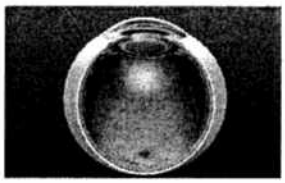
Intraocular Brachytherapy for Neovascular AMD

Wet AMD

- Wet (Neovascular) AMD is the leading cause of irreparable blindness in the elderly
  - Neovascular growth from the underlying vascular system invades the retina.
  - These rapidly growing vessels often leak blood and fluid
  - Damage occurs to the macula leading to loss of central vision
- In the U.S., ~ 200,000 people will develop Wet AMD each year.
- WHO estimates epidemic proportions by 2030

Advances in the Treatment of Wet AMD

- Dramatic advances in last several years
  - Intravitreal therapy with anti-VEGF agents
  - Stability in large majority of treated patients
  - Visual recovery in many



Why Look for More?

- Visual recovery in 30-40% means no significant improvement in 60-70%
- Need for frequent injections and/or frequent visits
  - Physical burden
    - Patients
    - Families
    - Clinicians
  - Financial burden

Why Radiotherapy for Wet AMD?

- Exudative AMD demonstrates characteristics composed of angiogenic, inflammatory and fibrotic components
- Ionizing radiation has proven anti-angiogenic, anti-inflammatory and anti-fibrotic properties
- Demonstrated synergism with pharmacotherapeutic approaches
  - Avastin & Radiation therapy in colon CA

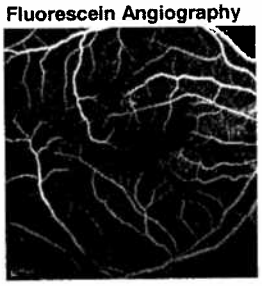
Diagnosis and Treatment of AMD

Patient Evaluation & Treatment Recommendation

Patient Evaluation

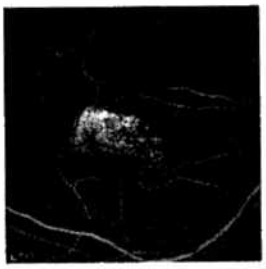
- Patient examined by retina specialist
- Diagnostic evaluation
- Discussion of treatment options

Fluorescein Angiography

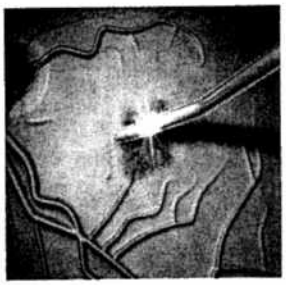


Treatment Approach

- Fluorescein-guided approach
- Decisions based upon lesion
  - Composition
  - Size
  - Location
  - Orientation



Probe Alignment

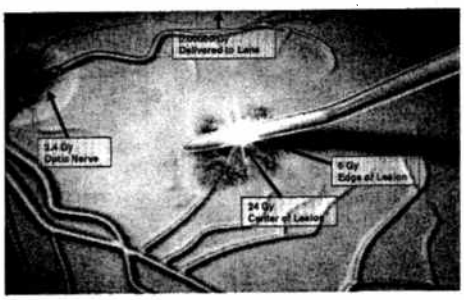


- Device orientation guided by
  - Lesion size
  - Lesion shape
  - Proximity to optic nerve
  - Proximity to normal vasculature

NeoVista Procedure

- Most recent FA image is brought to OR to help retinal surgeon confirm the placement position.
- A posterior vitrectomy procedure is performed
- The NeoVista device is introduced into the eye and placed in mid-vitreous position.
- The radiation source is delivered to the device tip by sliding the lever down the shaft of the device and locking in place.
- The NeoVista device is then brought to the retina with the tip lightly touching the retina outside the fovea and held in place for the prescribed dwell time.
- At the conclusion of radiation delivery, the NeoVista device is brought back to the mid-vitreous position.
- The radiation source is then returned by sliding the lever back to the original position and the device is removed from the eye.

Radiation Delivery Device Positioned Over Lesion



Threshold For Clinically Observable Damage

Tissue	Effect	Dose for Clinically Observable Damage	Dose Delivered by Epi-Rad90
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	2.4Gy

Reference: Finger PT, Berson A, Ng T, Szechter A. Ophthalmic plaque radiotherapy for age-related macular degeneration associated with subretinal neovascularization. Am J Ophthalmol. 1999 Feb;127(2):170-7. Adapted from Bardenstein, Char and Rosenblatt

Retinal Surgeon

- Trained to handle radiation device in the eye
- The NeoVista procedure has basic treatment planning requirements as it pertains to radiation dose
- Placement and orientation of radiation device is the only changing component of the procedure and must be done by a retinal specialist

Scenario in Case of Device Malfunction

- Withdraw the Delivery Device from the eye and move away from all operating suite staff.
- Slide open end of Emergency cap over cannula end of the Delivery Device

- Gently push the Emergency cap and Delivery Device together until a firm seal is achieved

- Place the Delivery Device back into the storage/ sterilization tray.
  (Note: Radiation personnel may ask that the Delivery Device be put directly into the lead vault storage container for safety.)
- Replace the lid on the storage/ sterilization tray and close completely
- Remove the storage/ sterilization tray from the sterile field.
- **NOTIFY RADIATION SAFETY PERSONNEL IMMEDIATELY OF THE SITUATION.**

Listed Concerns from June 2007 NRC Meeting

Listed Concerns from June 2007 Meeting

- Used by ophthalmologists with little or no radiation training
- Little or no radiation oncologist input
- Primitive dosimetry
- Useful technology that may die away if inadequate multi-disciplinary input

Used by Ophthalmologists with Little or no Radiation Training

- 35.491 for "Training for ophthalmic use of strontium-90":
- (1) Has completed 24 hours of classroom and laboratory training applicable to the medical use of strontium-90 for ophthalmic radiotherapy. The training must include--
- (i) Radiation physics and instrumentation;
- (ii) Radiation protection;
- (iii) Mathematics pertaining to the use and measurement of radioactivity; and
- (iv) Radiation biology; and
- (2) Supervised clinical training in ophthalmic radiotherapy under the supervision of an authorized user at a medical institution that includes the use of strontium-90 for the ophthalmic treatment of five individuals. This supervised clinical training must involve--
- (i) Examination of each individual to be treated;
- (ii) Calculation of the dose to be administered;
- (iii) Administration of the dose; and
- (iv) Follow up and review of each individual's case history

Little or no Radiation Oncologist Input

- Strontium 90 utilization in the NeoVista device is a fixed treatment plan for each and every procedure.
- Far different than treatment planning in ocular tumor therapy.

Primitive Dosimetry

- Previous technique for brachytherapy dosimetry used data based on calculations from either Quimby, Patterson-Parker or Johns – the accuracy was not less than 1 mm.
- NeoVista now utilizes radiochromic film computer algorithms and NIST traceable sources. We can now work in the 100 micron range

Useful Technology That May Die Away if Inadequate Multi-disciplinary Input

- Strontium 90 epiretinal brachytherapy has shown to be promising therapy in previous Phase II studies.
  - Open cooperation between Radiation Oncology/ Medical Physics and Ophthalmology
- Phase III study also requires this cooperation in 45 sites globally

NeoVista Procedure in ASC vs HOPD

- Rapidity of disease onset, coupled with urgency of treatment application, lead to several caveats in the timely delivery of this therapy
  - 1-3 patients with new-onset exudative AMD seen in average busy retina specialist's clinic daily
  - Treatment outcomes believed best if delivered within relatively short period (1-several days)
  - Coordination of retina specialist, radiation oncologist, and OR time in a semi-urgent situation, with regular frequency is extremely unlikely

NeoVista Procedure in ASC vs HOPD

- Procedure best suited for ASC
  - Frequency of cases
    - Potential for cases daily
    - Inability to schedule
    - Easier to "add-on" to ASC than HOPD
  - Need for efficient operation
    - Retina surgeons will need to incorporate this procedure into their "daily" routine
    - Trend towards retina procedures performed in ASC an acknowledgment of this need in all surgeries

Prior Utilization of Strontium 90 Applicators for the Treatment of Ocular Disorders

Post Operative Beta Radiation of Vascularized Pterygium

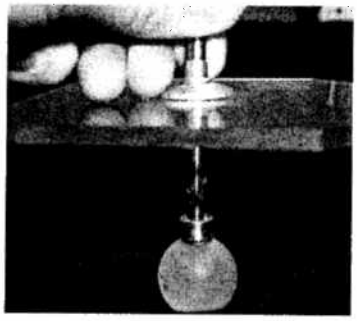
Safety of Strontium Applicators for the Post Operative Treatment of Vascularized Pterygium

Nishimura Y, et al. Post Operative treatment of 490 lesions with 31-42 Gy. *Int J Radiat Oncol Biol Phys.* 2000
- scleromalacia (scleral thinning) in 4 eyes
- adhesion of eyelids in 3 eyes
- scleral ulcer in 2 eyes

MacKenzie FD, et al. Post Operative treatment of 764 lesions with a mean of 22 Gy. Ophthalmology, 1991
- Scleromalacia of varying degrees in 103 (4.5% of the study group had severe thinning)
- endophalmitis in 2 eyes

Wilder RB, et al Post Operative treatment of 338 lesions with a mean of 24 Gy. *Int J Radiat Oncol Biol Phys.* 1992
- No severe complications developed
- Ocular irritation in 17 eyes
- decreased visual acuity in 11 eyes
- scleral telangiectasia in 6 eyes
- photophobia in 6 eyes
- granuloma formation in 3 eyes
- cataracts in 3 eyes
- scleral atrophy in 2 eyes

Typical extravitreal Strontium-90 Eye Applicator

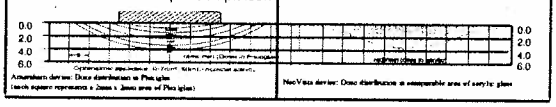


NeoVista Pterygium Device

Strontium-90 Applicators for Pterygia
Similar Characteristics

Side-by-Side Comparison of Amersham and NeoVista device

Amersham Device	NeoVista Device
Dose Distribution and Depth Comparison	



Summary

- NeoVista therapy is unique with regards to the interaction between the Specialties of Ophthalmology and Radiation Oncology
  - The application of radiation therapy for ocular tumors has required significant input/planning from both
  - 100% of the planning in this procedure (as it is in the surface applicator) is determined by the eye specialist

Summary

- The Safety of the device has been supported by 30 years of use in thousands of patients
  - The only complications have been ophthalmic in nature, and fully managed by the ophthalmologist
  - The level of recommended training is fully adequate to justify the use of this applicator inside the eye, which by all accounts should be safer with less risk of exposure to surrounding tissue

NeoVista Strontium 90 Device is Almost Identical to Ophthalmic Strontium 90 Surface Applicators

Strontium 90 Surface Applicator	NeoVista Strontium 90 Device
Fixed dosimetry over target area	Fixed dosimetry over target area
Applicator is positioned on cornea	Applicator is positioned on retina
Direct visualization and placement by surgeon	Direct visualization and placement by surgeon
Fixed Dosimetry	Fixed Dosimetry
No radiation management component	No radiation management component
General ophthalmologist must deliver the radiation	Retinal surgeon must deliver the radiation

We believe the NeoVista device should be viewed the same way as the strontium 90 surface applicator