

Stereotactic low-voltage x-ray irradiation for age-related macular degeneration

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ABSTRACT

The IRay stereotactic low-voltage x-ray irradiation treatment system for age-related macular degeneration consists of a low voltage x-ray tube, an eye tracking system, a robotically controlled delivery system, a coupling device to facilitate tracking and stabilisation, a graphical user interface and gating software. Low-voltage x-rays are delivered in a series of three spots to the macula in a non-invasive manner through the inferior pars plana. These beams are designed to overlap on the centre of the macula. Each beam delivers one-third of the total dose, such that the total macula dose is three times an individual beam's dose. The device is designed to run off standard domestic electrical power, and no special shielding is necessary for the room. This system has been validated in Monte Carlo simulations, human cadaver eye studies, pre-clinical animal studies and in a phase I clinical trial.

efficacy of monthly dosing regimens,^{1 2} variable dosing regimens based upon optical coherence tomography findings are dominant.^{3–5} Pharmaceutical combination therapy has been hypothesised to increase efficacy and durability of VEGF-I, despite the practical limitations of cost and complications such as endophthalmitis from multiple injections.⁶ Previously, radiation treatment of AMD resulted in poor visual acuity outcomes relative to VEGF-I.⁷ Recently, a surgical approach utilising pars plana vitrectomy with epiretinal strontium-90 β irradiation was reported.^{8 9}

The IRay (Oraya Therapeutics Inc, Newark, CA, USA) is a non-invasive low-voltage (low-energy x-ray) stereotactic treatment system for wet AMD designed to fit into a standard office and run off a 120 V wall socket without the need for special room shielding (figure 1). The IRay consists of an x-ray source mounted on a robotically controlled delivery system, connected to the patient via a contact lens and 25 mm Hg suction. The treatment coordinate system is defined by the geometric axis corresponding to the patient's eye following alignment with the I-Guide (figure 2). The

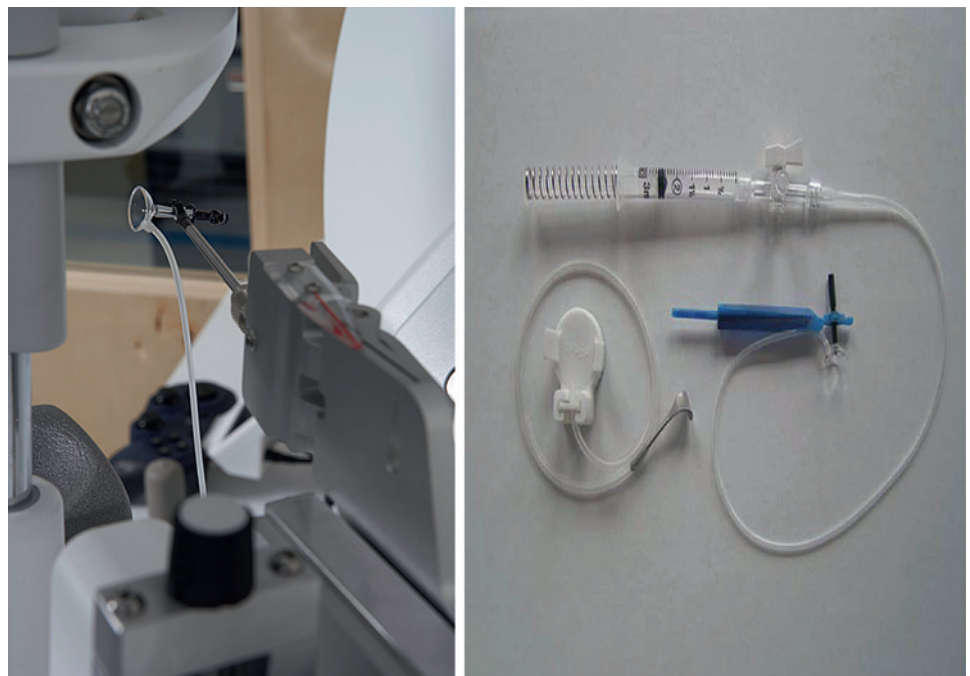
Vascular endothelial growth factor inhibitors (VEGF-I) have improved the prognosis for wet age-related macular degeneration (AMD).^{1 2} Despite the



Figure 1 The clinical IRay device is shown. The operator console is to the left of a leaded glass shield. The patient is seated to the right of the leaded glass shield. The maximal radiation dose to the operator is 1×10^{-7} Sv, equivalent to background radiation.

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Figure 2 The I-Guide is connected to the micromanipulator with an extension pole.



automated positioning system detects retroreflective fiducials attached to the lens and stabiliser bar of the I-Guide to automatically align to the geometric axis using a two-camera imaging system, resulting in initial alignment with the posterior pole (intersection of the geometric axis with the retina). A fixed offset is performed from the pole to the nominal fovea,¹⁰ minimising exposure to the optic nerve (0.2–0.24 Gy in males and females, respectively.)¹⁰ Exposure to the lower lid is avoided by the placement of a custom lid retractor. The only variable that is input into the graphical user interface is axial length, determined from an a-scan ultrasound. The IRay is designed to deliver a 3.5 mm beam through the inferior pars plana to a point 150 mm from the x-ray source, where the beam will be 4 mm. Three such overlapping beams delivered through the inferior pars plana are constrained to overlap on the macula with a resulting spot size of 6 mm after accounting for movement (figure 3). The combination of microsaccades (despite being held by the I-Guide) and the effect of

overlap results in a spot of 6 mm. In figure 3, the heat map demonstrates the 10–90% isodose of the three overlapped beams on the macula. The device is designed to deliver these three spots to that one location 150 mm from the x-ray source, while avoiding the lens and the optic nerve.¹¹ The IRay operator and patient are separated by a lead-lined glass shield that allows the operator to visualise the therapy from a distance of less than 1.53 m while receiving a radiation dose ie, equivalent to background radiation. The patient is secured to the chin-rest via a head restraint, ie, enclosed in a lead curtain to prevent radiation from travelling beyond the patient. The mean total intracranial dose ranges between 0.0109 and 0.0136 Gy for males and females, respectively.¹⁰

The software consists of the following: (1) treatment planning; (2) treatment monitoring; (3) safety and gating information; and (4) treatment verification. Patients are evaluated to determine if they are eligible for treatment based on the proximity of the optic

Figure 3 Three low-voltage x-ray beams enter the eye through the inferior pars plana and are configured to overlap on the macula. The outermost colour ring (blue) represents the 10% isodose, while the innermost colour ring (red) represents the 90% isodose. The beam size at the sclera is 3.5 mm and at the macula is 4 mm. Taking into account overlap and movement, the effective spot size at the macula is 6 mm.

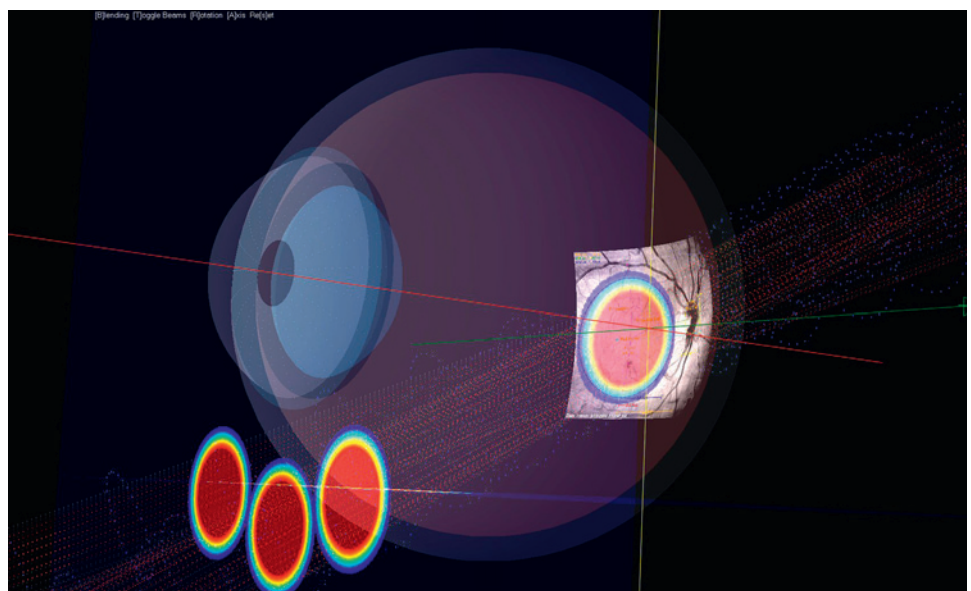
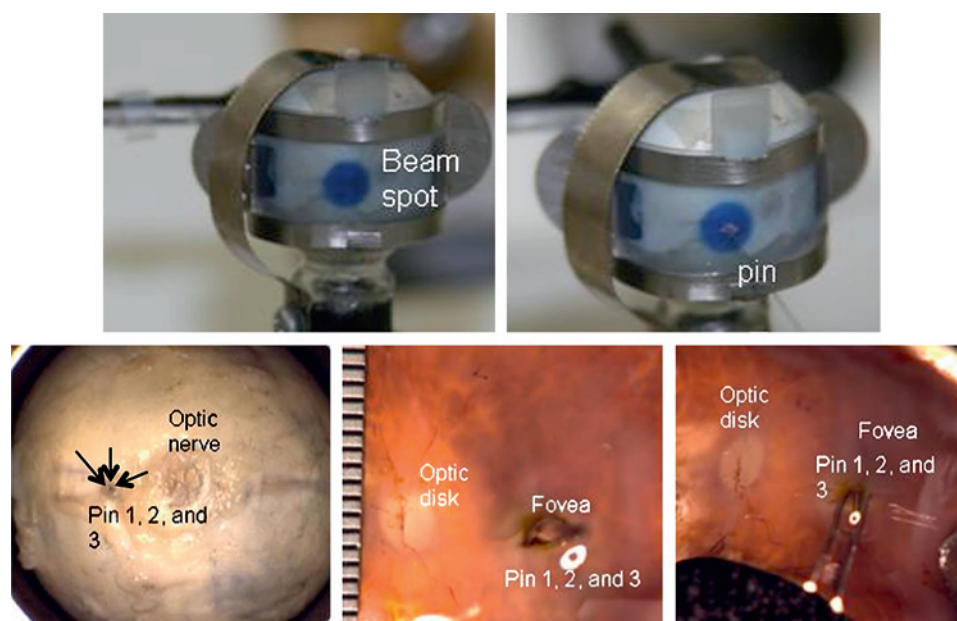


Figure 4 A cadaver eye with radiochromic film inside of a cassette mounted to the posterior sclera overlying the macula is shown top left after irradiation with low voltage x-rays. The centre of the fovea is pinned (top right), then the cassette and radiochromic film is removed and the pin is cut flush with the sclera. This was repeated three times to verify accuracy and precision of targeting (bottom left)—in this panel we see three pins cut flush with the globe and their relationship to the optic nerve. The pins overlap within 100 μm of the centre of the fovea (bottom middle, bottom right). The three pins can be seen extruding from the fovea, essentially on top of each other, with the optic nerve nasal (bottom left, arrows).



nerve to the macula. The axial length information is entered. The patient, the IRay and the I-Guide are coupled together and treatment is initiated. At present 16 Gy and 24 Gy have been evaluated, which involves three spots of approximately 2–3 min duration each. Treatment monitoring involves tracking the fiducials to determine the path of the three beams. This is contemporaneous with real-time gating algorithms that are enacted if the ocular movements exceed predetermined parameters. Additional safety mechanisms include automated IRay shutdown if the patient moves their head away from the chin-rest or if the handle-grips are released, and an emergency shutdown button on the control panel.

Monte Carlo simulations demonstrate 100% overlap of the three treatment beams. Cadaver eye studies using radiochromic film and pin piercings of the centre of the treatment spot demonstrate the three-beam overlap in the fovea (figure 4). Animal work in pigs has demonstrated that the 16 Gy and 24 Gy doses results do not result in any histopathological changes (unpublished data).

This system has been used to evaluate the effects of externally applied, non-invasive low-voltage irradiation to the macula of patients with wet AMD in an ongoing institutional review board (IRB)-approved phase I clinical trial at Asociacion Para Evitar La Ceguera En Mexico, in Mexico City, Mexico. Entry criteria include patients with wet AMD who are treatment naive or have received previous treatment with VEGF-I. The protocol is based upon combination therapy, utilising low voltage x-rays and ranibizumab. Patients receive ranibizumab at time zero, followed by IRay low-voltage irradiation for 16 Gy at week 1, followed by ranibizumab at month 1. Additional ranibizumab injections are provided for an increase in central foveal thickness of 100 μm , a decrease in visual acuity of 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, new classic choroidal neovascularisation or new haemorrhage. The rationale for combination with VEGF-I and irradiation is that the three main effects of radiation—anti-inflammatory, anti-neovascular and anti-fibrotic—fit neatly with immediate dehydrating effects of ranibizumab. Radiation has been demonstrated to be additive in combination with VEGF-I in the treatment of cancer.¹²

Clinically relevant radiation retinopathy is threshold-mediated and does not occur until 45 Gy or more has been delivered

to the retina, typically after 2.5 years.¹³ The main factors are total dose, volume of tissue irradiated and the fraction size.¹⁴ The Sr-90 epiretinal applicator has demonstrated no evidence of radiation retinopathy following 24 Gy at up to 24 months.^{8–9} Similarly, in 11 randomised controlled studies involving external beam radiotherapy (EBRT; dose 7.5–24 Gy), there were 0/1078 cases of radiation retinopathy or optic neuropathy.⁷ Unlike EBRT, the IRay has a small spot size, is constrained to deliver to one location and will gate for excessive ocular movements, decreasing the chances of radiation retinopathy.

The 1 year results of the phase I trial will be published shortly. A multicenter double-masked pivotal trial is enrolling in Europe and the phase III double-masked randomised controlled trial of x-ray irradiation for wet AMD will begin in the US soon.

Competing interests Financial Disclosure: DMM (consultant, Scientific Advisory Board, stock option grant), PKK (consultant, Scientific Advisory Board, stock option grant), MG (equity, intellectual property).

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