera. As such, the laser procedures discussed herein are most commonly performed by retina specialists in subspecialized medical settings. Table 2.1 summarizes current posterior segment laser applications. In many cases, similar procedures have been adapted for varying ophthalmic conditions.

Table 2.1 Major current posterior segment applications for laser in ophthalmology

Laser type	Procedure name	Wavelength (nm)	Disease/indication
Argon/krypton/dye	Pan retinal photocoagulation	488–647	• Proliferative diabetic retinopathy
Argon/krypton/dye	Focal laser photocoagulation	488–647	• Diabetic macular edema
Argon/krypton/dye	Photocoagulation of subretinal neovascular membrane/complex	488–647	• Age-related macular degeneration • Many other causes including: infections, inflammatory conditions, idiopathic central serous chorioretinopathy, retinal or choroidal tumors
Argon/krypton/dye	Retinopexy for retinal tear	488–647	Retinal tear demarcation to prevent retinal detachment
Photodynamic therapy (PDT)	PDT	689	• Age-related macular degeneration • Subretinal neovascular membranes due to infections or inflammatory conditions • Idiopathic central serous chorioretinopathy • Retinal or choroidal tumors
Diode	Transpupillary thermotherapy (TTT) or diode therapy	810	• Ocular tumors such as retinoblastoma or melanoma
Endolaser for vitreoretinal surgery (argon green or diode)	Pan-retinal photocoagulation	Varied	• Proliferative diabetic retinopathy • Intraocular tumors • In • In • Intraocular tumors

Argon Laser

- The three current common procedures for which argon laser is used are: pan-retinal photocoagulation (PRP), focal macular coagulation, and photocoagulation of choroidal or subretinal neovascular membranes or complex, and lasering of retinal holes or tears.
- The current treatment recommendations which incorporate the DRS findings and those of later large scale trials include: high risk proliferative diabetic retinopathy.
- The complications of PRP in the DRS were generally mild and included a decrease in visual acuity of 1 or more lines in 11% and peripheral visual field loss in 5%.

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Indications

Pan-Retinal Photocoagulation

Full scatter PRP is a treatment approach which was first established on a widespread basis in the 1970s in the Diabetic Retinopathy Study (DRS) [3] and then further explored in the 1980s and early 1990s in the Early Treatment Diabetic Retinopathy Study (ETDRS) [4]. The theory behind PRP for proliferative diabetic retinopathy (PDR) is that by destroying the peripheral retina, it decreases the stimulus for the growth of new abnormal blood vessels. The DRS enrolled 1742 patients, 876 of whom were randomized to the argon group and 875 to the xenon group [5]. In the end, the harmful effects of xenon coagulation were more significant than for argon, thus argon laser became the standard of care.

The current treatment recommendations which incorporate the DRS and DRCR findings and those of later large scale trials include: high risk proliferative diabetic retinopathy which is defined as: mild neovascularization of the optic disc (NVD) with vitreous hemorrhage, moderate to severe NVD with or without vitreous hemorrhage, or moderate neovascularization elsewhere in the retina (NVE) with vitreous hemorrhage (Figs. 2.1a, b and 2.2). High risk proliferative diabetic retinopathy is also defined in any case with three of the following four risk factors: vitreous or preretinal hemorrhage, presence of new vessels, location of new vessels on or near the optic disc, and moderate to severe extent of new vessels. In the DRS, the risk of severe visual loss

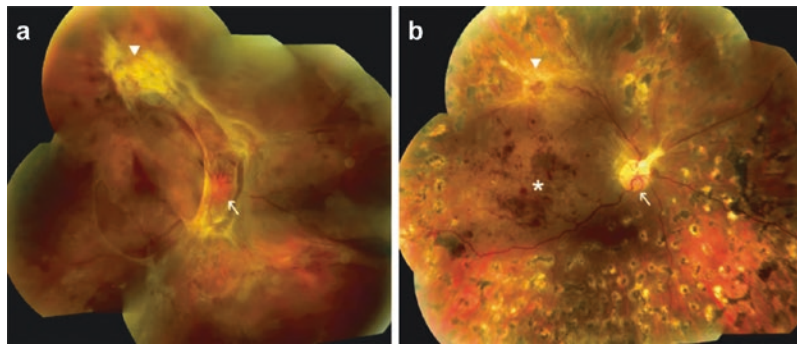

Fig. 2.1 59-year-old female with proliferative diabetic retinopathy, fundus photographs. (**a**) Extensive neovascularization of the optic nerve head (*arrow*) and along the superior macular vascular arcade (*triangle*) with associated fibrosis and retinal traction. (**b**) Five months after panretinal argon laser photocoagulation. Neovascular complexes involving the optic nerve head (*arrow*) and along the superior macular arcade (*triangle*) have regressed, with residual fibrosis. Foci of atrophic retina with pigment clumping are seen throughout the periphery at sites of laser treatment. Multiple, confluent dot blot hemorrhages are seen in the macula (*star*)

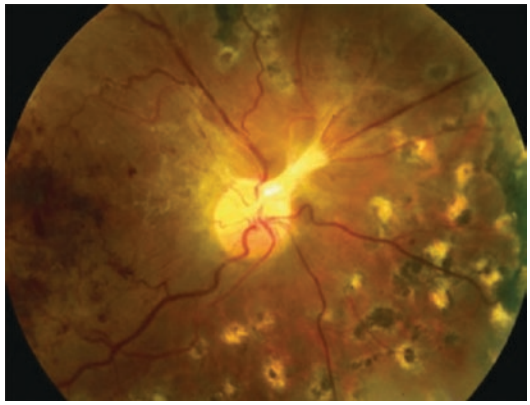

Fig. 2.2 59-year-old female with proliferative diabetic retinopathy, fundus photograph 5 months after pan-retinal argon laser photocoagulation. Fibrotic scar involving the optic nerve head is seen following regression of the neovascular complex. Foci of atrophic retina with pigment clumping are seen at sites of laser treatment. These foci are noted approximately 1 disc diameter from the optic disc and extend into the periphery

(defined as a visual acuity of <5/200) was 26% for patients with high risk proliferative diabetic retinopathy versus 7% in patients without the aforementioned high risk characteristics after 2 years [6]. PRP reduced this risk of severe visual loss by 50%. In addition to these criteria, many studies including ETDRS have suggested that PRP may be indicated for patients with severe nonproliferative diabetic retinopathy in special high risk situations such as poor compliance history, impending pregnancy, or impending cataract surgery [4].

Focal Argon Laser Photocoagulation

Macular edema is responsible for a major part of visual loss in diabetic retinopathy. Many of the current treatment paradigms are based on the results of the ETDRS [4]. The study enrolled 3711 patients between 1980 and 1985 who had either (a) no macular edema with visual acuity better than 20/40 or (b) macular edema with visual acuity better than 20/200. Clinically significant macular edema (CSME) was defined in the study as one of the following: thickening of the retina at or within 500 μm of the center of the macula, hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina, or a zone of retinal thickening of ≥1 disc area within 1 disc diameter of the center of the macula (Figs. 2.3a–c and 2.4a, b). The ETDRS results demonstrated that eyes with CSME benefited from focal laser photocoagulation by reducing the risk of moderate visual loss by at least 50% and increasing the chance of visual improvement [7]. This effect was maintained over time with moderate visual loss at 3 years of follow-up in 24% of treated patients treated versus 12% of untreated patients. The study concluded that patients with CSME and good vision should be considered for treatment based on other factors such as status of the fellow eye, anticipated cataract surgery, proximity of exudates to the fovea, or the presence of high-risk PDR [8].

Laser for Choroidal Neovascular Membranes in Neovascular ARMD and Other Conditions

For many years, laser photocoagulation was the only proven treatment for choroidal neovascularization associated with neovascular macular degeneration and other retinal conditions. In the late 1980s and early 1990s, the Macular Photocoagulation Study (MPS), a series of eight multicenter, randomized, prospective trials examining the use of argon and krypton laser for choroidal neovascular membranes was published [9]. This study evaluated the use of laser for extrafoveal and juxtafoveal lesions in three conditions: neovascular ARMD, presumed ocular histoplasmosis (POHS), and idiopathic choroidal neovascularization. One major drawback of these trials was the narrow eligibility criteria: no more than 15–20% of neovascular ARMD cases present with well-defined choroidal neovacularization as required by the trial.

In general, in all of the MPS trials, treatment did not decrease the patient's chance of maintaining stable visual acuity, but the proportion of eyes, treated or untreated, that maintained good or stable visual acuity was very small. The reason for this inadequate treatment effect is that despite treatment, many eyes continued to lose vision because of persistent or recurrent neovascularization that extended into the foveal center.

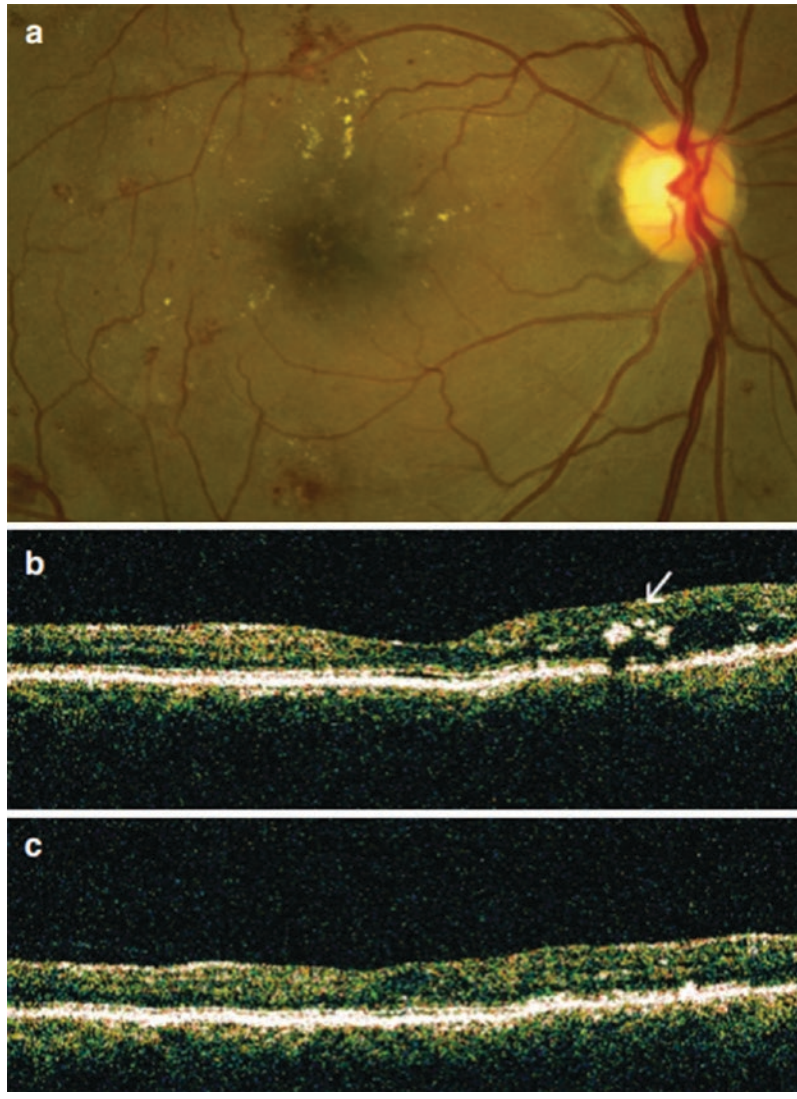

Fig. 2.3 54-year-old man with diabetic macular edema treated with focal argon laser. (**a**) Fundus photograph: clinically significant macular edema in the right eye. Yellow, refractile, hard exudates superiorly indicate an area of retinal thickening. (**b**) Optical coherence tomography (*OCT*): vertically oriented scan with the retinal area located inferior to the fovea represented on the left and the retinal area located superior to the fovea represented on the right. The superior retina is thick compared to the inferior retina because of diabetic macular edema. Intraretinal hard exudates (*arrow*) are seen in the superior retina as manifested by shadowing, with diminished detection of the more posterior retinal layers. (**c**) OCT of the same retinal area as shown in (**b**): 3 months after focal argon laser treatment. The superior retina is no longer thick and there has been resolution of the intraretinal hard exudates

Subfoveal recurrences were not treated with laser in these trials due to concerns about permanent central visual loss. Due to its deleterious effect on normal surrounding neural retina, the use of argon laser for choroidal neovascularization near the fovea sharply decreased with the advent of photodynamic therapy (see below) and antivascular endothelial growth factor therapies. However, argon laser does continue to have a rarely used but important role in that it is highly effective for extrafoveal isolated choroidal neovascular lesions. Patients should always be informed that this treatment induces a permanent scotoma.

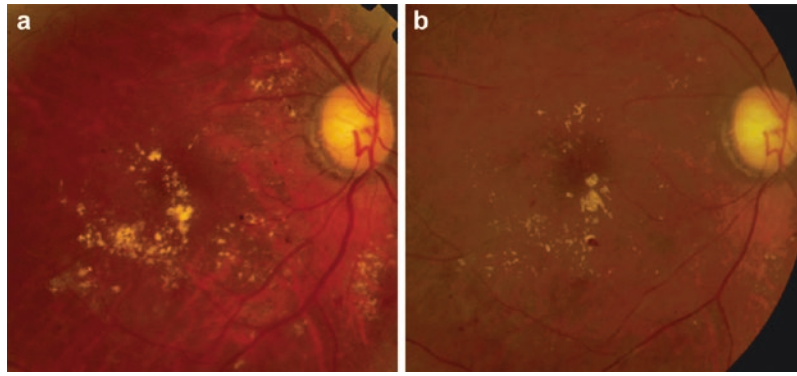

Fig. 2.4 60-year-old female with diabetic macular edema treated with focal argon laser. (**a**) Fundus photograph: clinically significant macular edema in the right eye. Yellow, hard exudates indicate areas of retinal thickening. (**b**) Fundus photograph: marked resolution of hard exudates 5 months after focal argon laser treatment

Fig. 2.5 Slit-lamp based delivery of argon laser photocoagulation. The patient is seen seated to the left with her face firmly placed in an ophthalmic microscope modified for laser delivery. The ophthalmologist views the retina and applies argon laser burns through a corneal contact lens seen in the physician's right hand

Fig. 2.6 Commonly employed ophthalmic lenses. A multitude of lenses can be used for argon laser treatment application depending on the desired magnification and field of view. Such lenses can be broadly categorized as either corneal contact lenses (five lenses located on the left: ocular Mainster 165, ocular three mirror, ocular Yannuzzi fundus, ocular Reichel-Mainster and ocular Mainster wide field) or indirect lenses (two lenses located on the right: 20-diopter and 28-diopter)

Technique

Pan-Retinal Photocoagulation

Argon laser can be applied for PRP from a slit-lamp based or indirect ophthalmoscopic system (Fig. 2.5). The slit lamp-based system is used for a seated patient and consists of a modified slit-lamp (specialized microscope for ophthalmoscopic exam) mounted on a table. The retina is visualized by using a wide-field contact lens (Fig. 2.6). The indirect system is composed of a headset worn by the ophthalmologist which emits the laser directly. For this system, the patient is typically reclined in an examining chair and the retina is visualized by using a 20-Diopter or 28-Diopter lens (Fig. 2.7).

The standard technique for PRP currently involves the placement of 800–1600 laser burns with a 500 ∝ m spot size, spaced 0.5 burn widths apart from each other with 0.1–0.2 s of duration [10]. Intensity is regulated so that mild white bleaching is obtained (Fig. 2.8). The treatment reaches from the temporal arcade to the equator, and up to 2 disc diameters temporal to the macular center. Typically 1 disc diameter or space is spared around the optic nerve to avoid central visual field defects.

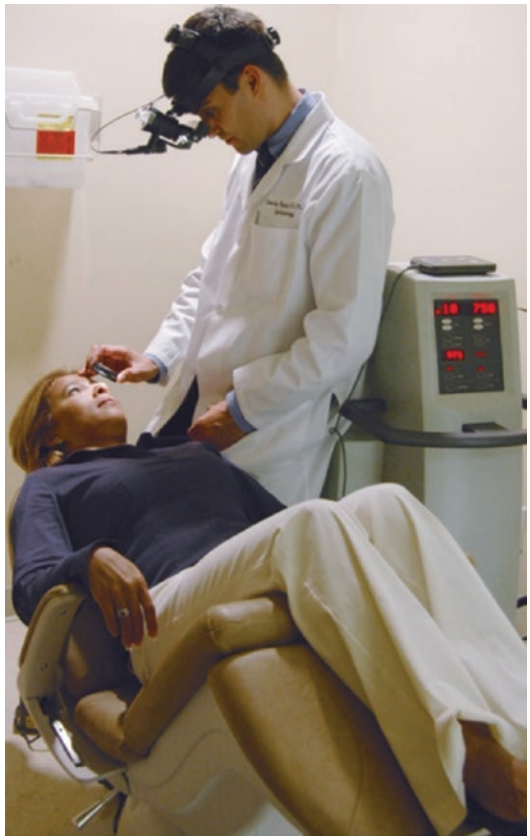

Fig. 2.7 Indirect-ophthalmoscopic based delivery of argon laser photocoagulation. The patient is seen reclined in an examining chair. The ophthalmologist applies argon laser spots using a headset-based laser and visualizes the retina using either a 20-diopter or a 28-diopter lens seen in the physician's right hand

Focal Argon Laser Photocoagulation

Focal laser is typically applied using a slit-lamp based system for a seated patient (Fig. 2.5). A magnifying contact lens is held by the ophthalmologist for detailed viewing of small retinal features (Fig. 2.6). Focal laser treatment typically consists of 50–100 μm laser burns of 0.05–0.1 s duration applied to microaneurysms between 500 and 3000 μm from the center of the macula with the clinical endpoint defined as a color change to a mild whitening. For more diffuse macular edema, a grid pattern is typically applied in the following manner: 100–200 burns of a 50–200 μm spot size spaced 1 burn width apart within 2 disc areas of the fovea. In the ETDRS, an average of 3–4 treatment sessions

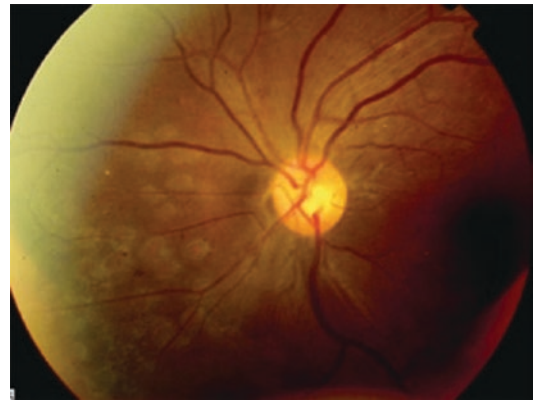

Fig. 2.8 42-year-old female with proliferative diabetic retinopathy underwent pan-retinal argon laser photocoagulation. Fundus photograph of retinal burns 3 h after application. Discrete, cream-colored round lesions are seen deep to the retinal vasculature. Over the ensuing weeks to months, these subtle lesions will evolve into more noticeable areas of retinal atrophy, often with associated pigment clumping, as seen in Figs. 2.1b and 2.2

2–4 months apart were required [7]. The grid technique has been demonstrated in several more recent studies to be more effective than milder focal techniques in reducing retinal thickening based on detailed measurements taken with the optical coherence tomography (OCT) and thus continues to be the standard of care [11].

Laser for Choroidal Neovascular Membranes in Neovascular ARMD and Other Conditions

Laser for choroidal neovascular membranes is typically applied using a slit-lamp based system for a seated patient. A magnifying contact lens is held by the ophthalmologist for detailed viewing of small retinal features. In the MPS studies, argon laser was applied to cover the choroidal neovascular membrane (location judged on fluorescein angiogram) and 100 μm beyond the edge of the lesion, but was never applied closer than 200 μm from the center of the fovea. The laser was set initially at a 200 μm spot size, 0.2–0.5 s duration, and 100–200 mW power. The power was adjusted to achieve an intensity sufficient enough to produce a uniform whitening of the overlying retina.

Adverse Events

Pan-Retinal Photocoagulation

The complications of PRP in the DRS were generally mild and included a decrease in visual acuity of 1 or more lines in 11% and peripheral visual field loss in 5% [12]. The DRS and ETDRS also indicated that macular edema can be worsened by PRP leading to moderate visual loss [4].

Focal Argon Laser Photocoagulation

The side effects and complications of focal laser in the ETDRS included: paracentral scotoma, transient increased edema/decreased vision, choroidal neovascularization, subretinal fibrosis, photocoagulation scar expansion over time, and inadvertent foveal burns [4, 7].

Laser for Choroidal Neovascular Membranes in Neovascular ARMD and Other Conditions

Complications from argon laser for choroidal neovascularization include: hemorrhage, perforation of Bruch's membrane, retinal pigment epithelial tear, and arteriolar narrowing [9, 13]. Persistent or recurrent neovascularization is common: in the MPS, 34% of patients treated for new subfoveal neovascularization had persistent or new neovascularization over 3 years of follow-up [14]; 53% of eyes treated for extrafoveal neovascularization in the MPS had recurrent neovascularization [15]; 32% of eyes treated for juxtafoveal neovascularization had persistent neovascularization, and an additional 42% had recurrent neovascularization at 5 years of follow-up [9, 13].

Future Directions

Pan-Retinal Photocoagulation and Focal Argon Laser Photocoagulation

The uses of PRP for proliferative diabetic retinopathy and focal laser for diabetic macular edema have been reliable mainstays of treatment for diabetic patients for decades. Pars plana vitrectomy (PPV) has also been used successfully for a decade for refractory diffuse macular edema which demonstrates a tractional component [16]. In the last decade, there has been a shift in the use of antivascular endothelial growth factors (anti-VEGF) formulated as intravitreal injections to serve as alternatives or supplements to laser treatments [45]. Many early studies have found these agents to be beneficial for these conditions, especially in the short term [17–19]. Recent trials have found monotherapy with anti-VEGF agents non-inferior to PRP over the course of 2 years with fewer vitrectomies and better central visual acuity [46–48]. However, there is still significant concern regarding the chronic dependence for anti-VEGF agents in diabetic retinopathy and the possible masking of ischemic changes with intravitreal treatments.

Laser for Choroidal Neovascular Membranes in Neovascular ARMD and Other Conditions

Argon laser photocoagulation is limited in its use for choroidal neovascularization due to narrow eligibility criteria, immediate visual loss due to scotoma, and high recurrence rates [21]. These shortcomings prompted research into other treatment modalities which have since proven to be safer and more effective in preserving and improving vision, such as intravitreal anti-VEGF agents.

Photodynamic Therapy (PDT)

Indications

Ocular PDT was first introduced as a novel treatment for neovascular (wet) age-related macular degeneration (ARMD) and choroidal neovascularization in the mid to late 1990s. At the time, it was hoped that the narrow eligibility requirements and high recurrence rates of the MPS would be improved with PDT. Two large prospective multicenter randomized trials were completed with long-term follow-up examining its use for these conditions with extended follow-up, the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study [22], and

the Verteporfi in Photodynamic Therapy Study Group (VIP) study [23]. The TAP study examined the use of PDT for certain subtypes of wet ARMD (those with some classic component on fluorescein angiography) and demonstrated benefit over placebo for patients with predominantly classic lesions. Vision in these patients remained stable with extended follow-up. In the VIP study, there were two arms: patients with choroidal neovascularization secondary to pathologic myopia and patients with wet ARMD with occult neovascularization. Patients in both arms had a visual benefit over placebo at 24 months, although subset analyses revealed a decrease in vision in treated patients over controls when the treated lesion size was large and baseline vision was better than 20/50.

Since the completion of the TAP and VIP trials, the off-label use of PDT has been reported in many small series for the treatment of many inflammatory, infections, trauma-related and idiopathic conditions associated with choroidal neovascularization including: idiopathic polypoidal choroidal vasculopathy (IPCV); chorioretinitis including presumed ocular histoplasmosis syndrome (POHS), punctate inner choroidopathy (PIC), multifocal choroiditis; angioid streaks; chronic idiopathic central serous chorioretinopathy (ICSC); macular dystrophies; and choroidal rupture [24]. For many of these conditions, the advent of anti-VEGF pharmacotherapies has largely replaced the use of PDT over the past several years. PDT has also been reported in small case series for the treatment of intraocular tumors including: in tuberous sclerosis; choroidal hemangioma; capillary hemangioma; retinoblastoma; uveal melanoma; angiomas in Von Hippel Lindau disease; and squamous cell carcinoma of the conjunctiva [25, 57]. Among these tumors, the largest body of evidence exists for the use of PDT for subretinal exudation and serous retinal detachment associated with choroidal hemangioma (Fig. 2.9). First reported by Barbazetto et al. in 2000 [26], there are now more than ten small case series reporting its successful use including the largest series which had 19 patients [27]. Given its success with minimal complications, PDT has emerged as the new standard of care for this disease entity.

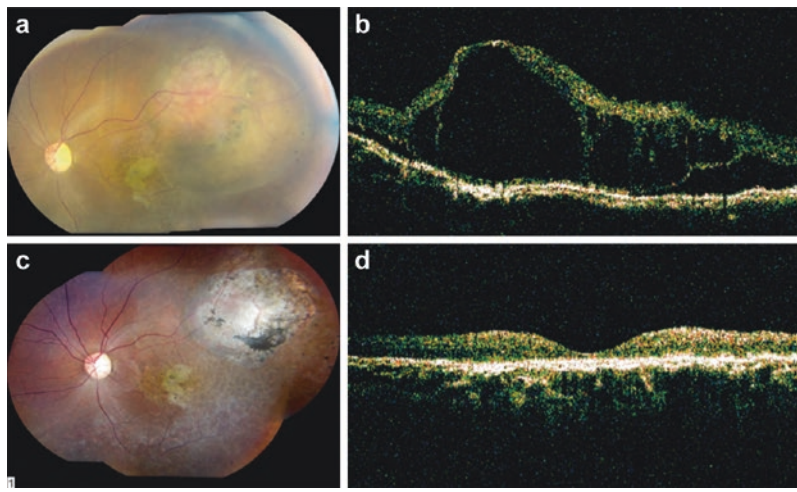

Fig. 2.9 45 year-old male with a large choroidal hemangioma, left eye. (**a**) Fundus photograph demonstrating the orange-red tumor at presentation. (**b**) Optical coherence tomography (*OCT*): vertically oriented scan with the retinal area located inferior to the fovea represented on the left and the retinal area located superior to the fovea represented on the right. There is a large amount of subretinal fluid (black cystic-appearing space under the retina) associated with the tumor. (**c**) Fundus photograph 9 months after photodynamic therapy (*PDT*). The tumor has regressed with associated chorioretinal scarring and atrophic changes in the retinal pigment epithelium. (**d**) OCT demonstrating resolution of the subretinal fluid

Technique

The protocol for the application of PDT was established in the TAP and VIP trials [22, 23], and generally a similar or identical protocol is used for off-label uses other than wet ARMD or pathologic myopia. PDT is performed by using the photosensitizer verteporfin (Visudyne, Novartis Ophthalmics, Switzerland) which selectively targets vascular endothelial cells [22]. The procedure has two steps: first, the verteporfin is injected intravenously for 10 min (at a dose of 6 mg/m^2 body surface area). Five minutes later, selective activation of the dye in the target tissue is achieved by applying a diode laser emitting light at 689 nm to an area 1000 ∝ m larger than the greatest dimensions of the lesion of interest. The dose of light delivered is 50 J/cm^2 at an irradiance of 600 mW/cm^2 over 83 s. PDT's presumed mechanism of action is the selective vascular occlusion of the intraluminal portion of exposed vessels without damaging adjacent neural structures [24].

Adverse Events

Minor adverse events reported in the TAP and TAP extension trials included: injection site inflammation, infusion-related back pain, allergic reactions, and photosensitivity reaction [22]. Rare ocular adverse events included vitreous hemorrhage and retinal capillary nonperfusion. Visual disturbance, defined as any visual complaint including visual field defect irrespective of its relationship to the treatment, occurred in 22% of treated patients versus 15% of controls at 24 months of follow-up [28]. Acute severe acuity visual decrease was extremely rare (<1%).

Future Directions

With the successful introduction of anti-VEGF, the use of PDT for wet ARMD has diminished dramatically. It will likely continue to be used as a secondary treatment option in patients who do not respond to anti-VEGF therapy and seek an alternative. Recent studies have shown that in some cases it may be used in combination with anti-VEGF agents to decrease the intravitreal injection burden [49, 50]. PDT may continue to play in important role in the treatment on intraocular tumors [57, 58].

Diode Laser

Indications

The current primary application of diode laser in the posterior segment is the treatment of ocular tumors such as retinoblastoma, the most common primary intraocular malignant tumor in children, and uveal melanoma, the most common primary malignant intraocular tumor in adults. Diode laser has also been used effectively in other rare pediatric retinal conditions [51, 52]. Guidelines and indications for the use of diode laser for these tumors are highly variable by center, and no clear standard has been established.

For retinoblastoma, laser treatment is most commonly used as an adjunctive therapy along with systemic chemotherapy. In the largest published study, 188 tumors in 80 eyes of 50 patients were treated with chemotherapy and laser, and 86% demonstrated regression [29]. In another study of 91 small tumors in 22 eyes of 24 patients treated with laser alone, 95% of tumors 1.5 disc diameters or smaller underwent long-term regression without any other treatment [30].

For uveal melanoma, several groups of authors have reported the use of argon or diode laser in combination with plaque radiotherapy with the goal of ensuring better local tumor control, especially for tumors located near the optic nerve and fovea [31–35]. The largest of these studies examined the local tumor control rates in 270 patients treated with Iodine-125 plaque therapy followed by three sessions of transpupillary thermotherapy administered at plaque removal and at 4-month intervals [33]. Kaplan Meier estimates of tumor recurrence were 2% at 2 years and 3% at 5 years. These local control rates appear to be higher than those observed in the Collaborative Ocular Melanoma Study (10.3% failure at 5 years), but

cannot be compared easily due to short follow-up time in the study. When compared with patients treated with radioactive plaque therapy alone, tumors treated with radioactive plaques and argon laser appear to regress faster but result in more short-term visual acuity loss [35]. Larger randomized prospective trials are needed comparing radioactive plaque therapy alone to plaque therapy with adjunctive laser and/or transpupillary thermotherapy.

Technique

For retinoblastoma, thermal energy is delivered from the 810 nm infrared lased by one of three techniques: (1) using an adaptor on the indirect ophthalmoscope and a 20-Diopter or 28-Diopter lens which delivers a large 1.6 mm spot size; (2) using a pediatric laser gonioscopy lens and an adaptor on the operating room microscope which delivers a 3 mm spot size; or (3) using a transconjunctival diopexy probe which delivers a 1 mm spot size [36]. The laser is generally set on 350 mW to start the procedure and adjusted until a gray-white color change is noted in the tumor. Some centers utilize a method called transpupillary thermotherapy (TTT) which consists of modifi to the diode laser's hardware and software. Typically, the laser beam is aimed directly at the tumor, and the tumor surface is completely covered with overlapping laser spots to ensure that no areas are missed. The mechanism by which diode laser causes tumor cell death is thought to be different from the mechanism by which classic laser photocoagulation destroys tumors. The temperature of the diode laser is thought to be lower (45–60 °C) and the thermal effect leads to direct apoptosis of the tumor cells. For this reason, the laser is directed at the tumor rather than at its feeder vessels [36].

One controversy regarding the use of laser for retinoblastoma is whether to apply the laser directly to the macula. Some centers advocate the use of laser with avoidance of application directly to the fovea to decrease the risk of severe treatment-related central visual loss [37]. Other centers have reported results when using chemotherapy alone without and laser [38]. Our group recently published an analysis of our series of retinoblastoma patients treated with 4–9 cycles of three-drug chemotherapy and diode laser ablation [39]. All of the patients in this cohort had retinoblastoma presenting in the macula and each patient was treated aggressively with diode laser at every examination under anesthesia until the patient's tumor was noted to be inactive for at least 6 months (Fig. 2.10a–d). Hundred percent of the patients with early stage disease and 83% of patients with advanced disease avoided external beam radiation and enucleation at 3 years. These tumor control rates far exceed those published at other centers. Furthermore, 57% of patients maintained 20/80 or better vision.

Adverse Events

Reported complications from diode laser include: focal iris atrophy, focal lens opacities, sector optic disc atrophy, retinal traction, optic disc edema, retinal vascular occlusion, serous retinal detachment, choroidal neovascular membrane, peripheral anterior synechiae, and corneal edema [29, 39]. The most common side effect is focal iris atrophy which is associated with an increasing number of treatment sessions and an increasing tumor base diameter [29].

Future Directions

No standardized protocols have been established for the application of diode laser therapy for intraocular tumors and other rare retinal entities. Optimal technique-related approaches, such as when and how often to treat, how much power to use, which areas of the tumor to treat, and whether to treat the fovea remain uncertain. Prospective standardized studies are essential in the future in order to establish the ideal treatment method and clinical standardization, especially for retinoblastoma given the current disparate tumor control rates at different institutions.

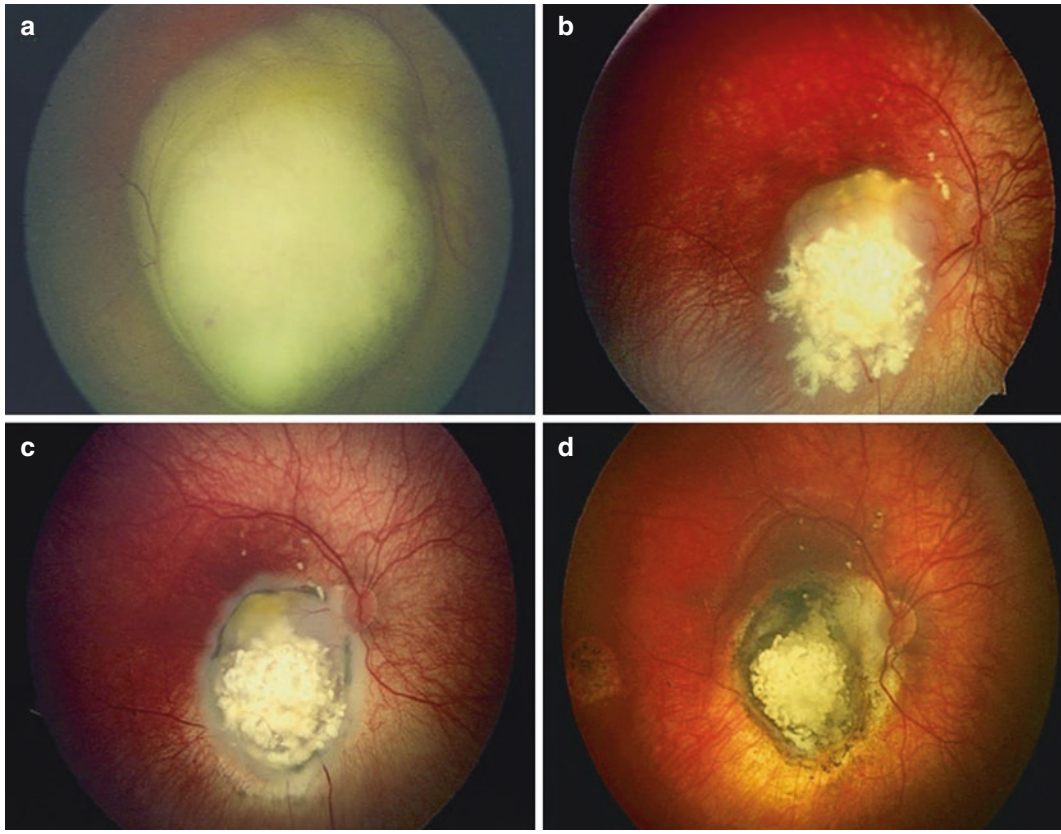

Fig. 2.10 Right eye of an 11 month-old male with advanced retinoblastoma, fundus photographs. (**a**) At presentation, the large tumor obscures the macula and optic nerve. (**b**) Dramatic shrinkage of the tumor is observed after two cycles of intravenous chemotherapy and two diode laser treatments. (**c**) Additional reduction in the size of the tumor is noted after four cycles of intravenous chemotherapy and nine diode laser treatments. (**d**) Chorioretinal scarring and complete tumor regression with typical calcified appearance. The patient underwent a total of six cycles of intravenous chemotherapy and nine diode laser application sessions. The patient developed an additional tumor focus temporal to the macula (left margin of photograph) that was treated with laser. The final visual acuity in this eye was 20/60 (Figures reproduced from Schefler et al. [39] with permission)

Endolaser During Vitreoretinal Surgery

Indications

First developed in 1979 by Charles, the introduction of endophotocoagulation was a significant advance in vitreoretinal surgery [40]. In his original system, he used a fiber optic probe attached to a portable xenon arc photocoagulator. The xenon arc was not ideal for surgery, however, and several years later, Peyman developed an argon laser probe that enabled more rapid firing, had a more comfortable and safe working distance, and didn't generate as much heat [41]. The argon green and diode lasers are currently used most frequently.

During vitrectomy procedures, the endolaser is used most commonly to create a laser barricade around retinal hole, surround retinectomy edges or giant retinal tear margins, and deliver scatter pan-retinal photocoagulation. It can also be used for primary treatment of some intraocular tumors such as secondary angiomas, choroidal hemangiomas, capillary hemangioblastomas, and small choroidal melanomas.

For retinal holes, the goal is to achieve 360° of laser encircling the tear. In order to achieve an effective laser burn, subretinal fluid under the

hole must be fully aspirated or the retinal pigment epithelium will not absorb the laser energy effectively. For retinectomies and giant retinal tears, laser spots are generally placed around large areas of detached retina or to wall off the area of prior detachment such as in cases or proliferative vitreoretinopathy or viral retinitis. Reattached retina is typically lasered overlying a scleral buckle which is typically a silicone band placed around the outside of the eye to maintain the reattached position of the retina. Endolaser can be placed through perfluorocarbon liquids which are often used to hold the retina in position. Afterword, perfluorocarbons are exchanged with air, reducing visibility and making lasering more difficult.

For panretinal laser photocoagulation, the goal is similar to pan-retinal photocoagulation performed using slit-lamp or indirect ophthalmoscopic systems. The endolaser typically enables easier access to more peripheral retina than the nonoperative systems, particularly if wide-angle intraoperative viewing systems are used.

Endophotocoagulation can also be applied to neovascular tissues prior to removing them or to healthy retina prior to a retinectomy to minimize bleeding. The argon green laser is generally used for this purpose because it is best absorbed by blood. Diathermy can also be used.

For intraocular tumors, the goal is varied. In choroidal hemangiomas, the goal is to create a chorioretinal scar that blocks fluid from reaching the fovea. In secondary angiomas and capillary hemangioblastomas, it can be used as the primary treatment at the time of vitrectomy. In small choroidal melanomas, the goal is to increase the intratumoral temperature and denature proteins associated to the tumor.

Techniques

The endolaser probe is an instrument that is available in several forms including: different gauges, straight or curved, blunt or tapered, simple or aspirating [42], or illuminating (Fig. 2.11) [43]. The straight probe with a blunt or tapered tip is used most commonly. The curved tip is useful for applying laser to the difficult-to-reach anterior superior retina or peripheral retina near the surgeon's dominant hand. The aspirating tip can be used to drain subretinal fluid or blood from the edge of retinal holes while lasering. The illuminating probe frees the opposite hand for use of another instrument [44]. More recently, thinner probes have been developed including 23-gauge, 25-gauge and 27-gauge systems. These probes can be used in smaller sclerotomy incisions enabling a sutureless closure at the end of the surgery and enhanced post-operative comfort for the patient.

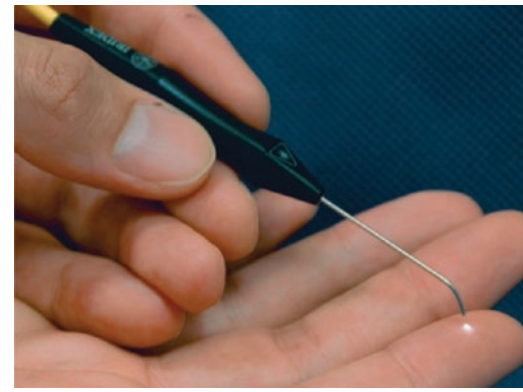

Fig. 2.11 Endocoagulation is performed using an argon laser probe. The fiber optic probe shown is a self-illuminating instrument with a curved tip. During vitrectomy, the probe is inserted through a sclerotomy. Common clinical indications for endolaser use include creating a laser barricade around a retinal hole, surrounding retinectomy edges or giant retinal tear margins, and delivering scatter pan-retinal photocoagulation

The initial settings of the argon laser are typically for 0.1–0.2 s with a power of 200 mW. For the diode laser, the settings are generally 0.2–0.3 s, and 200–300 mW. The power is typically adjusted gradually in 50 mW steps until a gray-white color change is noted. A continuous setting is helpful for treating active hemorrhage or around retinotomies.

When treating intraocular tumors, it is important to apply treatment continuously to the tumor surface and avoid any skip areas. Overtreatment should be avoided to minimize postsurgical complications.

Adverse Events

Complications from endolaser are rare but can include: retinal tears, choroidal neovascularization, and retinal necrosis from overly intense treatment. Inadvertent overtreatment can occur by placing the probe too close to the retina or by not titrating the laser energy slowly upward based on a retinal color change.

Future Directions

Recent studies have shown that tumoral genetic expression profile (GEP) is the most important prognostic measurement associated to choridal melanoma [53, 54]. Endophotocoagulation may be used at the time of transvitreal GEP biopsy to primarily treat small choroidal melanomas. Endophotocoagulation at the time of transvitreal biopsy may also decrease vitreous hemorrhage and vitreous seeding postoperatively. Recent reports have shown that endophotocoagulation can be used prior to transvitreal biopsies for small, medium, and large choroidal melanomas [55, 56]. The ongoing trend towards GEP characterization in choroidal melanoma may lead to increased use of the endolaser in the management of malignant uveal tumors. This treatment approach may decrease the use of brachytherapy and improve the historically poor visual outcomes.

The endolaser is a highly critical component of vitreoretinal surgery. When placed on proper settings and applied carefully, it can be performed safely with minimal risks. As smaller gauge systems have recently been developed, the number of available probes and configurations has increased, enabling greater choice and versatility for the surgeon. Endophotocoagulation will no doubt continue to be an integral aspect of vitreoretinal surgery for a long time.

Conclusions

Laser technology has been used for many years in ophthalmology with great success. Some previously common indications for the use of laser have become largely obsolete in recent years such as the use of argon laser for the treatment of juxtafoveal choroidal neovascular membranes. This shift in treatment approach has occurred due to the introduction of newer, more effective treatments. Nonetheless, the use of laser will no doubt continue to have an important role in ophthalmology. Given its accessibility and transparent media such as the cornea, aqueous, and vitreous, the eye remains an organ that is particularly amenable to this form of treatment. Direct inspection both during and after laser procedures enables easy assessment of the efficacy of laser use. Furthermore, the uveal tract, made up of the iris, ciliary body, and choroid, contains melanin pigment, allowing effective absorption of photothermal laser energy. As more clearly defined indications for the use of new pharmacotherapies such as anti-VEGF drugs are developed, laser procedures will likely develop an important combination therapy/adjunctive role for rare conditions such as intraocular tumors as well as for more common diseases such as proliferative diabetic retinopathy, diabetic macular edema, and choroidal neovascularization.

Disclaimer No conflict of interest or financial interest exists for any author.

References

1. Abramson DH. The focal treatment of retinoblastoma with emphasis on xenon arc photocoagulation. Acta Ophthalmol Suppl. 1989;194:3–63.
2. Neubauer AS, Ulbig MW. Laser treatment in diabetic retinopathy. Ophthalmologica. 2007;221(2):95–102.
3. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. Ophthalmology. 1978;85(1):82–106.
4. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology. 1991;98(5 Suppl):766–85.
5. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol. 1976;81(4):383–96.
6. The Diabetic Retinopathy Study Research Group. Indications for photocoagulation treatment of diabetic retinopathy: diabetic retinopathy study report no. 14. Int Ophthalmol Clin. 1987;27(4):239–53.

7. Early Treatment Diabetic Retinopathy Study Research Group. Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Arch Ophthalmol. 1995;113(9):1144–55.
8. Ferris FL III, Davis MD, Aiello LM. Treatment of diabetic retinopathy. N Engl J Med. 1999;341(9):667–78.
9. Macular Photocoagulation Study Group. Laser photocoagulation for juxtafoveal choroidal neovascularization. Five-year results from randomized clinical trials. Arch Ophthalmol. 1994;112(4):500–9.
10. Moutray T, Evans JR, Lois N, Armstrong DJ, Peto T, Azuara-Blanco A. Different lasers and techniques for proliferative diabetic retinopathy. Cochrane Database Syst Rev. 2018;3:CD012314.
11. Fong DS, Strauber SF, Aiello LP, et al. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. Arch Ophthalmol. 2007;125(4):469–80.
12. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. Ophthalmology. 1981;88(7):583–600.
13. Macular Photocoagulation Study (MPS) Group. Evaluation of argon green vs krypton red laser for photocoagulation of subfoveal choroidal neovascularization in the macular photocoagulation study. Arch Ophthalmol. 1994;112(9):1176–84.
14. Macular Photocoagulation Study Group. Persistent and recurrent neovascularization after laser photocoagulation for subfoveal choroidal neovascularization of age-related macular degeneration. Arch Ophthalmol. 1994;112(4):489–99.
15. Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. Arch Ophthalmol. 1991;109(8):1109–14.
16. Mason JO III, Colagross CT, Vail R. Diabetic vitrectomy: risks, prognosis, future trends. Curr Opin Ophthalmol. 2006;17(3):281–5.
17. Scott IU, Edwards AR, Beck RW, et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. Ophthalmology. 2007;114(10):1860–7.
18. Ahmadieh H, Ramezani A, Shoeibi N. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. Graefes Arch Clin Exp Ophthalmol. 2008;246(4):483–9.
19. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006;113(10):1695.e1–e15.
20. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H. Twelve-month safety of intravitreal injections of bevacizumab (Avastin(R)): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol. 2007;246(1):81–7.
21. Martidis A, Tennant MT. Age-related macular degeneration. In: Yanoff M, Duker JS, editors. Ophthalmology. 2nd ed. St. Louis, MO: Mosby; 2004. p. 925–33.
22. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials – TAP report. Arch Ophthalmol. 1999;117(10):1329–45.
23. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial – VIP report no. 1. Ophthalmology. 2001;108(5):841–52.
24. Mennel S, Barbazetto I, Meyer CH, et al. Ocular photodynamic therapy – standard applications and new indications (part 1). Review of the literature and personal experience. Ophthalmologica. 2007;221(4):216–26.
25. Blasi MA, Pagliara MM, Lanza A, Sammarco MG, Caputo CG, Grimaldi G, Scupola A. Photodynamic therapy in ocular oncology. Biomedicine. 2018;6(1):17.
26. Barbazetto I, Schmidt-Erfurth U. Photodynamic therapy of choroidal hemangioma: two case reports. Graefes Arch Clin Exp Ophthalmol. 2000;238(3):214–21.
27. Jurklies B, Anastassiou G, Ortmans S, et al. Photodynamic therapy using verteporfin in circumscribed choroidal haemangioma. Br J Ophthalmol. 2003;87(1):84–9.
28. Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. Arch Ophthalmol. 2001;119(2):198–207.
29. Shields CL, Santos MC, Diniz W, et al. Thermotherapy for retinoblastoma. Arch Ophthalmol. 1999;117(7):885–93.
30. Abramson DH, Schefler AC. Transpupillary thermotherapy as initial treatment for small intraocular retinoblastoma: technique and predictors of success. Ophthalmology. 2004;111(5):984–91.
31. Shields CL, Cater J, Shields JA, et al. Combined plaque radiotherapy and transpupillary thermotherapy for choroidal melanoma: tumor control and treatment complications in 270 consecutive patients. Arch Ophthalmol. 2002;120(7):933–40.
32. Augsburger JJ, Kleineidam M, Mullen D. Combined iodine-125 plaque irradiation and indirect ophthalmoscope laser therapy of choroidal malignant melanomas: comparison with iodine-125 and cobalt-60 plaque radiotherapy alone. Graefes Arch Clin Exp Ophthalmol. 1993;231(9):500–7.
33. Dogrusöz M, Jager MJ, Damato B. Uveal melanoma treatment and prognostication. Asia Pac J Ophthalmol (Phila). 2017;6(2):186–96.

34. Seregard S, Landau I. Transpupillary thermotherapy as an adjunct to ruthenium plaque radiotherapy for choroidal melanoma. Acta Ophthalmol Scand. 2001;79(1):19–22.
35. Fabian ID, Stacey AW, Harby LA, Arora AK, Sagoo MS, Cohen VML. Primary photodynamic therapy with verteporfin for pigmented posterior pole cT1a choroidal melanoma: a 3-year retrospective analysis. Br J Ophthalmol. 2018.
36. Abramson DH, Schefler AC. Update on retinoblastoma. Retina. 2004;24(6):828–48.
37. Shields CL, Mashayekhi A, Cater J, et al. Macular retinoblastoma managed with chemoreduction. Arch Ophthalmol. 2005;123:765–73.
38. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of intraocular retinoblstoma with vincristine and carboplatin. J Clin Oncol. 2003;21:2019–25.
39. Schefler AC, Cicciarelli N, Feuer W, et al. Macular retinoblastoma: evaluation of tumor control, local complications, and visual outcomes for eyes treated with chemotherapy and repetitive foveal laser ablation. Ophthalmology. 2007;114(1):162–9.
40. Charles S. Endophotocoagulation. Retina. 1981;1(2):117–20.
41. Peyman GA, Grisolano JM, Palacio MN. Intraocular photocoagulation with the argon-krypton laser. Arch Ophthalmol. 1980;98(11):2062–4.
42. Peyman GA, D'Amico DJ, Alturki WA. An endolaser probe with aspiration capability. Arch Ophthalmol. 1992;110(5):718.
43. Peyman GA, Lee KJ. Multifunction endolaser probe. Am J Ophthalmol. 1992;114(1):103–4.
44. Awh CC, Schallen EH, De Juan E Jr. An illuminating laser probe for vitreoretinal surgery. Arch Ophthalmol. 1994;112(4):553–4.
45. Parikh R, Ross JS, Sangaralingham LR, Adelman RA, Shah ND, Barkmeier AJ. Trends of Anti-Vascular Endothelial Growth Factor Use in Ophthalmology Among Privately Insured and Medicare Advantage Patients. Ophthalmology. 2017;124(3):352–8.
46. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C, Melia M. Beck RW; Diabetic retinopathy clinical research network. aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123(6):1351–9.
47. Glassman AR. Results of a randomized clinical trial of aflibercept vs panretinal photocoagulation for proliferative diabetic retinopathy: is it time to retire your laser? JAMA Ophthalmol. 2017;135(7):685–6.
48. Gross JG, Glassman AR, Jampol LM, et al. Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA. 2015;314(20):2137–46.
49. Gallemore RP, Wallsh J, Hudson HL, Ho AC, Chace R, Pearlman J. Combination verteporfin photodynamic therapy ranibizumab-dexamethasone in choroidal neovascularization due to age-related macular degeneration: results of a phase II randomized trial. Clin Ophthalmol. 2017;11:223–31.
50. Dong Y, Wan G, Yan P, Chen Y, Wang W, Peng G. Effect of anti-VEGF drugs combined with photodynamic therapy in the treatment of age-related macular degeneration. Exp Ther Med. 2016;12(6):3923–6.
51. Villegas VM, Gold AS, Berrocal AM, Murray TG. Advanced Coats' disease treated with intravitreal bevacizumab combined with laser vascular ablation. Clin Ophthalmol. 2014;8:973–6.
52. Villegas VM, Hess DJ, Wildner A, Gold AS, Murray TG. Retinoblastoma. Curr Opin Ophthalmol. 2013;24(6):581–8.
53. Walter SD, Chao DL, Feuer W, Schiffman J, Char DH, Harbour JW. Prognostic implications of tumor diameter in association with gene expression profile for uveal melanoma. JAMA Ophthalmol. 2016;134(7):734–40.
54. Field MG, Durante MA, Decatur CL, et al. Epigenetic reprogramming and aberrant expression of PRAME are associated with increased metastatic risk in Class 1 and Class 2 uveal melanomas. Oncotarget. 2016;7:59209.
55. Villegas VM, Gold AS, Latiff A, Wildner AC, Ehlies FJ, Murray TG. Phacovitrectomy. Dev Ophthalmol. 2014;54:102–7. https://doi.org/10.1159/000360455.
56. de Alba MA, Villegas VM, Gold AS, Wildner A, Ehlies FJ, Latiff A, Murray TG. Clinical findings and genetic expression profiling of three pigmented lesions of the optic nerve. Case Rep Ophthalmol Med. 2015;2015:590659.
57. Huang C, Tian Z, Lai K, Zhong X, Zhou L, Xu F, Yang H, Lu L, Jin C. Long-term therapeutic outcomes of photodynamic therapy-based or photocoagulation-based treatments on retinal capillary hemangioma. Photomed Laser Surg. 2018;36(1):10–7.
58. Kim JW, Jacobsen B, Zolfaghari E, Ferrario A, Chevez-Barrios P, Berry JL, Lee DK, Rico G, Madi I, Rao N, Stachelek K, Wang LC, Gomer C. Rabbit model of ocular indirect photodynamic therapy using a retinoblastoma xenograft. Graefes Arch Clin Exp Ophthalmol. 2017;255(12):2363–73.