Benign Diseases

Review

2014

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Radiation Therapy of Benign Diseases

- **Eye/Orbit:** pterygium, Graves's ophthalmopathy, orbital pseudotumor, macular degeneration
- **Skin:** keloids, plantar warts, keratoacanthoma
- **Blood vessels:** AVM, hemangioma, coronary re-stenosis
- **CNS:** benign brain tumors, trigeminal neuralgia
- **Soft tissues:** desmoid, Peyronie's disease
- **Bones:** heterotopic ossification, giant cell bone tumors, histiocytosis, ameloblastoma
- **Glandular tissues:** gynecomastia, ovarian ablation, sialorrhea
- **Lymphoid tissues:** hypersplenism, organ transplant, TLI auto-immune disorders

Discontinued uses of XRT

- Infections
- Abortion
- Peptic ulcer
- Acne
- Inflamatory conditions

Shoe-Fitting X-ray Unit

http://www.museumofquackery.com/devices/shoexray.htm

General considerations

- Proper selection of radiation modality, dose, fractionation, and organ at risk.
- Careful on treatment depth and shielding
- Avoid treating infants and children with radiation
- Avoid organs sensitive to low-dose radiation: thyroid, gonads, female breast, bone marrow, eye

Selected Benign Diseases

- **Thyroid Associated Opthalmopathy**
- **AVM**
- **Orbital Pseudotumor**
- **Macular Degeneration**
- **Pterygium**
- **Keloids**
- **Gynecomastia**
- **Heterotopic Ossification**
- **Peyronie's Disease**
- **Coronary Re-stenosis (Endovascular radiation)**

Thyroid-associated Ophthalmopathy

- Bilateral exopthalmos
- Extraocular muscle dysfunction
- Diplopia
- Blurred vision
- Eyelid and periorbital edema
- Chemosis= swelling of the eye surface membranes
- Lid lag and retraction
- Compressive optic neuropathy

Treatment

- Treatment of underlying thyroid disorder
- Mild symptoms—no treatment, eye drops, elevating head of bed
- Moderate—steroids, cyclosporine or other immunosuppressives
- **Radiation Therapy**
- Severe—emergency decompressive surgery

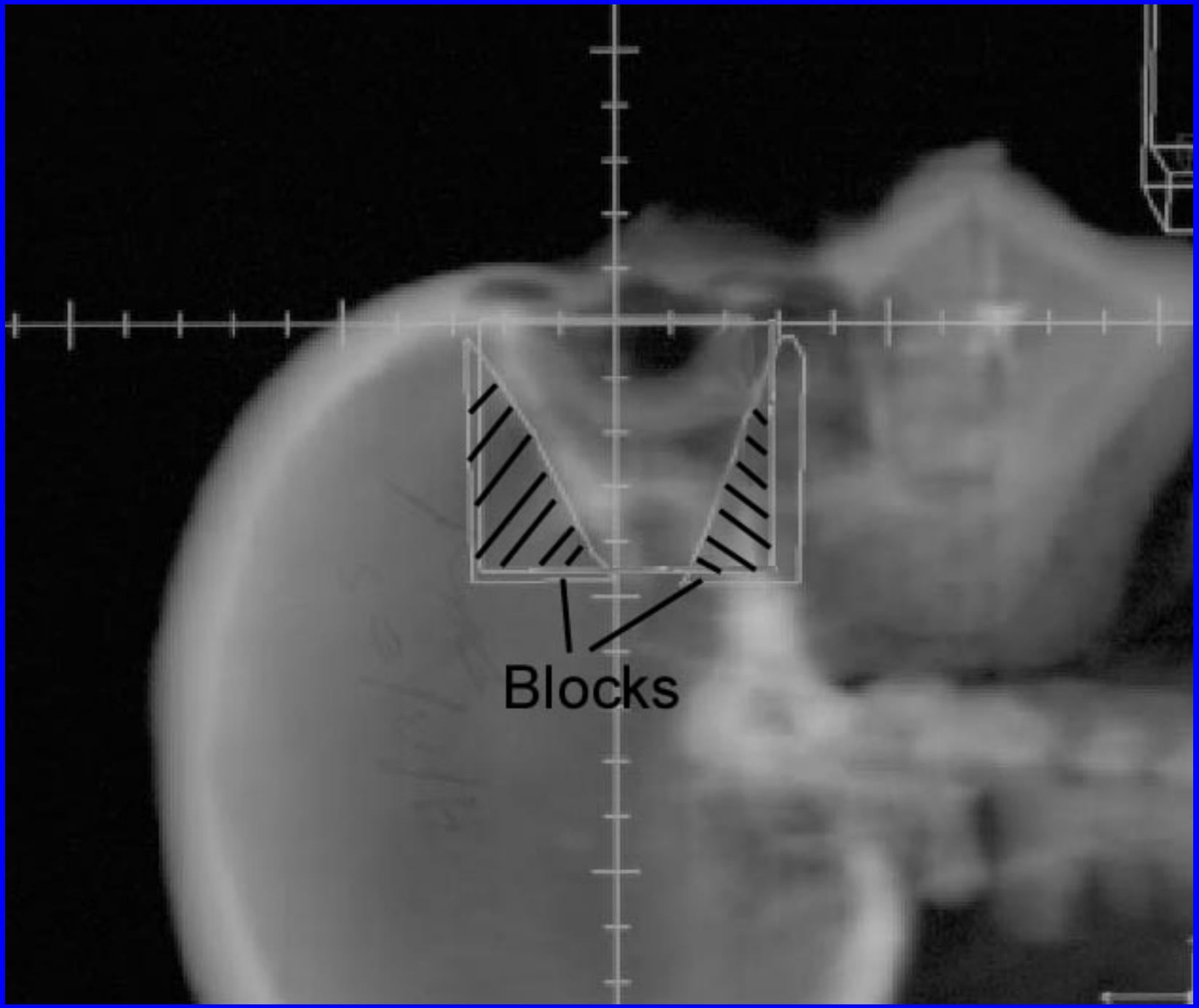
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Table 2 Summary of selected treatment results of Grave's ophthalmopathy

Author/year	Number of Patients	Treatment	Results	Comments
Kulig et al. 2004 (12)	101	20 Gy /2 weeks + steroids	Donaldson's ophthalmopathy index decreased significantly. Right eye: from 6.35 to 1.2; left eye: from 6.1 to 1.15.	Combined therapy is an effective. Persistent diplopia in 16/101 patients.
Prummel et al 2004 (13)	88 (RT vs. Sham RT)	20 Gy /2 weeks	52% vs. 27% responded	Less need for follow up in RT group
Alpert et al. 2003 (14)	47 (30 with optic neuropathy)	20 Gy /10fx	75% improved. (retropulsion improved in 83 %)	Early intervention (<6 months) better
Pitz et al. 2002 (15)	104 (29 RT, 75 RT + steroids)	10-20 Gy	75% pain improved. 25% motility improved 75% stable.	No additional benefit seen with steroids. No adverse side effects up to 16 yrs.
Mourits et al. 2000 (17)	60 (RT vs. Sham RT)	20 Gy /10fx	Qualitative improvement (diplopia): 60% vs. 31% Protosis, lid swelling not better.	25% RT patients spared from additional strabismus surgery
Beckendorf et al. 1999 (16)	199	20 Gy /2 weeks	26% excellent response; 50% partial response. 19% stable 5% progression.	Patients treated within 7 months after having opthamo-pathy had better responses.

Arteriovenous Malformation (AVM)

- Complex tangle of abnormal arteries and veins
- Characterized by presence of one or more A-V fistulas creating a high-flow shunt
- Lack a capillary bed
- Thought to develop at embryonic stage of vessel formation

Characteristics

- Course is unpredictable - can grow, regress of remain stable
- Prevalence is thought to be around 0.1% or 300,000 in the US

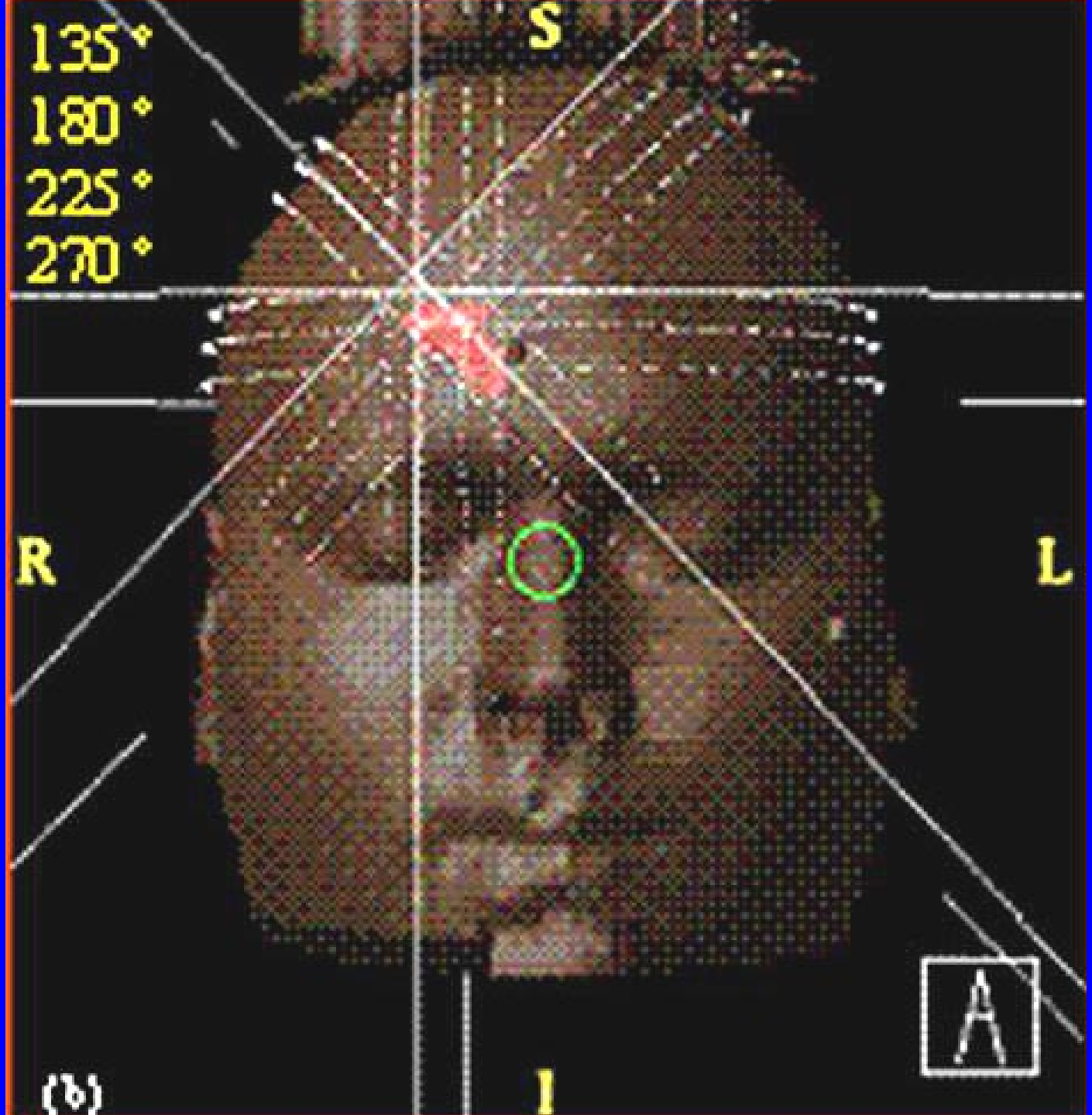
Presentation

- Intracranial hemorrhage
  - 10-15% fatal
  - overall morbidity 50%
- Seizures not caused by hemorrhage
- Headache - no consistent characteristic features
- Focal neurologic symptom – rare
- Symptoms resolve 70 % after radiosurgery

https://www.emoryhealthcare.org/stroke/treatments/malformation-example.html

Treatment

- Surgical resection
  - Often difficult if lesion has deep feeding or draining vessels
  - Success rate excellent if completely resected
  - Complications – 16% permanent neurological deficits in 8%
  - Hemorrhage, damage to surround in brain, edema/swelling
- Stereotactic Radiation Therapy (SRT)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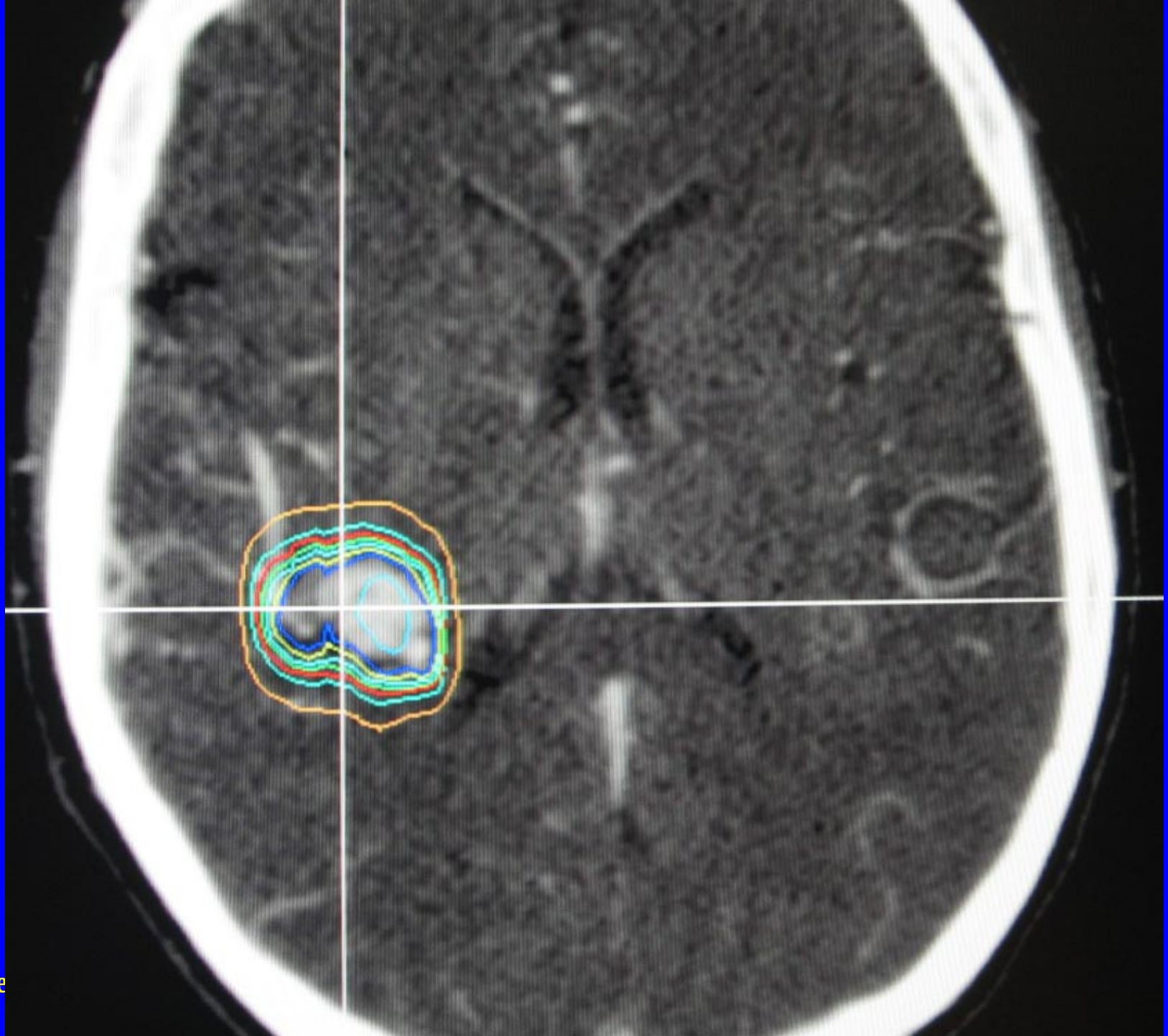

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Table 1. Summary of selected radiation treatment results of AVM

Author, Year	Total # Patients	Technique	Dose	Results
Marayuma et al. 2005 (3)	500 patients	GKS	20 Gy	**91% obliteration at 6 years 6.6% complication rate 5.8% hemorrhage after RS**
Vernimmen 2005 (8)	64 patients	Protons	10-22 GyE	**67% obliteration rate (vol <14cc) 43% obliteration rate (vol ≥14cc)**
Nicolato et al. 2005 (4)	63 children, < 16 yrs	GKS	16-26 Gy	**77% obliteration rate at 4 yrs 2 with complications No hemorrhage reported**
Zabel et al. 2005 (5)	110 patients	Linac SRS	18 Gy	**67% obliteration at 4 yrs 0% complications 8% hemorrhage after RS**
Bollet et al. 2004 (6)	**118 patients**	**Linac SRS**	**10-25 Gy**	**77% obliteration rate 6.7% complications 6% hemorrhage**

GKS = Gamma Knife Radiosurgery
SRS=Stereotactic Radiosurgery

Orbital Pseudotumor

- First described in the 1900s
- AKA “Idiopathic Orbital Inflammation”, or “nonspecific Orbital Inflammatory Disease”
- Nonmalignant space occupying lesion involves orbital tissue and simulates a neoplasm
- Etiology unknown
- 3rd most common cause of orbital inflammation

Orbital Pseudotumor Clinical Presentation

- Typically acute – but can be insidious
- Painful
- Usually unilateral
- No real pattern of muscle involvement
- Ocular findings include:
  - Diplopia
  - Decreased Visual Acuity
  - Proptosis
  - Edema
- Absent systemic symptoms

Treatment

- Systemic Corticosteroids
  - Usually rapid clinical response and resolution of pain
- Radiotherapy
  - 2nd line therapy
  - Adjuvant treatment when incomplete response
  - 1st line therapy if steroids contraindicated
- Immunomodulators/Immunosuppresants

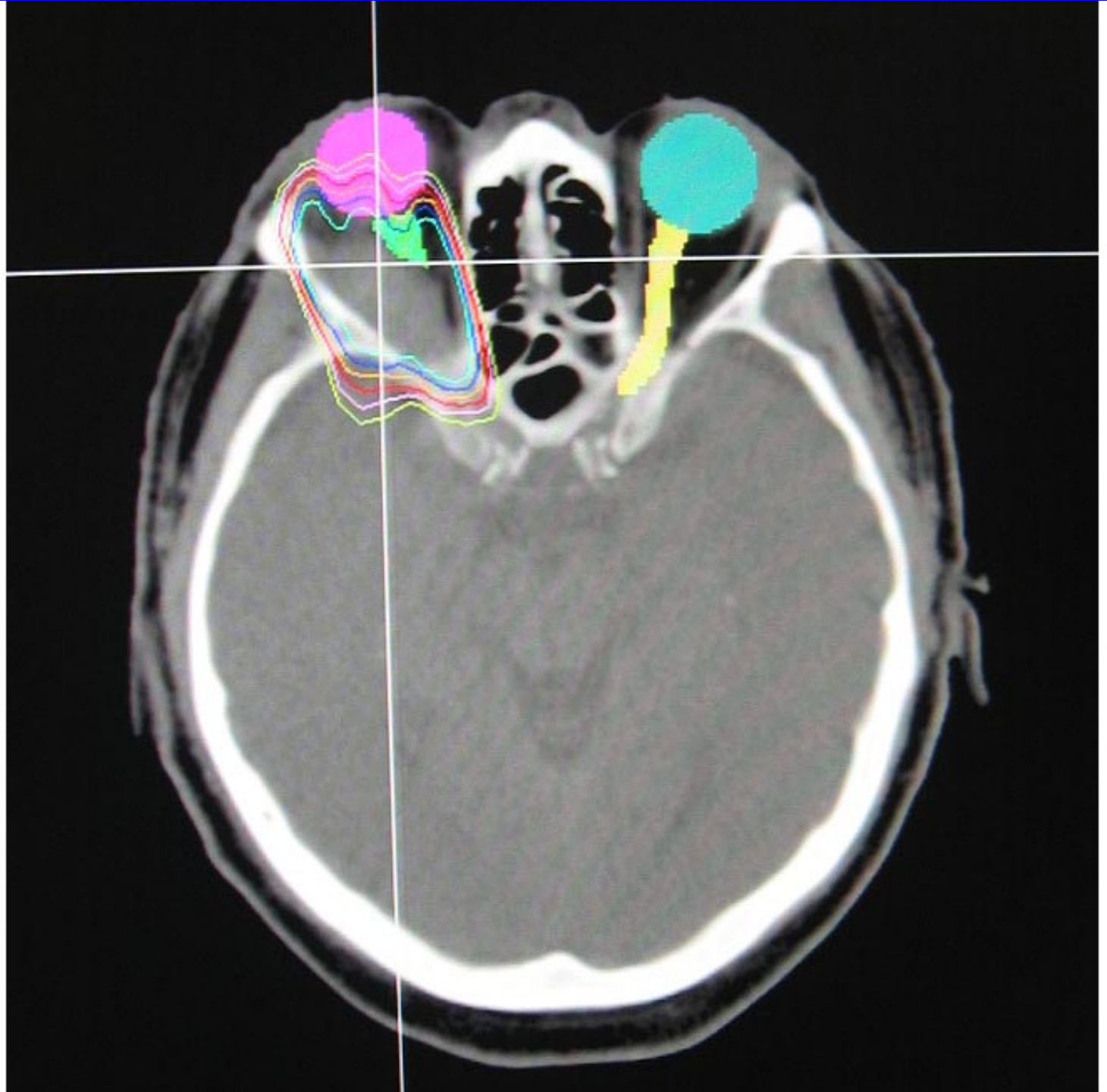


Table 3. Summary of selected radiation treatment results of orbital pseudotumor

Author /year	# Pts (orbits)	RT treatment	Outcomes	Comments
Keleti et al. 1992 (13)	28 benign 20 lymphoma 17 indeterminanat	20-30 Gy/10-15 fx's	RT efficacious in all groups. 84% DFS at 42 months med F/U; Benign group did better.	**Cataracts=46% of the patients treated with anterior-posterior fields**
Lanciano 1990 (5)	23 (26)	2000 cGy/10 fx over 2 weeks	Overall CR 66% Soft tissue swelling 87% CR Proptosis 82% CR Extraocular dysfunction 78% Pain 75% CR Durable local 77% (Median f/u 41 months)	**70% recurrence during steroid taper, 17% no response to steroids, 13% no steroiods treatment prior to RT.**
Mittal et al. 1986 (14)	20 benign 12 lymphoma 10 indeterminanat	Conventional	100% ultimate control rate	**Very high local control, minimal morbidity**
Austin-Seymour 1985 (1)	20 (20)	Mean dose 2360 cGy (2000 - 3000 cGy)	75% Complete resolution	**Majority steroid refractory disease; No complications.**
Sergott 1981 (8)	**19 (21)**	**1000-2000 cGy**	**Improvement 74% (decreased proptosis, lid edema, and conjunctival injection, improved ocular motility and visual acuity)**	**79% recurrence during steroid taper prior to RT. RT responders remained recurrence free x 25 months f/u with no further steroids.**

Macular Degeneration

-Macular Degeneration is a group of progressive eye conditions which involve deterioration of the macula, the central region of the retina.

-The root causes of AMD are still unknown

-Types of Macular Degeneration:

- Age-Related Macular Degeneration
- Juvenile Macular Degeneration (Macular Dystrophy)

AMD

- AMD is the leading cause of irreversible vision loss and blindness in persons over 65 years of age, (the fastest growing segment of the US population)
- Over a 5-year time span, it is estimated that 1 in 3 people over the age of 70 years will develop signs of AMD
- Caucasians > African Americans
- Women > Men

Treatments

- Supportive for most patients
- Laser Photocoagulation
- Radiation (EBRT)
- Photodynamic Therapy (verteporfin)
- Investigational drugs

Table 4. Summary of selected treatment results of macular degeneration

Author, Year	Number of patients/eyes	Treatment	Results	Notes
Jaakkola et al. 2005 (10)	86/88	15 Gy 12.6 Gy (Sr90)	VA loss > 3 lines: Control 84% RT 80%	No long-term (at 35 months) benefits
Marcus et al. 2004 (11)	88 (randomized RT vs no RT)	5 x 4 Gy	At 6 months, 26% vs. 43% 3 line VA loss. At 12 months, 42% vs. 49% 3 lines VA loss.	RT had a short-term benefit in preserving visual acuity.
Prettenhofer, et al 2004 (12)	80	14.4 Gy 25.2 Gy	VA deteriorated in 85% (14.4 Gy) and 65% (25.2 Gy) of patients	After 4 years irradiated eyes were similar to the natural course of the disease.
Hart et al. 2002 (13)	203 (randomized RT vs. no RT)	12 Gy in 6 fx.	RT better than control group but not statistical significance	Negative trial
Valmaggia, et al. 2002 (14)	161 (prospective double-blinded study)	1 Gy (4x.25 Gy) vs. 8 Gy (4x2Gy) vs. 16 Gy (4x4Gy)	No difference among treatment groups. Classic CNV, initial VA >20/100 benefited more from higher does.	Higher doses resulted in stabilization of the VA without any difference in efficacy.
Schittkowski, et al. 2001 (15)	118/126	2 Gy in 2 weeks	VA decreased but most had decreased metamorphopsia and increased color and contrast perception with RT.	8 patients reported epiphora, and 4 patients complained of transient sicca syndrome.

Pterygium

- Often bilateral
- Almost always situated at the nasal or temporal limbus
- Associated with prolonged UV exposure

- May be associated with chronic dryness, inflammation, and exposure to wind and dust or other irritants
- Prevalence increases with proximity to equator
- Encroaches on cornea in wing-like fashion

Pterygium Treatment

- Observation
- Excision indicated if persistent irritation, vision distortion, significant (> 3-4 mm) and progressive growth toward visual axis, restricted ocular motility, and atypical appearance
- Adjuvant Radiation Therapy (beta emitter)
- Adjuvant Topical: Mito-C, 5-FU
- Laser or Thermal Cautery
- PDT

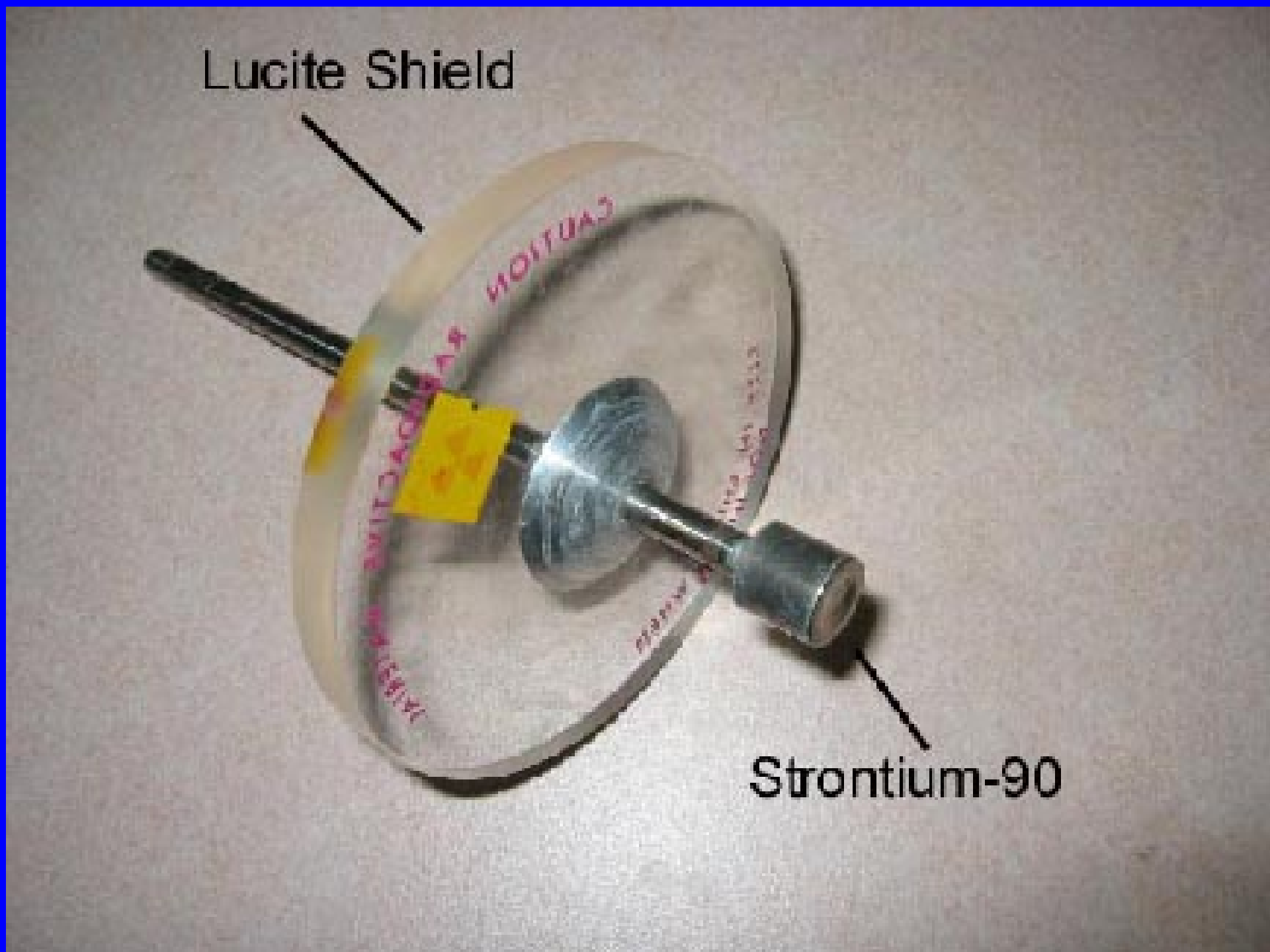

Lucite Shield
Strontium-90

Table 5. Summary of selected treatment results of pterygium

Authors/year	Number of lesions	Dose	Recurrence	Comments
Schultze et al 1996 (16)	64	5 Gy x 6	12.5% (median f/u5.5 years)	0% recurrence for primary lesions treated within 3d after surgery
Paryani et al 1994 (14)	825	10 Gy x 6	1.7% (median f/u 8 years)	No complications with high doses
Dusenbery et al 1992 (13)	36 (recurrent lesions)	24 Gy (median) in 2-4 fx's	28%	36% complications, higher if previously irradiated.
Wilder et al. 1992 (15)	258	8 Gy x 3	12.8%	
Morselise et al. 1984 (17)	135	6 Gy x 3	7.4%	Relatively low doses were used
Alaiz-Calamino et al. 1982 (4)	485	7-8 Gy x 4	4.3%	
Van Den Brenk et al. 1968 (5)	1300	8-10 Gy x 3	1.7%	Largest number reported

Keloids

- Non-cancerous fibrous proliferations that occur in the dermis after trauma or injury to the skin
- Keloids grow beyond the boundaries of the original wound site (vs. hypertrophic scar)
- Etiological factors that determine how a scar becomes a keloid remain unknown

Keloids

- Individuals with darker-pigmented skin or who freckle are more predisposed
- Africans, African-Americans, Hispanics, and Asians
- Familial/genetic predisposition
- Immunological causes

Treatment

- Surgical excision alone
  - Often recur
- Adjuvant Radiation Therapy
- Post-surgical treatment agents:
  - Intralesional corticosteroid injection
  - Mitomycin C solution
  - The dietary compound quercetin
  - Imiquimod 5% topical cream
  - Topical silicone gel sheets

Table 6 Summary of selected treatment results of keloids
WLE-wide local excision; RF-relapse free.

Study	No. pts	Cohort	No. lesions	Dosage implemented (Gy)	Response rate (%)	Notes/findings
Malaker et al. 2004 (12)	64	RT alone	86	37.5 /5fx	97	Unresectable keloids; 63% satisfied with outcome.
Ogawa et al. 2003 (9)	129	WLE + RT	147	15 /5fx	67	
Ragoowansi et al. 2003 (13)	80	WLE + RT	80	10 /1fx	84	100% RF at 4 weeks 91% RF at 1 yr 84% RF at 5-years
Maarouf et al. 2002 (11)	100	WLE + RT	134	9-15 /3-5fx	84	
Klumpar et al. 1994 (10)	83	WLE + RT (electrons vs orthovoltage)	73 53	varied	85 79	Electron beam = orthovoltage therapy
Doornbos et al. 1990 (4)	203	RT or WLE +RT	278	4.5-18 /varied fx	74	Recommended dose $\geq$ 9: 9 Gy LC 70.4% 6 Gy LC 36%.
Lo et al. 1990 (5)	199	WLE + RT	354	2-20 Gy /1fx	87% ($\geq$9 Gy); 43% (<9Gy)	Difference non-significant statistically.
Sallstrom et al. 1989 (14)	124	WLE + RT		18 /3fx	92	93% satisfied at 24 months

Gynecomastia

- Enlargement of the male breast due to hormonal imbalance (rel. ↑ estrogens)
- Physiologic; seen at puberty or old age
- Pathologic; associated with cirrhosis, functional testicular tumours, certain drugs (alcohol, marijuana and anabolic steroids)

Gynecomastia

- Associated with increased levels of estradiol and decreased levels of testosterone
- The majority of patients will present with:
  - nipple tenderness and sensitivity

Gynecomastia

- Observation
- Radiation
- Pharmacotherapy
  - Estrogen receptor modifiers (tamoxifen or raloxifene)
  - Aromatase inhibitors
- Surgical Correction

Table 7. Summary of selected treatment results of gynecomastia

Author, Year	Total # Patients	Dose	Results	Comments
Widmark et al. 2003 (10)	253 (randomized, RT vs. no RT)	12-15Gy /1fx	Gynecomastia rate: 28% vs. 71% (p<.001)	**Prophylaxis**
Tyrrell et al. 2004 (11)	106 (randomized, RT vs No RT)	10Gy /1fx	Gynecomastia rate: 52% vs. 85% (p<.001)	**Prophylaxis**
Van Poppel et al 2005 (12)	27 w/gynecomastia 38 with pain	12 Gy /2fx	Gynecomastia improved or resolved 33%; Breast pain improved or resolved 39%	**Treatment**
Fass et al. 1986 (13)	**87**	**12-15 Gy /3 fx**	**Lower rate of gynecomastia with RT**	**Prevention; No long-term complications seen**

Langerhans cell histiocytosis

(Langerhans cell granulomatosis, Histiocytosis X)

- Abnormal clonal proliferation of Langerhans cells
- Children mostly
- Adults
- Incidence: 0,5-1 case /100 000 a year
- Localization: bone (pain, fractures, vertebral collapse), soft tissues
- Skin; lungs – adult smokers
- LN, liver, BM
- Mortality - variable

Background

- Eosinophilic Granuloma (80%)
  - Localized benign form
  - Isolated to bone
- Hand-Schuller-Christian disease (15-20%)
  - Skull lesions
  - Exopthalmos
  - Diabetes Insipidus
- Letterer-Siwe disease (>10%)
  - Disseminated lesions involving multiple visceral organs

Treatment

- Systemic Chemotherapy
- Topical steroid, Intralesional injection of steroids, NSAID
- Local Radiation Therapy
- Phototherapy
- Stem cell transplantation,

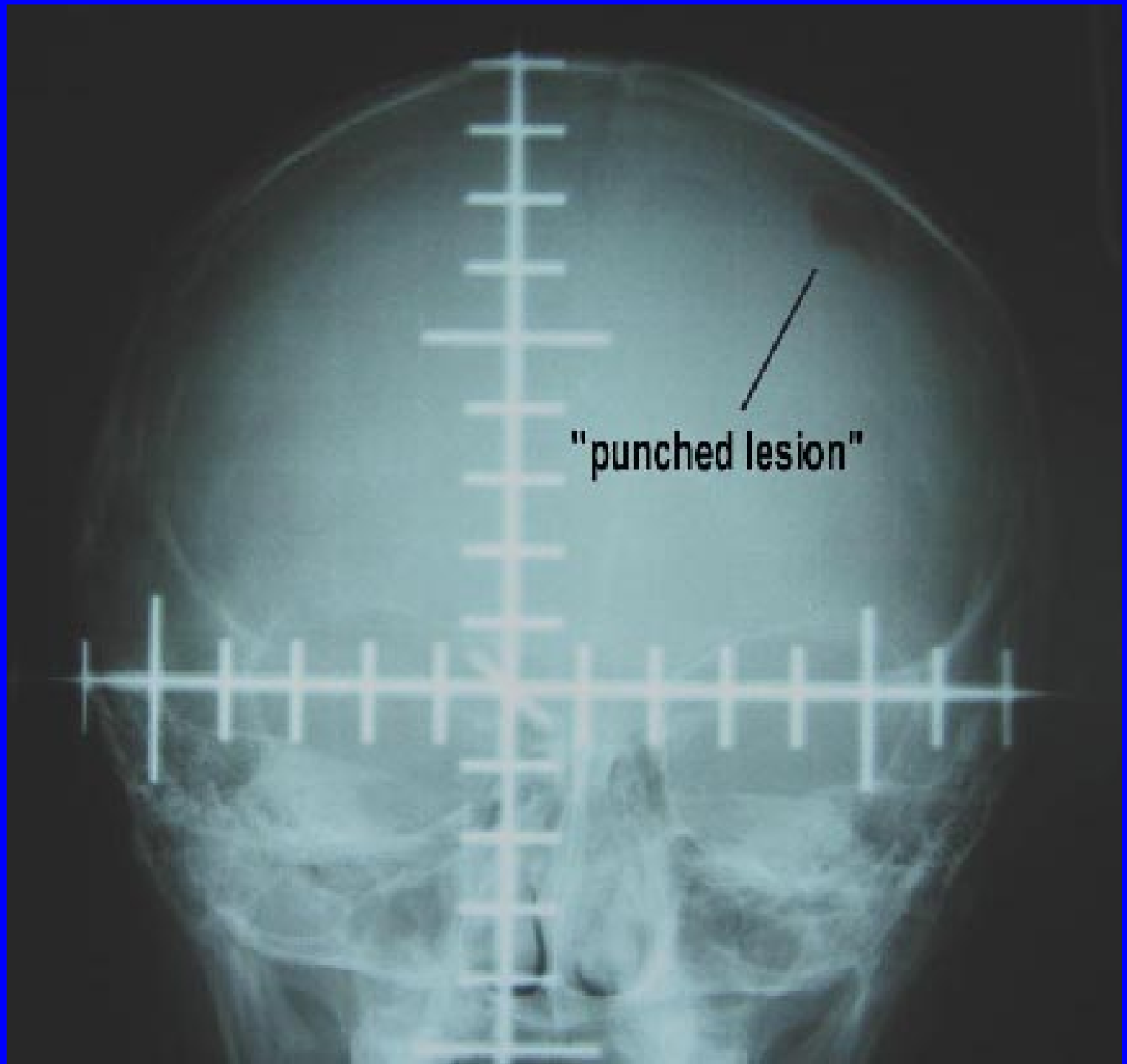

"punched lesion"

Table 9. Summary of selected treatment results of Histiocytosis

Authors, year	Number of patients	F/U	Treatment	Outcome	Comments
el-Sayed et al. 1992 (26)	15	1-20 yrs	Low doses RT	14/15 bone CR; 2/2 (DI) responded	
Selch et al. 1990 (25)	22 (40 bony, 16 soft tissue sites)	1-13 yrs	6-26 Gy Med 9 Gy bone Med 15 soft tissue	LC 82% Bone 88% Soft tissue 69%	Pediatric LC 100%
Minehan et al. 1992 (41)	47 diabetes insipidus	Med 14.7 years	10-11 Gy mean (hypothalamic-pituitary RT vs. no RT)	RT: 22% CR and 14% PR No RT: 0% CR/PR	Actuarial survival at 40 yrs was 65%
Rosenzwei et al. 1997 (41)	14 diabetes insipidus	7.3 yrs		14% CR	Early disease responded
Jahraus et al. 2004 (38)	24	Med 28 months	3-20 Gy /varied fx sizes	1.8-2.0 Gy/fx: score 1.29 <1.8 Gy/fx: score 2.1 (p=0.013)	Recommended fx >1.8Gy

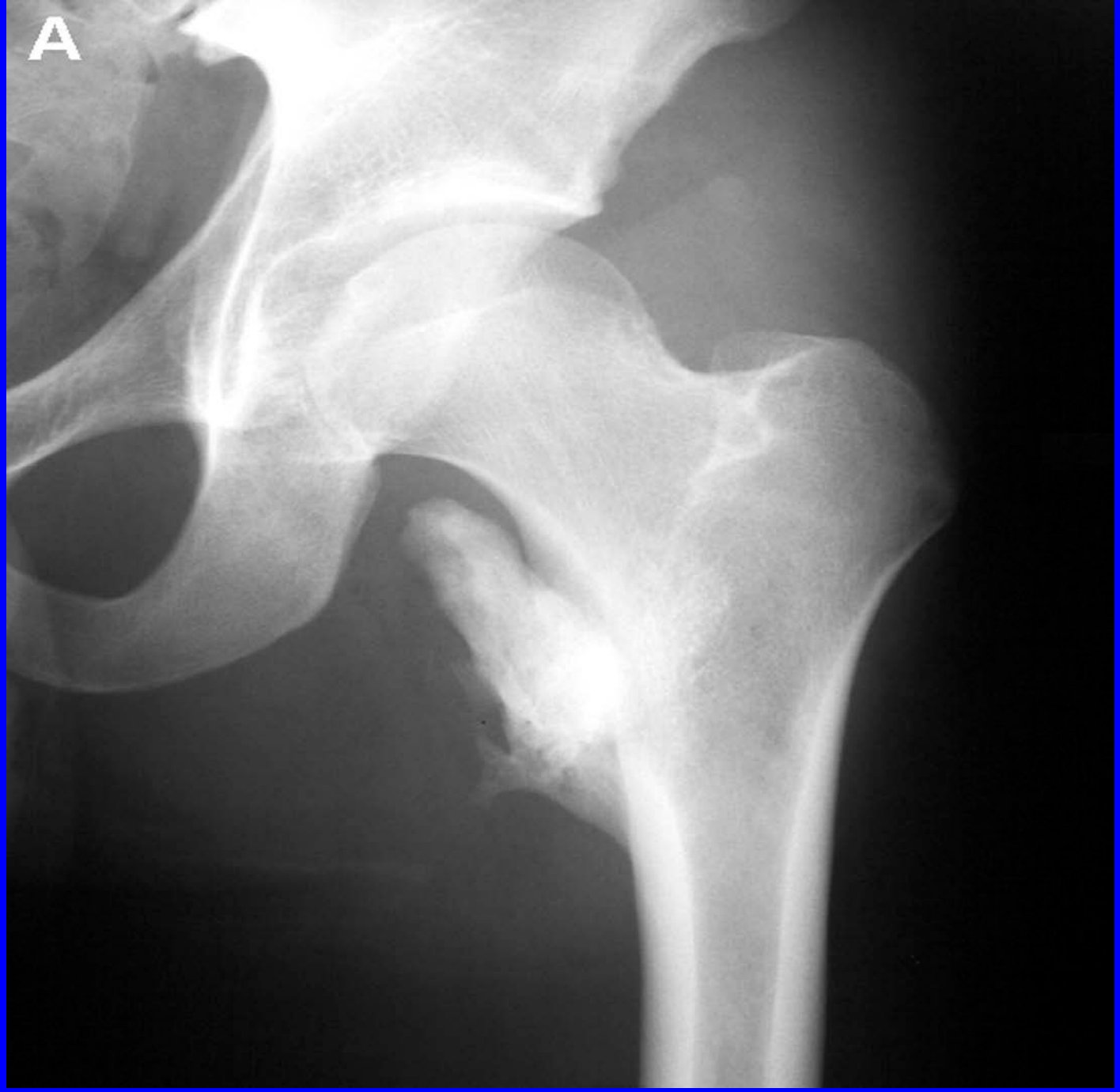
Score system: 1=CR, 2=>50% PR, 3=<50% PR, 4=NR; CR-complete response, PR-partial response, NR-no response; Rt-radiation therapy; fx-fraction; med-median; DI- diabetes insipidus; yrs-years.

Heterotopic Ossification (HO)

- After surgery or trauma
- Hips, legs, elbows, shoulders, jaw…
- Varying severity
- 50%-90% developed HO following a hip arthoplasty
- Mechanism is unknown
- Symptoms: warm, tender, swelling and decreased ROM

Treatment

- Prophylactic radiation therapy
  - 7-8 Gy in a single fx, 24–48 hrs of surgery
- Antiinflammatory agents
  - Indomethacin, Ibuprofen and Aspirin
- Range of motion exercises
  - adjunct to pharmacological treatments



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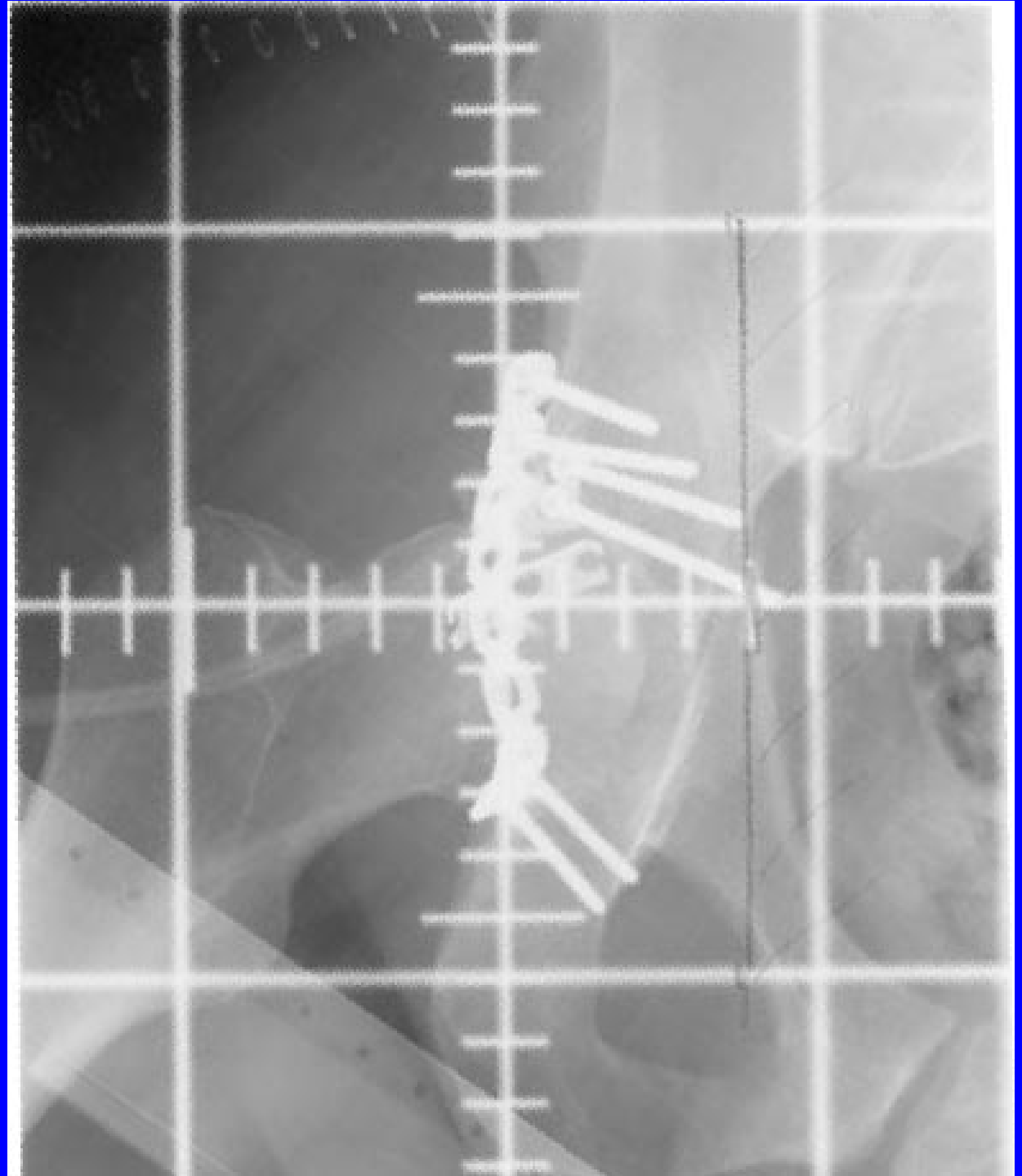
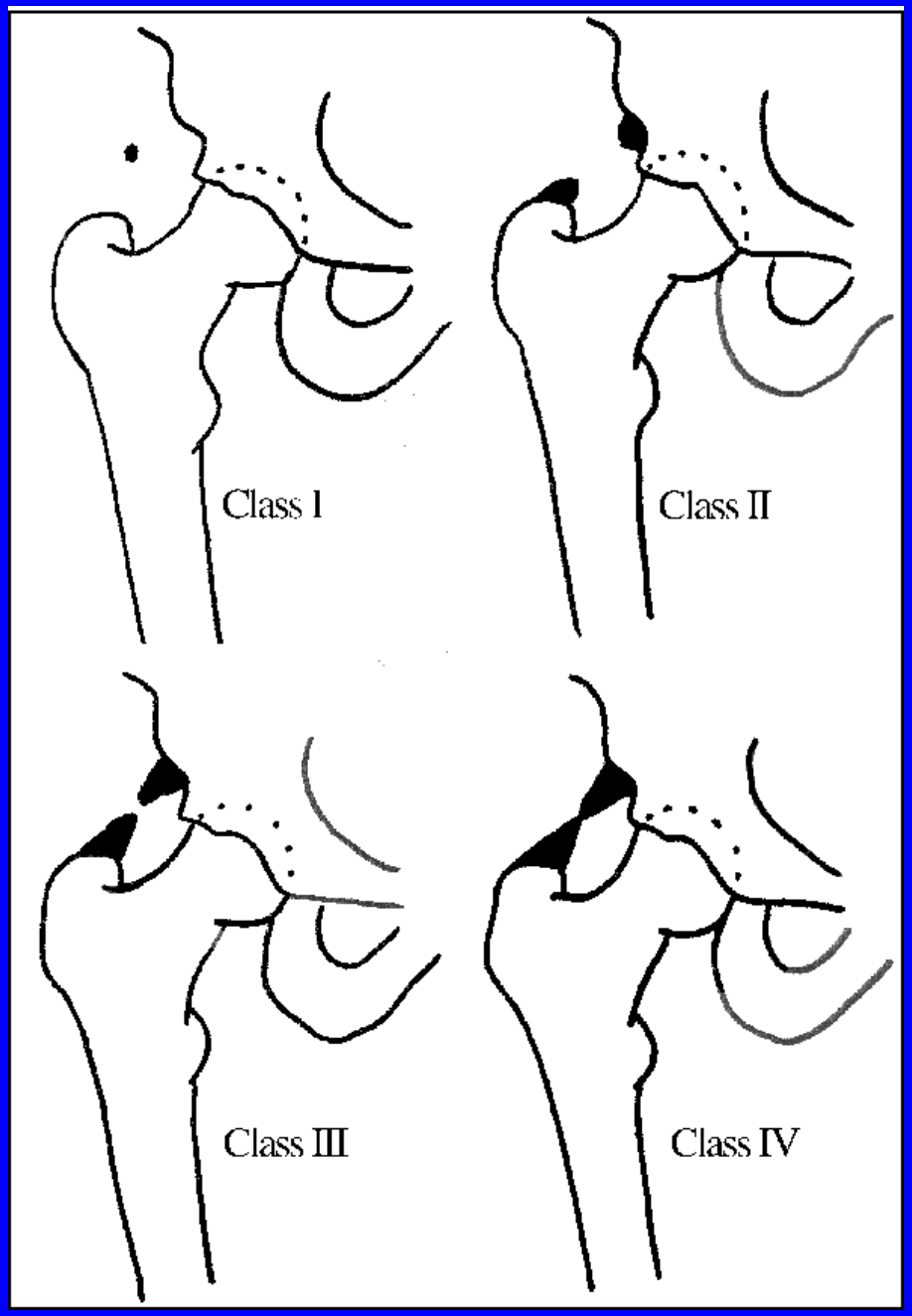




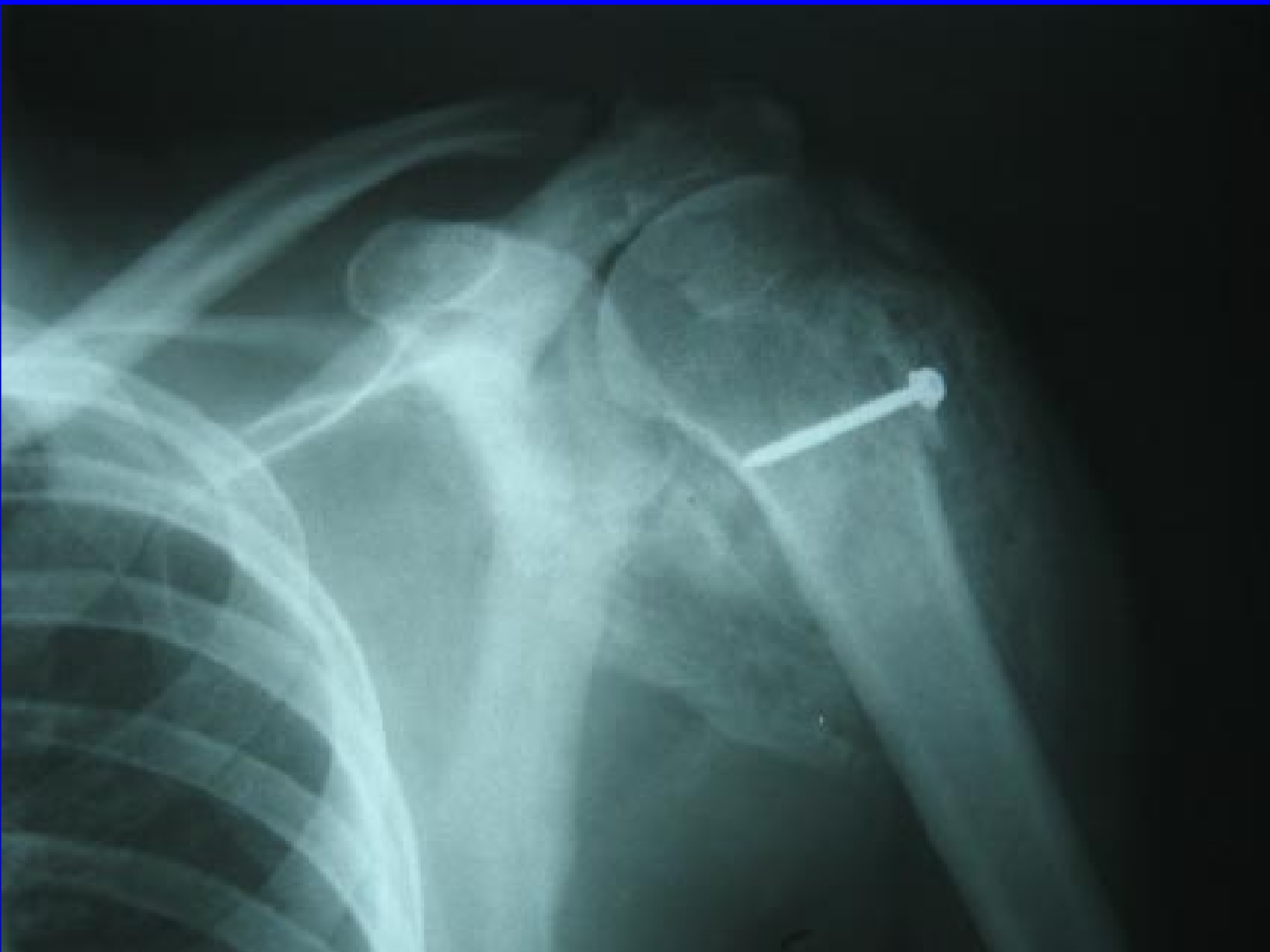
The Brooker Classification of Heterotopic Ossification around the hip joint.

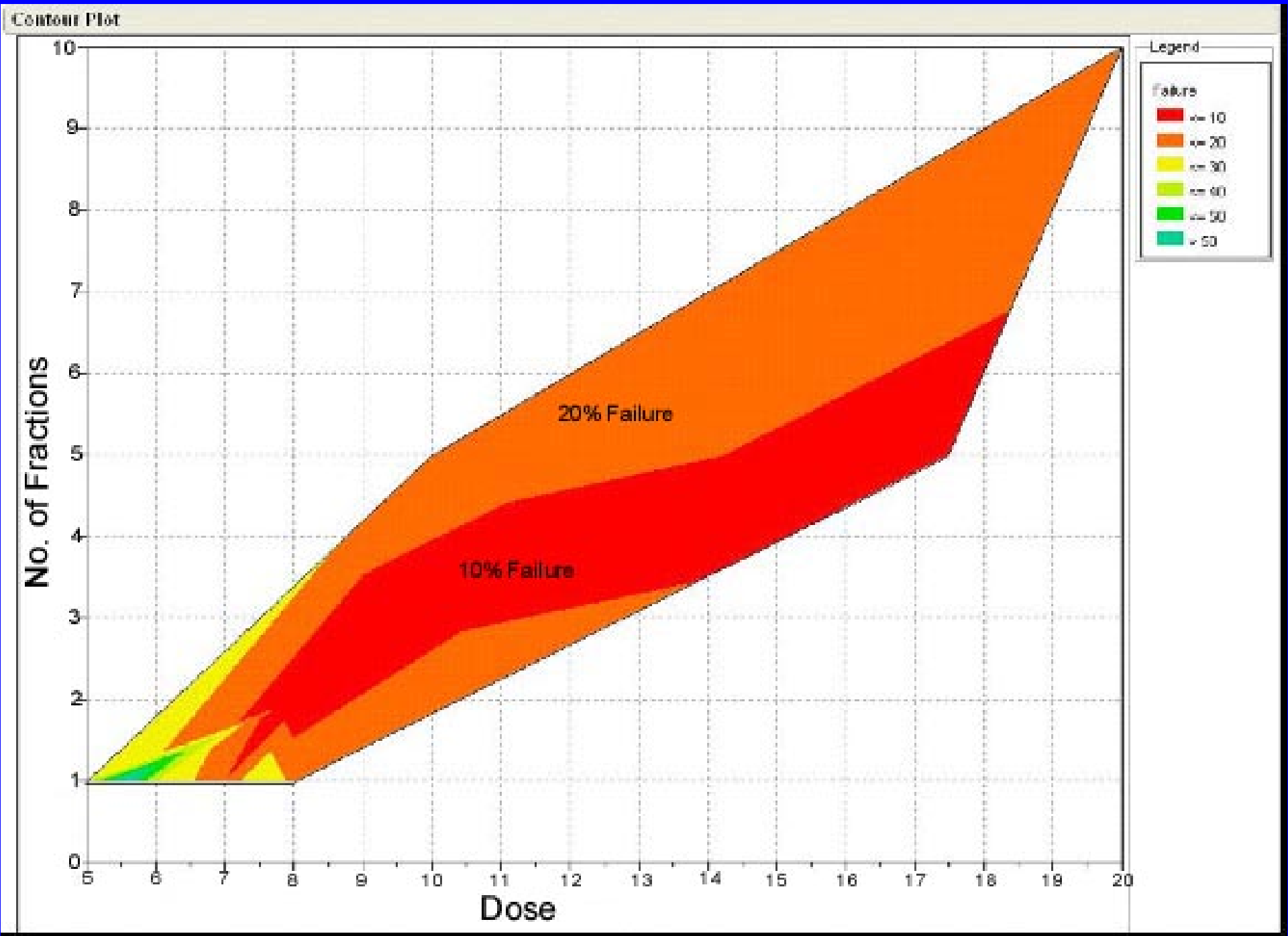
Class I has islands of bone within the soft tissues.

Class II has bone spurs from the pelvis or proximal end of the femur, leaving at least 1 cm between opposing surfaces.

Class III has bone spurs from the pelvis and/or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm.

Class IV shows apparent bone ankylosis of the hip

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Peyronie's disease

- Development of fibrous plaques or nodules in the substance of the penis
- Pain, lump formation, deformity of the penis on erection, and impotence
- Cause of this disease is not known

Treatment

- Reduce pain & stop the progression of the fibrotic process
  - Oral medications
  - Radiation therapy
  - Topical applications
  - Electrical therapy
  - Ultrasonic treatment
  - Locally injectable agents


Wax-coated
Lead shields

Table 11. Summary of selected radiation treatment results of Peyronie's disease

Author year	# Pts	RT treatment	Outcomes	Comments
Incrocci et al. 2000 (7)	179	13.5 Gy /9fx x-rays or 12 Gy /6fx electrons	Pain relief 83% Deformity improved 23% Sexually active 72% Erectile dysfunction 48% Dissatisfied 49%	**82% responded to questionnaire regarding sexual functioning. 29% had post-RT penile surgery.**
Koren et al. 1996 (8)	265	Iridium-192 moulage	"Success" 66.4% fibromatous foci: CR 9% PR >50%: 29.7% PR <50%: 27.7% Pain relief: 61.4%	**Both pain relief and regression of deviation correlated w/ improved erectile function. 41 pretreated w/ potassium p-aminobenzoate, vitamins, topical corticosteroids, or XRT**
Rodrigues et al. 1995 (11)	38	9 Gy /5fx x-rays Reirradiation for minimal response: 9 Gy /5fx (16 patients)	Pain relief 66% (CR 12%, PR 54%) Improved Curvature 40% Sexual function 47% Plaque: CR 24%, PR 8% Re-rradiated group: Pain relief 25% Improved Curvature 28% Sexual function 28%	**Pre-treated w/Vitamin E. No RT morbidity. Vitamin E effects not clear**
Viljoen et al. 1993 (13)	98	25 Gy (10 x 2.5 Gy), 250 kV x-rays	Pain relief : 84% Angulation improved:38.6%. Sexual function: 87.2%	**Progression in 18%. Decline in sexual activity appeared age-related.**
Alth et al. 1985 (1)	636	Radium mold 6.6 - 8.2 Gy	Induration improved 70-85% Deviation improved 33-53% Pain relief 83-90%	
Mira et al. 1980 (9)	**56**	**1000-1400 R**	**Relief CR PR** **Induration 6% 38%** **Curvature 5% 33%** **Pain 51% 28%**	**Less benefit if persistence >5 months**

Cardiovascular Disease

- Heart and circulatory disease are the biggest killers.
- In US, cardiovascular disease caused over 50% of deaths for men in the US, and killed over 600,000 people.
- Coronary arterial disease causes about 380,000 deaths a year : approximately one in four deaths in men and one in six deaths in women.
- Total cost $108.9 billion each year in the United States

http://www.cdc.gov/heartdisease/facts.htm

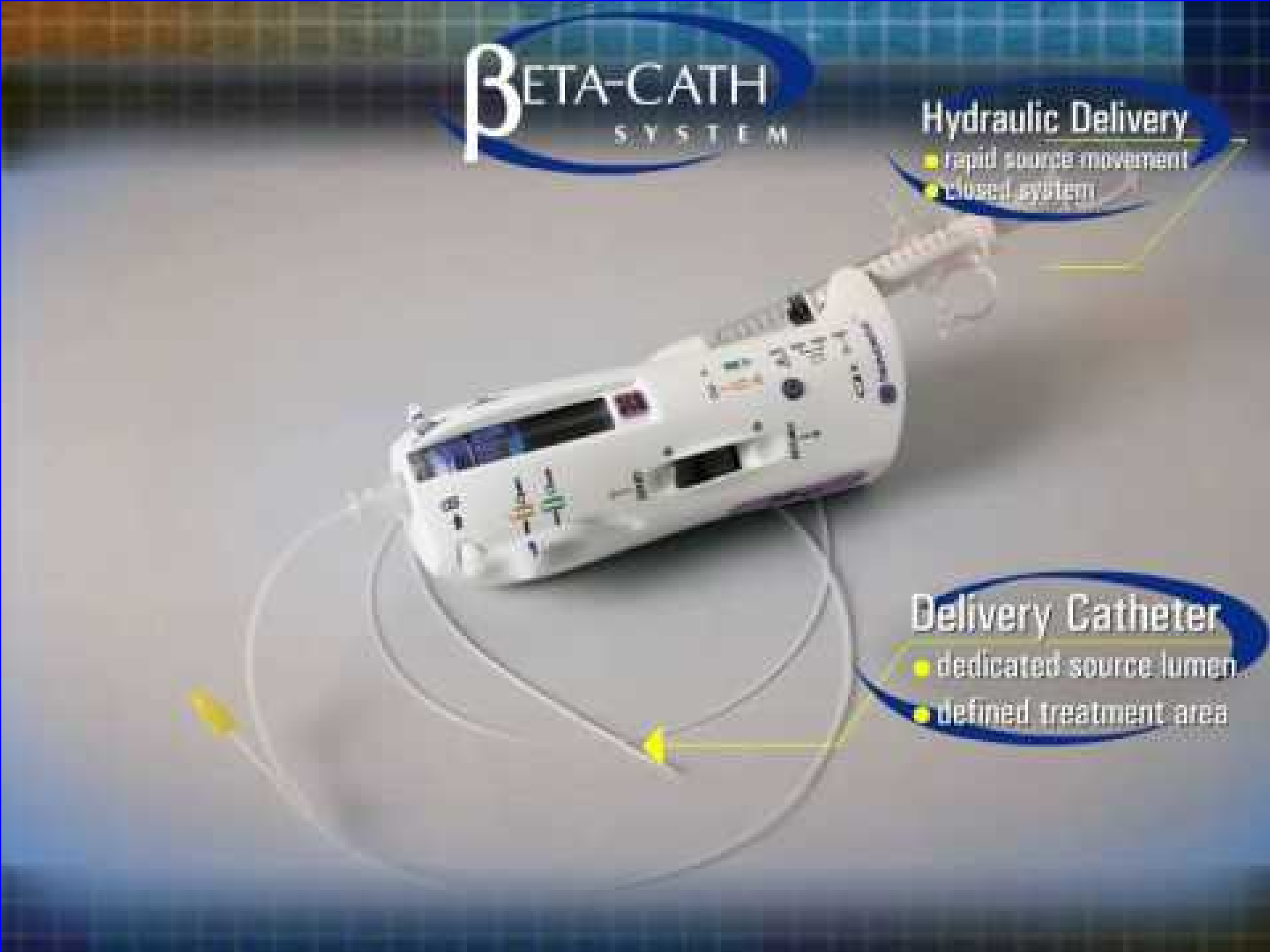
Revascularisation techniques

- Coronary Artery Bypass Graft (CABG)
- Percutaneous Coronary Intervention (PCI)
  - Angioplasty
  - Plus **stenting**
    - Drug-eluted stents
    - Endovascular brachtherapy

The problem with stents.

Restenosis.

Rate depends on lesion type, length and severity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dedicated source lumen
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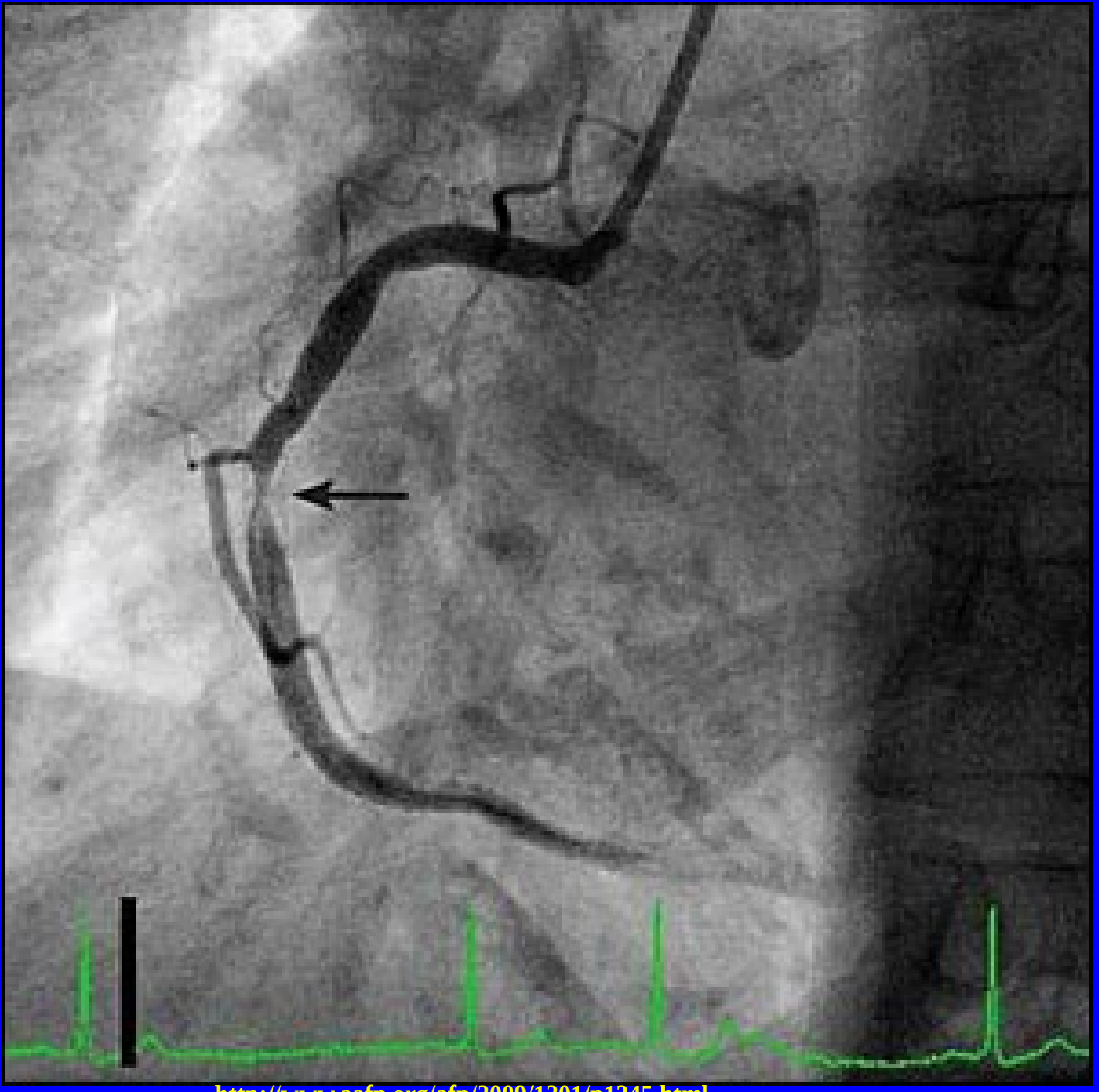

Right coronary artery: severe narrowing within a previous bare-metal stent.

http://www.aafp.org/afp/2009/1201/p1245.html

Table 8. Summary of selected treatment results of endovascular coronary radiation

Randomized Trials	No. of patients	Source	F/U	Restenosis Rates	
				Control	Treated
START 2002 (5)	476	Sr-90/Y-90	8 months	41%	14%
INHIBIT 2002 (6)	162	P-32	9months	52%	26%
SVG-WRIST 2002 (4)	120	Ir-192	12 months	44%	21%
GAMMA-1 2001 (3)	252	Ir-192	6 months	51%	22%
SCRIPPS 2000 (12)	55	Ir-192	3 yrs	64%	33%
WRIST 2000 (2)	130	Ir-192	6 months	58%	19%
PREVENT 2000 (13)	105	P-32	6 months	39%	8%

Which one runs faster:

a fat cabbage or a skinny carrot?

A cabbage is always “a head” !

QUESTIONS?