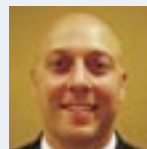


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Role of Radiation in the Treatment of Wet AMD: Facts & Myths

The incidence of wet age-related macular degeneration (AMD) is increasing around the world with the aging population. Although the FDA has approved anti-VEGF therapies that have remarkable efficacy in treating neovascular AMD, the patients typically require multiple treatments at a high cost, often for extended periods of time. The logistic and economic burden of administering this treatment has proved increasingly challenging. The goal of newer treatment strategies is not only to improve outcomes but also to minimize the treatment burden for both the patient and the physician.

Epimacular beta radiation is a novel technique for the treatment of wet AMD that attempts to prevent the progression of choroidal neovascularization (CNV) by the use of ionizing radiation. This radiation technique has been studied both as a monotherapy treatment and in combination with bevacizumab (Genentech).

The purpose of this overview is to describe the rationale for beta radiation therapy as a viable treatment option for wet AMD.

Background

Age-related macular degeneration (AMD) is the leading cause of permanent vision loss in people older than 65 who are of European descent.¹ Moreover, the Eye Disease Prevalence Research Group found that an estimated 175 million people have AMD, with 15 percent of Caucasian women over age 80 having neovascular AMD and/or geographic atrophy.¹ It is estimated that 12 percent of people with unilateral neovascular AMD and 50 percent of patients with bilateral neovascular AMD will become legally blind (visual acuity of 20/200 or worse) within five years of disease onset.² Approximately 2 percent of patients 65 years old or older have visual acuity of 20/200 or less in one eye due to AMD.³⁻⁵ By 2020, it is estimated almost 3 million people in the United States will have ocular findings of AMD.¹

Worldwide, the figures are staggering: between 20 and 25 million people are affected by AMD, a figure that will triple with the increase

in the aging population in the next 30–40 years.⁶ Patients at risk to develop severe visual loss are typically seen only if the disease progresses to the neovascular form or if they develop significant geographic atrophy that involves the foveal center.^{6,7-8}

Choroidal neovascularization is a process in which choroidal blood vessels grow through Bruch's membrane and enter the retinal pigment epithelium (RPE), where they begin to proliferate and cause damage to the photoreceptor layer of the retina in a mechanical fashion by moving photoreceptor orientation as well as leaking fluid that can cause independent damage.⁹ Various modalities—such as thermal laser photocoagulation, photodynamic therapy, antiangiogenic therapy, surgery, and radiation—have been used to treat wet AMD. Radiation has been used to treat retinal neovascularization for more than 50 years. Recently, Chakravarthy et al. showed the beneficial effects of radiation for choroidal neovascularization in the 1990s.¹⁰ However, since then the data on the effects of external beam radiation on CNV is conflicting. Some reports of radiation retinopathy after external proton-beam radiation have raised concerns about the safety of that procedure, and of radiation treatment for CNV in general.

A new approach for the treatment of CNV secondary to AMD combines both an antiangiogenic therapy with localized beta radiation therapy. The epimacular brachytherapy system (NeoVista, Fremont, CA) is designed to treat CNV using strontium-90 beta radiation to kill or disable the local inflammatory population and, over time, the endothelial cells of the neovascular vessel. This type of epimacular brachytherapy is delivered through a standard vitrectomy procedure.

Concerns with radiation therapy for exudative AMD have focused on the appropriate dose/delivery modality that gives patients the maximal visual acuity (VA) benefit while minimizing radiation-induced adverse events.

The three primary types of radiation therapy for the treatment of ocular diseases are proton-beam therapy, external beam therapy, and brachytherapy. External proton-beam radiation has been discussed extensively in literature.

HISTORICAL BACKGROUND REVIEW

AMD Treatments

There are currently multiple approved treatments for neovascular AMD with proven efficacy in large-scale randomized clinical trials:

The Bottom Line

- Beta radiation may have a role in the treatment of exudative AMD due to its broad spectrum of action.
- A novel delivery system is encouraging for effective and safe radiation dosing.
- A synergistic triad of radiation, anti-VEGF mediation and vitrectomy may be effective in the treatment of exudative AMD.
- Phase 2 data shows that the NeoVista epimacular device has the potential of being effective and reducing treatment burden in exudative AMD.

laser photocoagulation, photodynamic therapy with verteporfin, and antiangiogenic therapy with ranibizumab.

Thermal laser photocoagulation of the entire CNV lesion is the most widely investigated and accepted technique for treatment of extrafoveal¹¹ and juxtafoveal¹² lesions of the classic neovascular form of AMD. The technique involves using the heat of a laser to coagulate the choroidal neovascular membrane. The goal of this therapy is to ablate the abnormal treated vessels. The main disadvantage of laser photocoagulation is that treatment itself causes thermal injury to the overlying retina and is associated with an absolute scotoma that is often poorly tolerated.

Photodynamic therapy was originally developed as a cancer therapy for the reduction of neovascularization of tumors.¹³⁻¹⁵ Visudyne (verteporfin), a photosensitive dye, is administered intravenously and allowed to perfuse the CNV, as well as the remainder of the body. The advantage of photodynamic therapy is that considerably less energy is required from the laser, and the treatment results in significantly less damage to overlying healthy cells than laser photocoagulation. Nevertheless, photodynamic therapy rarely restores vision that has been lost, and does not treat the underlying cause of vision loss.

The current standard of care for neovascular AMD is antiangiogenic therapy. Two compounds have been approved to treat AMD: Macugen (pegaptanib, OSI), an aptamer specifically designed to bind VEGF₁₆₅; and Lucentis (ranibizumab, Genentech), a humanized antigen binding fragment (Fab) that binds to all known isoforms of VEGF-A. A third antiangiogenic compound, Avastin (bevacizumab, Genentech), is a full-length anti-VEGF antibody that binds to all known isoforms of VEGF-A. Avastin is approved for first- or second-line treatment of colorectal cancer, recurrent or metastatic nonsquamous-cell lung cancer, and metastatic HER2-negative breast cancer. It is widely used off-label to treat wet AMD.

Radiation Therapy

Ionization changes the characteristics of atoms and the character of the molecule within which the atom resides. This crucial change is the basis for the beneficial aspects of all forms of radiation therapy. Because of ionization, the radiation damages molecules within the cells, especially the proteins and DNA. Damaging the DNA destroys specific cell functions, particularly the ability to divide or proliferate.

COMPARATIVE TECHNIQUES

Radiation Therapy and AMD

Radiation therapy has known antiangiogenic and antifibrotic capabilities; it has been shown to destroy vascular tissue, and low-dose radiation can inhibit new blood-vessel growth.¹⁶⁻¹⁸

The Cochrane Collection published a major review of randomized clinical trials through 2004 on radiotherapy for the treatment of wet AMD. The review concluded that most studies through 2004 favored treatment but had inconsistent results.¹⁹ The review did note, however, that adverse effects were minimal, with no reported cases of radiation retinopathy or optic neuropathy.

The most commonly used type of radiation for the treatment of wet AMD, external beam using photons, has been in use for more than a decade.²⁰ The therapy consists of delivering protons, which are positively charged nuclear particles having a mass 1,800 times that of a beta particle or an electron. They interact primarily with target tissue electrons, but also with nuclei in complex ways, sometimes leading to neutron emission. Typical energy in proton-beam therapy ranges from 80 to 200 MeV (million electron volts). The protons take a direct path through tissue, with decreasing irradiation of normal tissues outside the beam and the fellow eye. The dose is nearly constant until the proton energy is sufficiently reduced, at which point the dose increases

rapidly to a peak some three to five times the plateau value and then drops rapidly to zero.

A second type of radiation therapy, brachytherapy, uses sealed radioactive sources (in the past, palladium-103, strontium-90²¹) that deliver radiation to a smaller field without damaging the surrounding ocular and other nontarget tissues. Brady et al. noted that the disadvantage to plaque brachytherapy included the need for suturing the plaque.²⁰

It is well known that the incidence of complications from radiation therapy is directly related to the treatment location and distance from treatment location. The most clinically significant of these complications/adverse events in ocular diseases is radiation retinopathy. In proton-beam radiation, levels are constant until the energy is sufficiently reduced. Radiation retinopathy is thought to occur after this treatment because a larger area of the retina is irradiated. It is a common side effect of external proton-beam radiation, having been reported after doses as small as 14 Gy.²² Published reports cite the complication occurring within 12-18 months of initial radiation exposure.

Ophthalmic plaque radiotherapy has been shown to increase the dose to the neovascular disease with less irradiation to surrounding tissues than external beam radiation. Finger et al. found no complications from radiation after plaque radiation with single doses of 12.5-24 Gy.²³ In a follow-up study, Finger et al. continued to find no complications after seven years. They also reported that radiation doses for clinically observable damage from radiation range from 2 Gy in the lens (result: cataract), 30-55 Gy in the cornea (result: edema), 35-55 Gy in the retina (result: radiation retinopathy), 55-75 Gy in the conjunctiva (result: conjunctivitis), and > 55 Gy in the optic nerve (result: optic neuropathy).²³

Strontium-90, used in the epimacular brachytherapy device from NeoVista, has a rapid fall-off of radiation, approximating 10 percent for every 0.1 mm away from target. This translates into a targeted dose of 24 Gy in the retina (in the lesion center), falling to 2.4 Gy effective dosing in the optic nerve, to as little as 0.00039 Gy in the cornea. (See Table 1.) As such, it is reasonable to presume the isotope would not adversely affect the retinal vasculature nor induce radiation retinopathy.

Ocular structure	Radiation dose to effect clinically observable damage; resultant damage*	Strontium-90 dose delivered through epimacular beta radiation system
Cornea	30-55 Gy; edema, keratitis	0.00039 Gy
Lens	2 Gy; cataract	0.6 Gy
Optic nerve	> 55 Gy; optic neuropathy	2.4 Gy
Retina	35-55 Gy; radiation retinopathy	6.0 Gy at lesion edge 24 Gy at lesion center

*Adapted from: Finger et al. *Am J Ophthalmol* 1999; 127:170-177.

Table 1. Radiation Doses to Ocular Structures

In published reports on strontium-90, none of the complications found after proton-beam radiation have been noted. Jaakkola et al. found contrast sensitivity to be better in irradiated eyes than in fellow eyes of 20 patients with CNV after two years, and that eyes with signs of regression after treatment lost fewer lines than fellow eyes.²¹

Endothelial Cell Migration

In theory, radiation delivered precisely to the macula can inhibit chorioidal endothelial cell proliferation without destroying adjacent retinal

tissue or resulting in systemic side effects. Larger vessels or fibroblasts are not as sensitive as newer capillaries or vessels.²⁴

Two components of angiogenesis are endothelial cell migration and proliferation. Arterial endothelial regrowth, for example, occurs when healthy adjacent cells divide and migrate to reline the arterial surface. In the ocular system, Steinle et al. found that nerve growth factor regulates choroidal, but not retinal, endothelial cell migration.²⁵ In other studies, Steinle et al. found that beta-adrenergic receptors play a role in proliferation and migration of retinal endothelial cells.²⁶ It can be inferred that if no radiation toxicity is evident after 18 months or more, the likelihood of new manifestation is diminished as the endothelial cell population has been replaced due to natural mitosis.

Vascular endothelium responds in a similar fashion when exposed to radiation and injury, regardless of the initial site. This could explain why there has been no radiation retinopathy seen in this epimacular treatment, even in patients followed to 30 months. Other studies have not shown evidence of photoreceptor loss or damage with the development of fibrovascular changes in the CNV membranes.^{27,28}

Strontium-90 has been previously shown to have antifibrotic effects in the treatment of pterygia. Isohashi et al. retrospectively reviewed 1,147 patients treated with strontium-90; 15.2% had temporary radiotherapy-induced side effects, but no long-term serious side effects were noted.²⁹ Strontium-90 beta radiation has been further shown to prevent recurrence of pterygia without late side effects after follow-up that ranged from 18 to 351 months.³⁰⁻³³ Simsek et al. found strontium-90 to be more effective and safer than topical mitomycin C in 193 patients with primary and recurrent pterygia.³⁴

Patients treated with strontium-90 delivered in significantly higher doses (up to 2,000 Gy) than in the epimacular beta radiation procedure (24 Gy dosage) showed no acute or late morbidity, even after three or more years.³⁵⁻³⁷ It is logical to assert that strontium-90 will behave similarly when used to treat CNV lesions.

OPERATIVE TECHNIQUE

Epimacular Beta Radiation Vitrectomy Procedure

Patients receive comprehensive clinical evaluations at the baseline visit. The surgical procedure is performed in the operating suite under local anesthesia. Patients are prepped and draped in the standard sterile fashion for three-port pars plana vitrectomy. A partial "core" vitrectomy is performed to remove a minor amount of vitreous and create an access channel over the CNV. Removal of the vitreous allows for ease of placement of the delivery device and minimizes mechanical traction on the peripheral retina. Both 20- and 25-gauge instrument systems are used. When 25-gauge instruments are employed, the superotemporal sclerotomy is enlarged to 20-gauge to accommodate introduction of the delivery device. If the posterior hyaloid membrane is detached, it is removed; attached posterior hyaloid membranes, in most cases, are not removed.

Dosage

The strontium-90 dose rate in water at 2.6 mm is determined by the manufacturer using a National Institute of Standards and Technology (NIST)-traceable source for each radiation delivery device by NeoVista, and the dose rate is provided on each delivery device calibration certificate. The specified dose rate is then used to calculate the treatment time based on a predefined dose of 24 Gy to the CNV membrane, the dose at the peak of the dose-rate profile for the irradiated area as shown in Figure 1, which designates the peak dose within the irradiated area. Figure 2 illustrates the isodose curves at the treatment site. Each surgeon is trained and certified by utilizing a feedback eye model that measures device position and stability to ensure a minimal amount of movement during the treatment.

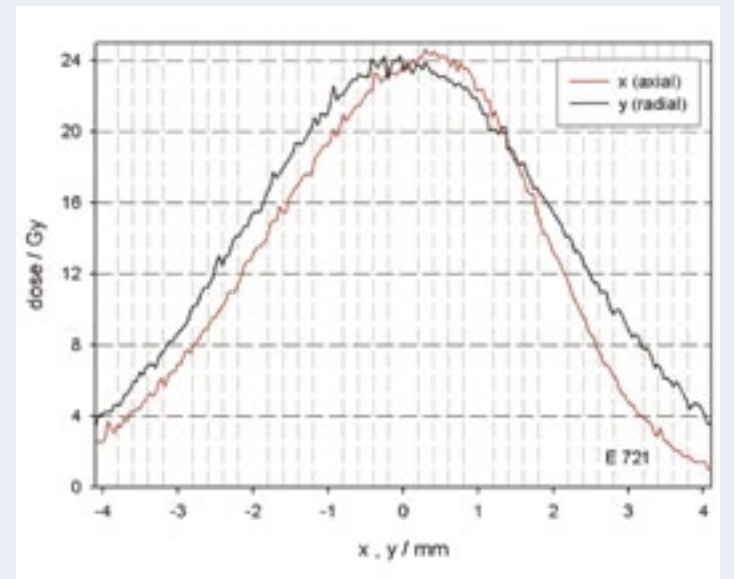


Figure 1. Dosing at the peak of the dose -Rate profile for the irradiated area

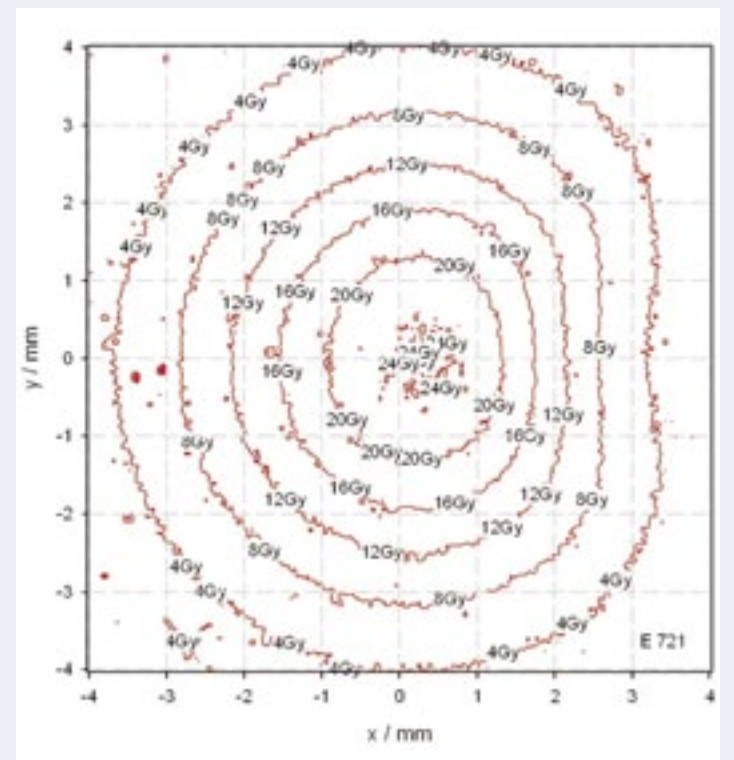


Figure 2. The isodose curves at the treatment site

Radiation Procedure

Each delivery device is calibrated to deliver a dose of 24 Gy over a pre-specified time that ranges from three to five minutes. As strontium-90 has a half-life of 29 years, the devices are recalibrated after one year or 10 uses, whichever comes first. Appropriate precautions for dealing with radioactive sources are maintained throughout the procedure, including personal monitoring devices and radiation surveys before and after surgery. The delivery device is steam sterilized prior to each use.

After removing the delivery device from the sterilization tray and

inserting the cannula into the midvitreal cavity, the surgeon orients the device in the desired position and lowers it to the point where the "cross" engraved on the cannula is centered over the fovea and the cannula tip is hovering at or just above the retinal surface (within 0.1 mm). This preliminary procedure allows the surgeon to locate the various landmarks that are used in the subsequent delivery of radiation. After this phase, the surgeon moves the cannula tip back to the midvitreal cavity, where the radiation source is moved down to the engaged, or "treatment," position. The surgeon then moves the cannula tip back to the intended treatment position, and the timer is started. The device is held by hand in the intended position for the full period of the treatment, which is specifically determined by the calibration of the device. Treatment time varies from approximately three to five minutes, depending on the source activity, but is specified to the nearest second. As soon as the treatment is completed, the cannula tip is pulled back to the midvitreal cavity and the source is retracted to the locked position. The delivery device is removed from the eye with the source fully shielded in the hand piece.

Closure and Postoperative Procedures

Standard closure techniques for sclerotomies are utilized. Subconjunctival injection of an appropriate prophylactic antibiotic and steroid is administered, 20-gauge sclerotomies are sutured, and the eye is patched. Patients are treated postoperatively with topical antibiotics and a tapering topical steroid regimen.

CONCLUSIONS

To the best of the authors' knowledge, the epimacular brachytherapy system is the first device designed to be placed temporarily into the vitreal cavity to deliver a focal dose of radiation to the target tissue (CNV). The device has similar handling requirements and precautions associated with plaque brachytherapy, and the procedure to deliver the radiation is similar to standard vitrectomy.

The epimacular brachytherapy device developed by NeoVista is in clinical trials for the treatment of neovascular AMD in combination with ranibizumab as part of a Food and Drug Administration-mandated study required for U.S. regulatory approval. That trial is a multicenter, randomized, controlled phase III clinical study (CABERNET) that has enrolled about 45 sites worldwide. The authors of this paper believe one-year results from the CABERNET trial will be available in late 2010. Previous results of the NeoVista epimacular brachytherapy system (when used in conjunction with bevacizumab) indicate a potentially synergistic effect of ionizing radiation with strontium-90 and anti-VEGF agents, and suggest it may prove to be a durable treatment for neovascular AMD.

As with any new treatment paradigm, the authors recommend further follow-up with patients undergoing epimacular radiation therapy. Treatment with radiotherapy and anti-VEGF compounds is a promising approach to treating AMD, and may improve a patient's quality of life with its one-time treatment approach compared to the indefinite treatment regimen with the currently marketed treatments. Longer-term results are recommended to verify the initial findings of strontium-90 radiation for the treatment of AMD. ■

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