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Radiobiology of Epimacular Brachytherapy for the Treatment of Choroidal Neovascularization Secondary to AMD

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Despite all the advances in studying treatments for wet age-related macular degeneration (AMD) in the past decade, the precise etiology of molecular events that cause the disease have only begun to be understood.[1] The neural retina, retinal pigment epithelium (RPE), Bruch's membrane, and the choroid are all affected.[1] Vascular risk factors may be linked to the development of AMD, and atherosclerotic deposits have similar molecular composition to drusen,[1] a preliminary indicator of AMD.

Several hypotheses of pathogenesis have been proposed for the progression of AMD and the formation of choroidal neovascular (CNV) membranes. Hypotheses include primary RPE and Bruch's membrane senescence, primary genetic defects, and primary ocular perfusion abnormalities. Oxidative insults have also been proposed as a contributing factor.[2-5]

The role of oxidative stress (cellular damage caused by reactive oxygen intermediates) in AMD has been well researched, and the retina remains especially vulnerable to oxidative damage because of its high oxygen consumption coupled with its high levels of cumulative irradiation.[6] The same reactive oxygen intermediates have been found to up-regulate vascular endothelial growth factor (VEGF) in RPE cells.[7] The underlying mechanism of neovascular AMD is not universally agreed upon, but science has provided a compelling argument that angiogenic growth factors are ultimately involved.[8-10] Although new advances have a significant impact on a patient's visual outcomes, the therapies also represent a tremendous treatment burden to the physician, patient, caregiver, and healthcare systems.

In retinal diseases, radiation is thought to be a potential treatment because it can inhibit proliferating endothelial cells, angiogenic cytokine-producing inflammatory cells, and cell types involved in scar formation, including the cytokine producing RPE.[11] AMD is likened to a proliferative wound healing process and as such the aforementioned effects reflect a multifaceted approach to treating this disease with one treatment.[12]

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USE OF RADIATION AS A THERAPEUTIC TREATMENT MODALITY

Ionizing radiation inhibits blood vessel growth, inflammation, and scar formation. Early studies found both choroidal hemangiomas and benign intracerebral arteriovenus malformations regressing after ionizing radiation.[13-15] The delivery of ionizing radiation during radiotherapy is defined by a multitude of variables including the type of ionizing radiation, total dose, biologic effect on the type of cell exposed to radiation, and delivery time of the dose.

Ionizing radiation could be delivered in the form of alpha particles, beta particles, X-rays, gamma rays, and neutrons. Alpha particles have the least energy and do not penetrate tissue. Beta particles possess adequate energy to penetrate the target tissue but the energy is limited to a range of 2 to 4 mm. X-rays and gamma rays are high energy photons with overlapping wavelengths and can penetrate multiple layers of tissues. Neutrons are highly energetic and have the highest penetration range. Therefore it is important to consider an appropriate choice of ionizing radiation to balance the radiation dose delivered to the CNV lesion and any damage caused to the collateral tissue. Equally important is how resistant (sensitive) to the radiation the target is.[16] (See **Figure 1.**)

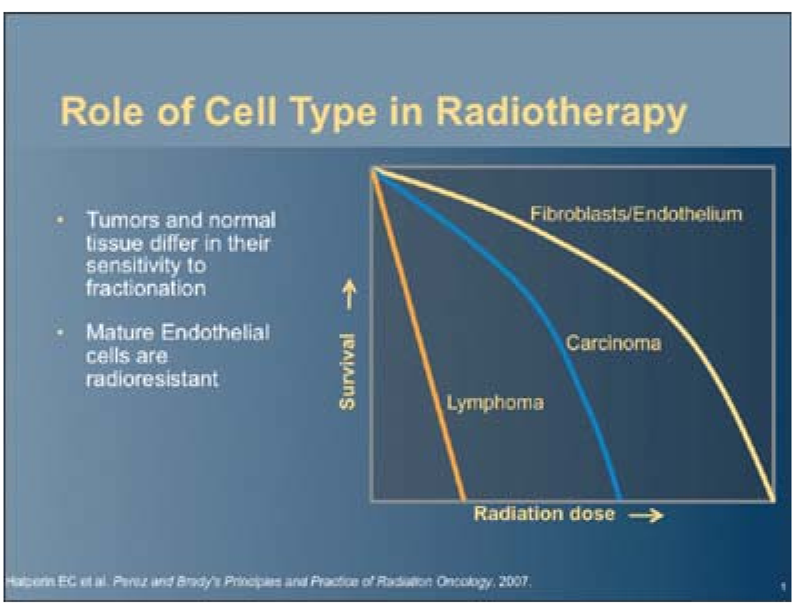

Figure 1. As noted in Halperin et al., the efficacy of radiotherapy is directly associated with the type of cell being irradiated. Lymphoma cells are highly sensitive to fractionation, whereas fibroblasts and endothelium are highly resistant to fractionation.

The biologic effect of ionizing radiation is closely related to its ability to cause double-stranded breaks to the DNA. Thus, proliferating endothelial cells are radiosensitive, whereas established endothelial cells are radioresistant.[17] Damaged cells may undergo programmed cell death (apoptosis) or they may not die until the next mitosis because they are unable to divide. Some types of cells, predominantly endothelial and fibroblasts, may be slow-dividing and thus, mitotic death is not immediately apparent. Alternatively, cells may survive by repairing their DNA. The ability of a cell to repair DNA is affected by its position within the cell cycle. (See **Figure 2.**) Cell cycle checkpoints may activate to allow time for DNA repair mechanisms.[17]

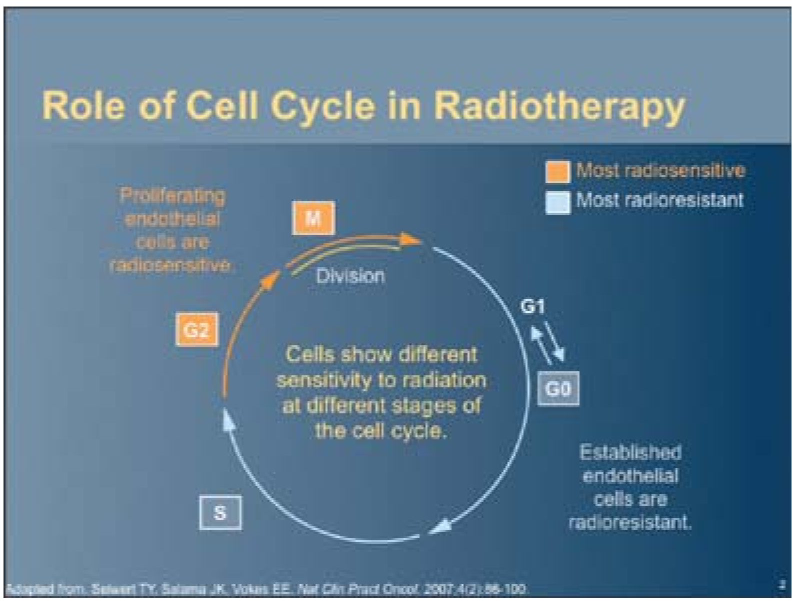

Figure 2. Selwert et al. were the first to describe cell survival via DNA repair, and noted a cell's success at repair is predetermined by its position within the cell's cycle. (Figure adapted.)

Apoptosis generally occurs early after the initial radiation exposure, whereas mitotic death is dependent upon the interval between the radiation exposure and cell division. The biologic response to radiation may not be apparent in slowly dividing cells (such as established endothelial cells) until weeks or months after the treatment. Further, single large fraction doses will cause cell death in both the fast-proliferating cells and the slow-dividing cells; low fractionated doses may only cause cell death in the fast-proliferating cells.

Chakravarthy was the first to show teletherapy could have a positive outcome in neovascular AMD at doses between 10 and 15 Gy.[18] Since then, other studies have shown a positive therapeutic effect.[19] Marcus noted numerous, nonrandomized, uncontrolled studies found no significant short-term adverse effects and no immediate visual loss.[20] Radiation has the added benefit of fewer treatments, which can present a significant quality of life advantage for the elderly.[11] Cochrane Collaboration published a major review of randomized controlled studies on the use of radiotherapy for AMD.[64] The authors concluded that "most trials showed effects (not always significant) that favored treatment with radiotherapy but with inconsistencies in the results."

Today, the current standard of care for neovascular AMD is antiangiogenesis inhibitors (anti-VEGF treatments). Anti-VEGF treatments target vascular endothelial growth factor (VEGF), a protein involved in promoting the angiogenic cascade, whereas radiation causes damage to any proliferating and mature cells that are exposed to the target dose. Radiation has a cytotoxic effect while anti-VEGF therapy a cytostatic one, thus there may be role for the concomitant use of these 2 treatment modalities. In oncology, the addition of anti-VEGF treatment to radiation substantially improved outcomes, suggesting the concomitant use may be more effective than either therapy alone.[21,22]

There are currently 2 anti-VEGF treatments approved in the United States for AMD. The first, pegaptanib sodium, is an aptamer specifically designed to bind $VEGF_{165}$. The second, ranibizumab, is a recombinant, humanized monoclonal antibody antigen-binding fragment (Fab) that binds various isoforms of VEGF-A. A third compound, bevacizumab, is a full-length anti-VEGF antibody commonly used to treat cancer and used off-label to treat AMD. Both approved compounds and bevacizumab require continuous dosing over an indefinite period of time to maintain treatment success.

RADIATION EFFECTS WITHIN THE EYE

Animal studies found a low-dose radiation applied to a targeted site reduces the vascularity of the granulation tissue; doses up to 16 Gy had no adverse affect on adjacent, healthy ocular tissue.[23] We now know localized radiation treatment has the ability to prevent proliferation of vascular tissue[24,25] by inhibiting neovascularization. After low-dose radiation, vascular endothelium demonstrates morphologic and DNA changes,[26-28] inhibition of replication,[29,30] increased cell permeability,[31,32] and apoptosis.[33] Fibroblast proliferation and subsequent scar formation, a hallmark of end-stage neovascular AMD, are also inhibited.[25]

Clinical experience with conventional fractionated irradiation for head and neck malignancies has shown that cumulative doses (multiple fractions) of up to 30 Gy cause no damage to the retina or optic nerve.[34] In wet AMD, the targets of radiotherapy are both proliferating tissue (new neovascular growth), inflammatory cells, and late responding tissues, such as the endothelium (mature choroidal lesion), and fibroblasts.

Indeed, early studies examining the effect of radiation in the eye have demonstrated that low dose radiation, while damaging CNV membranes, does not affect the overlying retina.[19,35] Furthermore, early publications report resolution of subretinal fluid, hemorrhages, and exudates after radiation therapy; and that vision was maintained in most subjects.[19,35-36]

An investigational strontium-90 applicator is being developed to treat CNV secondary to AMD (NeoVista, Fremont, CA). (See **Figures 3 and 4.**) Strontium-90 in a targeted delivery technique administered after a partial vitrectomy does not create thermal injury to the retina or surrounding tissue and has a rapid fall-off in radiation delivery, approximating 10% for every 0.1 mm away from the source. Radiation for epimacular therapy in this device is delivered as a single dose of 24 Gy.[37] A targeted dose of 24 Gy on the macula to the center of the choroidal lesion would equate to 2.4 Gy effective dosing in the optic nerve, and .00056 Gy in the lens. This is in stark contrast to earlier studies on external beam radiation, where radiation retinopathy, cataract, edema, and conjunctivitis were reported (**Table 1**).

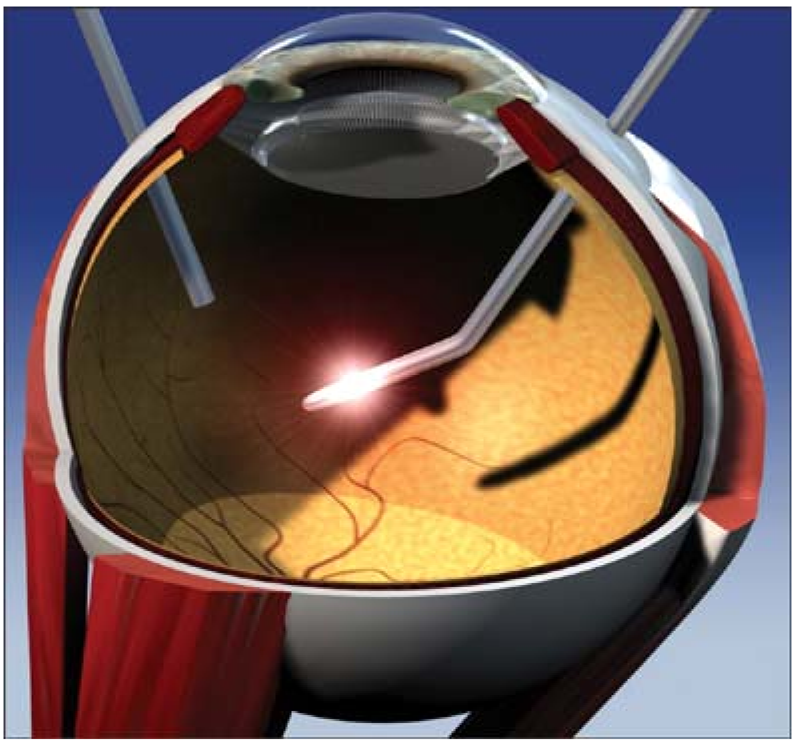

Figure 3. Illustration of the NeoVista device, where the bright tip of the applicator represents the limited radiation effect on surrounding tissue.

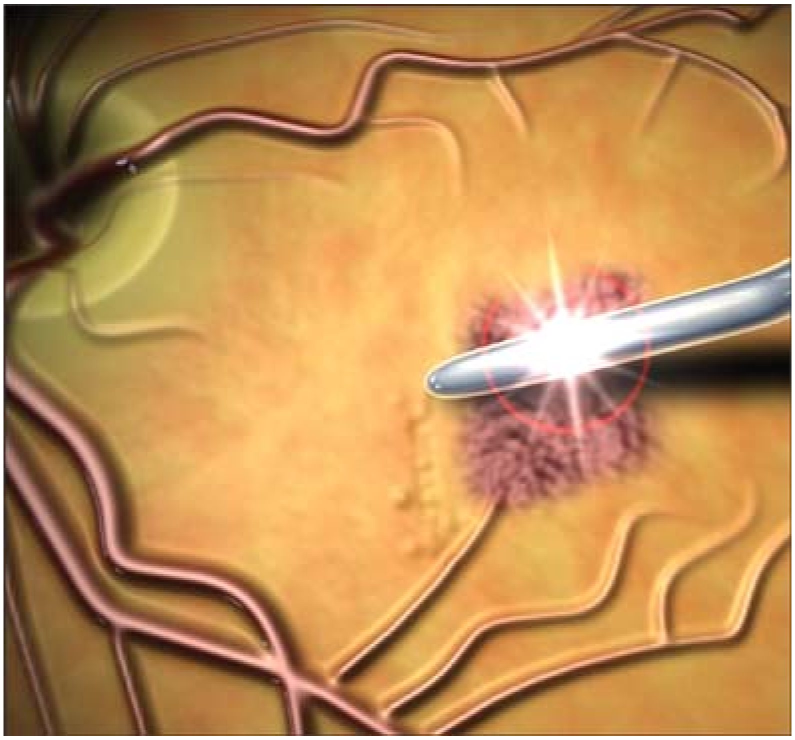

Figure 4. Illustration of the small effect volume of the applicator, delivering 24 Gy to the lesion, but significantly less elsewhere.

Table 1. Adverse Effect Thresholds and Epimacular Brachytherapy Dosing

Tissue	Effect	Dose for clinically observable damage	Dose delivered by epimacular brachytherapy
Cornea	Edema	30-50 Gy	.00039 Gy
Conjunctiva	Conjunctivitis	55-75 Gy	.00040 Gy
Lens	Cataract	2 Gy	.00056 Gy
Retina	Radiation retinopathy	35-55 Gy	24 Gy
Optic nerve	Optic neuropathy	> 55 Gy	2.4 Gy

Previous studies of external beam and proton irradiation have been with fractionated dosing;[38] the epimacular brachytherapy is delivered in one single fraction of 24 Gy over a total of 2 to 4 minutes.[39] The rationale for a single dose of this magnitude is based on the need to treat both radiosensitive and radioresistant cells in a very small, welldefined region of the eye.[40]

It is well known that the incidence of complications from radiation therapy is directly related to the treatment location and distance from treatment location.[41] 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.[42] Published reports cite the complication occurring months after initial radiation exposure.[11,43]

VITRECTOMY AND NEOVASCULAR AMD

Simple vitrectomy has been successful in the past to produce regression of CNV in cases of patients with AMD and vitreous hemorrhage;[44] this suggests the posterior vitreous membrane is implicated in the pathophysiology of AMD.[45] In one series, 66% of patients had some degree of CNV regression after simple vitrectomy, with 16% achieving complete disappearance of CNV 6 months after surgery.[45] However, the authors noted these particular successes were in cases of relatively small CNV with little involvement of the macula and where the CNV itself was within one-half of the optic disc diameter from the fovea.[45] Vitreous surgery in general affects oxygen distribution in the eye and reduces hypoxia in ischemic areas of the retina.[46] In the case of vitrectomy and lensectomy, the flow of relatively oxygen rich aqueous along the inner surface of the retina seems to provide the inner retina with additional oxygen. Vitrectomy and lensectomy reduce the oxygen tension in the aqueous humor in the anterior chamber.[47,48] Oxygen treatment has been shown to reduce diabetic macular edema, and oxygen appears to reduce the production of VEGF. Hashimoto also found partially increasing the oxygen pressure in the vitreous beneficial in CNV regression.[44]

As radiation acts by forming free radicals (primarily from water molecules) that cause irreparable damage to the DNA backbone,[49] oxygenation may enhance the therapeutic efficacy of the treatment. Tissue oxygenation has been employed as an enhancer of the radiation effect in the clinical setting.[50,51]

COMBINING ANTI-VEGF AND BRACHYTHERAPY

A combination of epimacular brachytherapy and bevacizumab has been investigated and may be a more effective and durable treatment option for patients with neovascular AMD.

The initial data on epimacular brachytherapy alone is promising. The 1-year results (n=34) of intraocular epimacular delivery alone of either 15 Gy or 24 Gy beta radiation for the treatment of subfoveal CNV secondary to AMD found no one lost more than 3 lines, and 50% of those treated with low dose (76% of those treated with a high dose) improved or maintained their visual acuity.[37] To date, there have been no reports of radiation-induced toxicity (some patients have had follow-up through month 24); the primary adverse events were directly related to the partial vitrectomy; 11 patients (42% of the phakic eyes) developed cataract.[37] When combined with intravitreal bevacizumab in a second study (n=34), 12 month results found no adverse events were associated with the exposure to radiation after single treatment with 24 Gy and two injections, 68% of patients improved or maintained BCVA, and 38% gained at least 3 lines on the ETDRS chart.[39] There were no serious adverse events reported; of the moderate adverse events, CNV leakage (21%) and cataract (25%) were the most predominant, with other mild to moderate events reported at under 10%; there were no instances of radiation-induced toxicity or any events related to the applicator.[39]

As explained previously,[37,39] the NeoVista device is designed to provide an effective dose of ionizing radiation to a very small area due to the short range of strontium-90 (**Figure 5**). A sharp decline in the radiation dose delivered minimizes collateral damage beyond the edges of the CNV lesion. The delivery device is designed to balance regression of the CNV lesion and the collateral tissue exposure to the radiation dose. However, longer follow up in a larger cohort of patients is warranted to confirm the preliminary safety data. Longer term results will help determine if the combination of radiation, anti-VEGF therapy and increased oxygenation via vitrectomy is able to sustain the reduction in additional injections initially seen at the 1-year follow-up.

The vitrectomy performed to successfully deliver the epimacular brachytherapy is not without its own risks, and the retina community needs to bear this in mind as future results become available. Cataract is common after vitrectomy; in the studies on the epimacular therapy the rate of cataract development is lower than expected when compared to studies on vitrectomy alone.[52-54]

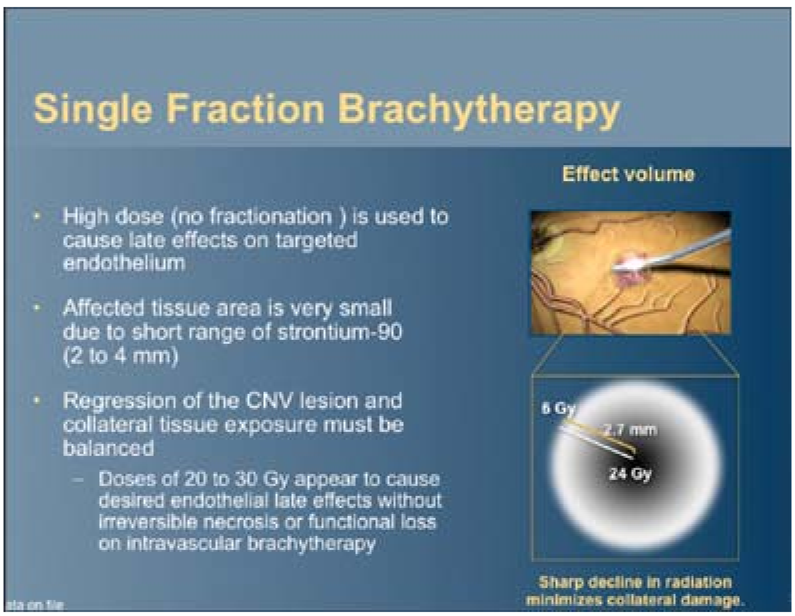

Figure 5. The NeoVista device delivers strontium-90 (which has a short range of about 2 to 4 mm), which allows it to target the lesion without affecting nontargeted tissue.

CURRENT UNMET NEED IN THE TREATMENT OF AMD

Continued investigation surrounding the benefits of radiation therapy and other modalities for AMD is still warranted, as there is no single treatment that exists that eradicates CNV. The safety and efficacy of epimacular brachytherapy is currently under evaluation in a phase 3 study called CABERNET (CNV Secondary to AMD Treated with BEta RadiatioN Epiretinal Therapy). It is a multicenter, randomized, controlled study that will enroll 450 subjects at clinical centers worldwide. The study will evaluate the safety and efficacy of epimacular beta radiation therapy delivered concomitantly with the FDA-approved antiangiogenic therapy Lucentis (ranibizumab) vs Lucentis alone.

One new study, the "Macular EpiRetinal Brachytherapy in Treated Age Related Macular Degeneration Patients (MERITAGE)" is evaluating the safety and efficacy of epimacular brachytherapy for the treatment of subfoveal CNV associated with wet AMD in patients that require persistent injections of anti-VEGF therapy to maintain an adequate response to treatment. MERITAGE will enroll 32 patients at 2 sites — 1 in the United States and 1 in the UK. This study is, in effect, concerned only with patients who cannot maintain their recovered vision without additional anti-VEGF injections. Recent data from a study on ranibizumab beyond 2 years (HORIZON) suggest that anti-VEGF therapy has to be administered indefinitely at frequent intervals beyond the 2-year endpoint to achieve and maintain optimal VA outcomes as seen in ANCHOR (ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD; Genentech, South San Francisco, CA), and MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD; Genentech).[55] Patients enrolled in MERITAGE will be treated with a single epimacular brachytherapy procedure to maintain the adequate response achieved in the prestudy phase with frequent anti-VEGF injections (either ranibizumab or bevacizumab). Anti-VEGF therapy will be administered on an as-needed basis as determined by the investigator based on lesion activity and visual acuity during the study phase. The study will follow patients for 36 months.

Early results from this study are encouraging.[56] A preliminary outcome is illustrated below. Before entering the trial, the patient had undergone seven previous anti-VEGF injections over the prior X months. At study entry the baseline visual acuity was 20/130. By month 2, the patient's vision had improved to 20/100 and continued to improve at the 3-month follow-up to 20/80 with no additional anti-VEGF injections. The central retinal thickness fluctuated in this patient, improving from a study baseline of 142 µm to 135 µm at month 2, and was 148 µm at month 3. As with other patients in the study, longer follow-up is mandated to determine if the effects of the epimacular brachytherapy can be sustained (Data on file, NeoVista, Fremont, CA).

SUSTAINABLE TREATMENT OPTIONS

There is an enormous cost to society for the treatment of wet AMD. Physicians must be continually available to administer intravitreal injections, thereby limiting the number of additional patients that can be treated in a given day; public healthcare funding will spend millions on treatments yearly. It is estimated that the direct medical costs for AMD are $575 million per year, with costs for AMD substantially higher in people over the age of 65. The cost is expected to rise to $845 million by 2020,[57] when about 3 million people are expected to be affected in the United States.[58]

There are about 200 000 new cases of AMD diagnosed yearly,[59-61] adding to the treatment burden.[62,63] The anti-angiogenic, anti-inflammatory, antifibrotic properties of ionizing radiation along with the increased oxygenation facilitated by vitrectomy and the additional concomitant therapy with anti-VEGF can potentially offer the desired multi-faceted approach to treating this disease. As early data suggests, such an approach can offer optimal VA outcomes with fewer treatments.[40,53] Epimacular brachytherapy is one promising option that may lead to both visual gain and treatment longevity. **RP**

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