Radiation Therapy for Choroidal Neovascularisation in AMD – A Review

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A Little Physics

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

\[ 1 \text{ Gy} = 1 \frac{J}{kg} = 1 \frac{m^2}{a^2} \]

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

Ocular Side Effects
• Keratitis sicca
• Cataracts
• Radiation optic neuropathy
• Radiation retinopathy

• Antiangiogenic
• Reduction in macrophage-mediated retinal inflammation that accompanies ARMD
• Capillary closure
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)
• Proton therapy (PT)
• Brachytherapy (EMBT – epimacular brachytherapy)

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
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

<table>
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<tr>
<th></th>
<th>16 Gy</th>
<th>24 Gy</th>
<th>Sham</th>
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<tbody>
<tr>
<td>Number Injections</td>
<td>2.64</td>
<td>2.43</td>
<td>3.74</td>
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<tr>
<td>Change in VA</td>
<td>0.28</td>
<td>0.40</td>
<td>1.57</td>
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<tr>
<td>&lt;15 letters lost</td>
<td>93%</td>
<td>89%</td>
<td>91%</td>
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<td>Angiographic lesion area change</td>
<td>1.15 mm²</td>
<td>0.49 mm²</td>
<td>0.75 mm²</td>
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<tr>
<td>OCT central thickness change</td>
<td>85.90</td>
<td>70.39</td>
<td>33.51</td>
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- The number of adverse events similar across arms
- No RR

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 doses of 79 Gy while sparing adjacent tissue

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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)
• $^{90}\text{Sr}$ 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 $^{90}\text{Sr}$ 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%).

**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.

- 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
**CABERNET**

- 457 treatment-naive 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.