Radiation Therapy for Choroidal Neovascularisation in AMD – A Review

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New hope for elderly victims of disease that causes blindness

Radiation therapy will reduce the need for regular injections

By Nick Collins, Science Correspondent

ELDERLY patients who suffer from a common eyesight problem that can lead to blindness if left untreated could be spared monthly hospital visits and eye injections with a new radiation treatment.

Thousands of people with wet age-related macular degeneration (AMD), the leading cause of blindness in Britain, manage their condition with an intensive programme of hospital visits and injections directly into the eyeball. But doctors say that the need for monthly appointments and six injections a year means many patients fail to keep up with the regime and lose their sight.

Now a US company is preparing to introduce a one-off radiation therapy to Britain that could lower a patient's need for injections, allowing some to go a year without further treatment.

A small-scale study carried out in 21 international centres, including King's College London and Manchester Royal Eye Hospital, found that patients given the radiation treatment needed on average a third fewer injections over the following year.

Some needed no injections, said researchers at the American Academy of Ophthalmology conference in Chicago. Although the radiation was designed only to prevent the condition from worsening, a small number of patients found that they were able to read one line further [illegible]

Dr Tim Jackson, an NHS eye surgeon who led the British trial, said: "What is really interesting is that certain groups of patients had a 50 per cent reduction in the number of injections needed and significantly better vision.

"These are good results but we would always want further long-term follow-up to establish the safety and effectiveness of the treatment."

Wet AMD, which typically develops after the less severe "dry" condition, is caused by the abnormal growth of blood vessels at the back of the eye, which causes a leakage of blood and fluid behind the retina.

The disease usually develops in old age and can cause the rapid loss of central vision, which is needed for reading, writing and driving.

An estimated 250,000 people in Britain suffer from macular degeneration, with 40,000 new cases diagnosed every year, and campaigners say demand for treatment is so great that four in 10 clinics are unable to treat patients in time.

The condition is currently managed by injections into the back of the eye that suppress the growth of blood vessels, but the new therapy uses low-dose X-rays aimed through the white of the eye to selectively kill the abnormal tissue.

The treatment takes no more than 20 minutes and has been licensed for use in Britain. It could soon be available in private clinics.

Jim Taylor, the chief executive of Oraya, which developed the therapy, said British clinics would initially have the capacity to treat up to 3,000 cases a year.

A spokesman for the Macular Disease Society said: "From what we have seen of the first year data, this looks like an interesting development. It does appear to be quite promising in terms of reducing the burden of care on patients."

A Little Physics

One gray is the absorption of one joule of ionizing radiation energy per kilogram of matter.

$$1\ \mathrm{Gy} = 1\ \frac{\mathrm{J}}{\mathrm{kg}} = 1\ \frac{\mathrm{m}^2}{\mathrm{s}^2}$$

Abdominal X-ray = 1.4 mGy

Abdomen & pelvis CT = 30 mGy

RT for a solid epithelial tumour = 60-80 Gy

How Does It Work?

- Ionizing radiation causes single- or double-stranded breaks in DNA
- Oxygen atoms are ionised, generating reactive oxygen species

=> cell death

- Aberrant proliferation of choroidal endothelial vessels => pathologic neovascularization of exudative ARMD
- Endothelial cells are highly radiosensitive

- Endothelial cell loss occurs up to 1 year after irradiation
- 1 fraction of 10 Gy radiation in animal model:
  - decreased vascular permeability,
  - increased blood flow velocity
  - improved stasis

=> **? Additional functional effects**

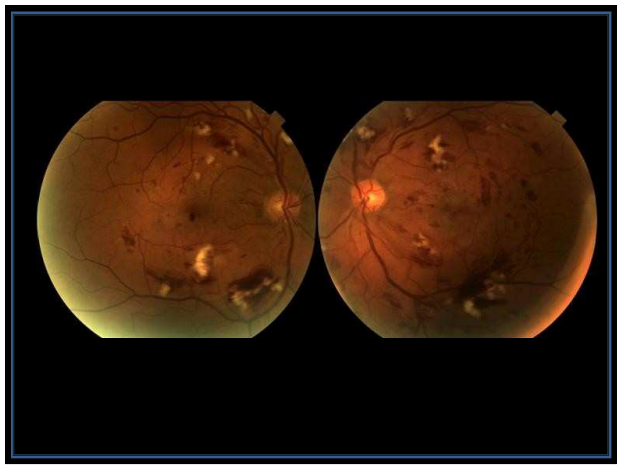
- Antiangiogenic
- Reduction in macrophage-mediated retinal inflammation that accompanies ARMD
- Capillary closure

Ocular Side Effects

- Keratitis sicca
- Cataracts
- Radiation optic neuropathy
- Radiation retinopathy

Radiation Retinopathy

- 6 months to 3 years from exposure
- Presents as vascular disease
- Damage to endothelial cells of retinal capillaries
- Cotton-wool spots, retinal hemorrhages, microaneurysms, perivascular sheathing, capillary telangiectasia, macular oedema, disc oedema.
- Retinal ischemia = > NVE/NVD/NVI



- Threshold dose for clinically detectable RR is 35 Gy (minimum reported 11 Gy)
- Visually significant RR is rare below 45 Gy
- Typical protocols for ARMD treatment involve fractionated doses of 2-34 Gy

- Endothelial cell death => migration of new endothelial cells for repair => incitement of neovascularization
- The gold standard treatment is photocoagulation (anti-VEGF therapeutics and corticosteroids show promise)
- Ongoing Treatment of Radiation Retinopathy Trial

The Origins

- Radiation therapy was used to treat ARMD as early as 1948 (and possibly as early as 1919):

Guyton JS, Reese AB.

Use of roentgen therapy for retinal diseases characterized by new-formed blood vessels; Eale's disease; retinitis proliferans

Arch Ophthal 1948;40:389-412

Treatment Modalities

- Standard photon external beam radiation therapy (EBRT)
- Stereotactic radiation therapy (SRT)
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- Brachytherapy (EMBT – epimacular brachythrapy)

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EBRT

- First phase 1 trial in 1993 (*Chakravarthy et al*)
- 19 patients treated with 6 megavoltage (MV) photons
- 10 Gy or 15 Gy in 5 fractions
- VA maintained or improved in 63% at 1 year
- CNV membrane regression in 77%
- All 6 controls showed VA decline and CNV progression
- SE= one cataract at 12 months in 1 patient

- 16 further phase I/Phase II studies
- Short follow up (most <2 years), lack of controls
- Pooled analysis of 409 patients:
  - 62.6% of eyes VA same or improved over 13 months
  - 22.5% moderate visual loss, 14.9% severe visual loss.
  - Severe visual loss 47% in untreated controls, 31% in photocoagulation controls

- 11 phase 3 RCTs
- Results variable in terms of changes in VA and size of CNV membrane
- Pooled analysis in 1242 patients, given medium-risk ARMD controls:

Average relative risk for severe visual loss at 12 months 0.62 (95% CI, 0.44-0.87)

Conclusions

- Can be beneficial, particularly in reducing the risk of severe visual loss
- Dose-dependent
- EBRT may not eliminate progression of CNV, as membranes progressed universally

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Stereotactic Radiation Therapy

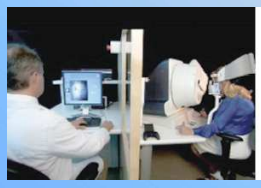
- Accurate and precise dose delivery to the target with steep dose drop-offs for adjacent tissues
- Focused radiation beams targeting a well-defined area
- Detailed imaging, computerized three-dimensional treatment planning
- “Gamma knife”

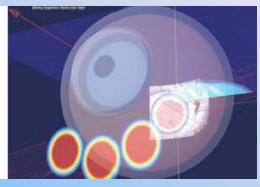
- In a pilot study (*Barak et al*), a linear accelerator used to deliver incremental doses of 20-40 Gy to 94 eyes with ARMD
- Mean VA was 0.82 before treatment and 0.89 at 12 months

- Central geographic atrophy developed in 49%
- Extensive CNV developed in 9%
- RR in 15%, mean time to develop 5.4 years
- RR manifestations included neovascular glaucoma and macular ischemia
- RR rate much higher than observed prior, likely because longer follow up

- Commercially developed IRay system (Oraya Therapeutics) may limit the risk of RR
- 100 kilovoltage (kV) photons, which scatter less than MV photons.
- The eye is immobilized with a suction-enabled contact lens, with the macula 150 mm from the source
- Delivers 24 Gy to the macula over 5 minutes via the inferior pars plana

IRay





Preliminary IRay Clinical Data

- 19 patients treated with 2 ranibizumab injections flanking a single 24-Gy fraction
- At 6 months, no patients lost >15 ETDRS letters, and 16% gained >15 letters (similar for 16 Gy)
- An additional 7 injections were performed.
- A “radiation-first” strategy using a 16-Gy fraction and salvage ranibizumab was not as promising
- INTREPID study compares IRay combination therapy with anti-VEGF therapy alone

INTREPID

- A randomized, prospective, double-blind, controlled trial
- 251 European sites
- Previously treated patients with CNV due to AMD
- Diagnosis within 3 years
- At least three ranibizumab or bevacizumab injections in the previous 12 months.
- 226 patients in a 2:1:2:1 randomization receive either 16 Gy or 24 Gy (or matching sham radiation) plus injection of ranibizumab.
- Control groups receive sham radiation plus ranibizumab

- Retreatment with ranibizumab guided by one of:
  - OCT findings (increase of 100 µm in the central foveal subfield from the best previous exam)
  - New or increased macular hemorrhage
  - >5 ETDRS letter decrease from baseline vision plus AMD activity.
- The primary outcome = number of injections in a 52-week period
- Secondary outcomes: changes in mean VA, loss of <15 ETDRS letters, gain of ≥15 ETDRS letters, gain of ≥0 ETDRS letters, and change in CNV size

1 year Outcomes

	16 Gy	24 Gy	Sham
Number Injections	2.64	2.43	3.74
Change in VA	0.28	0.40	1.57
<15 letters lost	93%	89%	91%
Angiographic lesion area change	1.15mm²	0.49mm²	0.75mm²
OCT central thickness change	85.90	70.39	33.51

•The number of adverse events similar across arms
•No RR

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Proton Therapy

- High doses of radiation to precise locations
- Low dose at tissue entry, a maximum dose at the target, an essentially nonexistent exit dose.
- 2- to 5-fold reduction in dose to adjacent structures
- Used to treat uveal melanomas with does of 79 Gy while sparing adjacent tissue

First report (*Yonemoto et al*):

•Mean follow-up 11.6 months
•19 patients treated with 8 CGE (cobalt Gray equivalent)
•58% had improved or stable VA
•No SE
•Dose escalation study: 8 vs 14 CGE in 48 eyes
•At 1 year, 44% of the eyes in the 8 CGE group and 75%
•of the eyes in the 14 CGE group had improved or stable VA
•CNV membranes decreased steadily in the 14 CGE group but not in the 8 CGE group.
•48% of the eyes in the 14 CGE group RR (3-30 months)

First RCT (*Ciulla et al*):

•37 patients, either sham irradiation or 16 Gy in 2 fractions

•A trend toward stabilization of VA, no RR

A subsequent RCT (*Zambarakji et al*):

•166 patients received 16 or 24 CGE PT in 2 fractions

•At 24 months, 62% and 53% of eyes in the 16 and 24 CGE groups respectively had moderate visual loss (P>0.05)

•RR in 12.7%, no significant visual loss.

•Suggestion that fractionation limits RR.

Combination treatment - PT and anti-VEGF therapy

•6 patients treated with 24 CGE PT in 2 fractions 24hrs apart

•Plus 4 monthly treatments with ranibizumab with prn retreatment

•No gain in VA at 24 months

•Among patients with newly diagnosed cases, there was a mean gain of 4.3 letters at 24 months.

•A mean of 10 injections by 24 months vs 24 monthly injections in most anti-VEGF monotherapy protocols.

•No cases of RR by 3 years.

•Two patients - severe vision loss, likely subsequent to disease progression.

Conclusions

- Effective, non-invasive modality to complement anti-VEGF therapy.
- Dose spillage => higher rate of RR than in SRT, so lower doses per fraction (to 12 CGE) needed
- Combination therapy with anti-VEGF may limit RR risk
- Ongoing sham controlled PBAMD2 trial will provide stronger evidence for the combination therapy.

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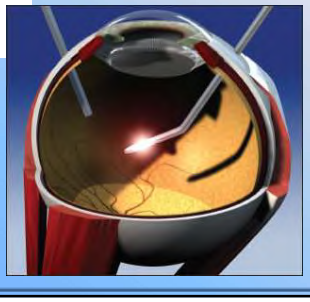
Epimacular Brachytherapy

- In traditional EBRT plans, the lens can receive as much as 30%-50% of the maximum dose
- In EMBT, much smaller doses:
  E.g. macular 24 Gy => optic nerve 2.4 Gy
  lens 0.00056 Gy

- Early techniques – episcleral plaque positioned for set time (minutes to hours)
- Now – vitrectomy by standard vitreoretinal techniques
- Sealed radiation source placed temporarily over the fovea in the vitreous cavity by means of an intraocular probe
- Local, focused delivery



Sub-Types

- Used also as ophthalmic plaque brachytherapy, particularly for choroidal melanomas

Two isotopes:

- gamma-emitter palladium 103 (^{103}Pd)
- beta-emitter strontium 90 (^{90}Sr)

- ^{90}Sr is superior for ocular brachytherapy:
  - long half-life (28.7 years)
  - rapid dose dropoff - dose rate attenuates by 50% after a depth of 1.5 mm
- Deep enough to target CNV without causing damage to nearby structures

Jaakkola et al

•32.4 Gy ^{90}Sr episcleral plaque therapy

•At 1 year, 15% of treated and 50% of control experienced severe visual loss, treated eyes losing significantly less VA ($P<0.05$).

•CNV markedly reduced (43.6% treated maculae dry at 24 months vs 31.3% in controls).

•One patient RR-like changes at 36 months.

Initial feasibility study for EMBT (intraocular)

Avila et al

•34 patients

•Either 15 or 24 Gy

•At 1 year, the 24 Gy group had a mean VA gain of 10.3 letters, the 15 Gy group had a mean loss of 1.0 letters

•No SE

- Subsequently 34 patients were treated with 24 Gy
- Follow up 3 years
- 90% of eyes lost <15 letters from baseline
- 21% gained 15 letters
- At 36 months, 11 eyes required additional bevacizumab injections (mean 3)

The VA stability achieved was comparable to that demonstrated in the ANCHOR and MARINA studies

MERITAGE Trial

- Patients who already required frequent injections of anti-VEGF therapeutics
- 53 patients treated with 24 Gy
- Monthly OCT follow up
- Before enrollment, the average rate of anti-VEGF injection was 0.45/patient/month
- During the 12-month follow up period, rate of
- retreatment was 0.29/patient/month.
- Common adverse events: conjunctival hemorrhage (71.7%), cataract (30.2%).

- High incidence of cataracts likely secondary to vitrectomy
- EMBT delivers 0.0056 Gy to the lens, the threshold for cataract formation is 2 Gy
- ?Vitrectomy itself may be helpful in treating ARMD by limiting vitromacular adhesion

Conclusions

- Combination therapy with EMBT can stabilize ARMD, decreasing the requirement for anti-VEGF therapy.
- Two large, randomized controlled trials will provide further data:

1. CABERNET study compares ranibizumab plus EMBT vs ranibizumab alone in treatment-naïve patients
2. MERLOT study - the same for patients already receiving ranibizumab.

No RR so far, but none with long enough follow up times

CABERNET

- 457 treatment-naïve wet AMD patients in a 2:1 randomization
- Two arms:
  - ❖ 24 Gy of EMBT with two injections of ranibizumab followed by PRN ranibizumab
  - ❖ modified PIER protocol ranibizumab dosing regimen.
- Prospective trial with a noninferiority outcome aimed at a percentage of patients losing fewer than 15 ETDRS letters.
- 2 year follow-up:
  - ❖ EMBT group received six ranibizumab injections and lost 2.5 letters
  - ❖ Ranibizumab group received 11 injections and a gain of 4.4 letters

MERLOT

- 363 patients receiving regular Lucentis treatment randomised in a 2:1 ratio
- **Arm A:** EMBT + Lucentis prn.
- **Arm B:** Lucentis prn
- The co-primary outcome measures of efficacy:
  - ➢ Mean change in ETDRS BCVA
  - ➢ The mean number of re-treatment injections of Lucentis per patient, per year.
- Secondary efficacy parameters:
  - ➢ Percentage of subjects losing ETDRS letters
  - ➢ Change in total CNV size by fluorescein angiography
  - ➢ Foveal thickness measured using OCT.

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Comparison of Modalities

- PT – greatest risk of RR, though fractions minimize risk.
- Kilovoltage SRT with 24 Gy in a single fraction (IRay) generates less internal scatter, however requires investment and training
- EMB - very precise dosing of large fractions, but requires vitrectomy. Leads to cataract, but the vitrectomy itself may also be beneficial

- All 3 modalities function well in concert with anti-VEGF therapy:
  - ➢ Radiation eliminates pathological endothelial cells and production of chemical mediators of pathological non-VEGF pathways while
  - anti-VEGF therapeutics antagonize further attempts at angiogenesis.
- Combination therapy could drastically decrease the frequency of injections needed to maintain VA

The strategy of using anti-VEGF therapy in conjunction with radiation may not only improve efficacy and reduce the frequency of anti-VEGF injections but also decrease the risk of RR.

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The X-ray beam that could end painful jabs for ageing eyes

By CAROL DAVIS

PUBLISHED: 23:23, 4 March 2013 | UPDATED: 10:09, 5 March 2013

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Patients with wet age-related macular degeneration need regular injections into the eye to preserve their sight.

Sheila Rossan, 75, a management consultant from London, was one of the first to undergo a new procedure that reduces the need for the painful jabs.

THE PATIENT

Glancing at my tiled kitchen floor four years ago, I was shocked to find that instead of running in straight lines, the grout between the tiles seemed to be doing a hula dance; it wiggled and waved all over the place.

Then when I picked up my crossword, the two final columns seemed to be falling away.

My sister, Mitzi had developed the same symptoms a few months earlier and been diagnosed with a degenerative eye condition, age-related macular degeneration

Thank you