Hyperbaric Oxygen and Radiation Injury: An Update

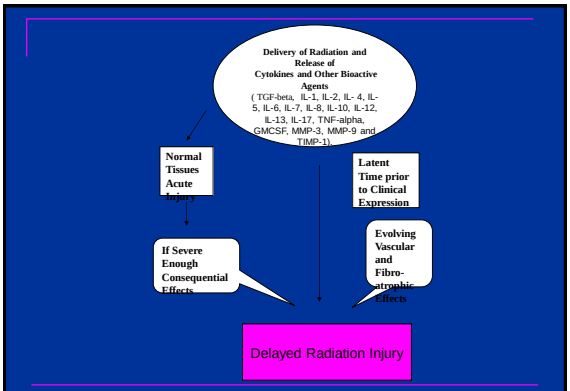
John J. Feldmeier, D.O.
FACRO,FUHM
Toledo Radiation Oncology
Professor
Radiation Oncology
University of Toledo

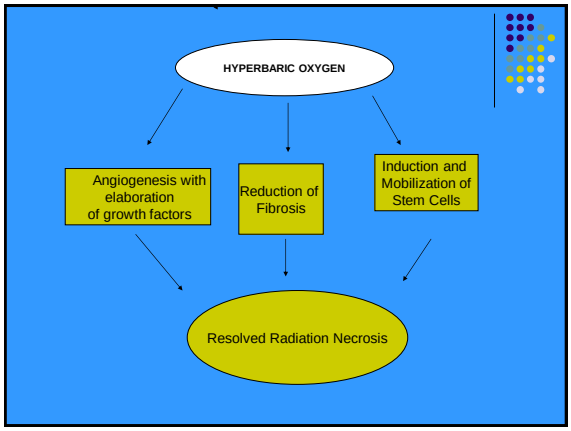
Modern Understanding of Radiation Injuries

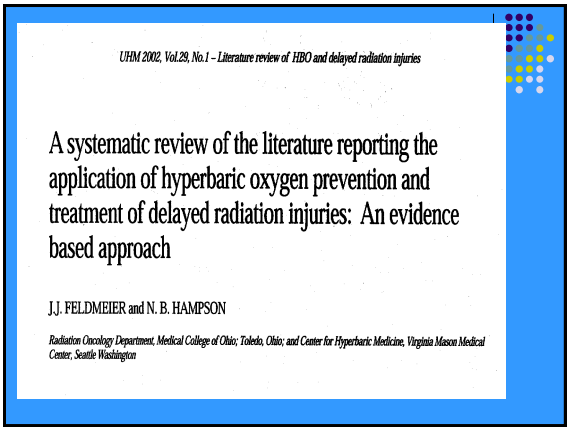
- Characterized by a Latent Period, generally 6 months or more
- The insult begins at the time of radiation with the release of fibrogenetic cytokines but requires adequate time to become manifest
- Clinically may occur many years later and be precipitated by a traumatic or surgical insult such as a tooth extraction

The Etiology

- Although several theories are advanced to explain the etiology of radiation injury, virtually all delayed radiation injuries are characterized by endarteritis with resultant ischemia and tissue hypoxia
- Radiation injury is also characterized by tissue fibrosis and loss of compliance
- Recent publications highlight the fibroatrophic effect







Clinical Published HBO2 Experience in the Following Entities

- Osteoradionecrosis of the Mandible
- Soft Tissue Necrosis of the Head and Neck
- Radiation Cystitis
- Radiation Proctitis/Enteritis
- Radiation Induced Brain Necrosis
- Radiation Induced Xerostomia
- Chest wall necrosis
- Extremity Necrosis
- Soft Tissue and Bony Necrosis of the Abdomen and Pelvic
- Neurologic Injury

ORN: Why is the Mandible Preferentially Affected?

- Prior to Megavoltage Radiation (Cobalt-60 and Linear Accelerators) ORN at other sites such as long bones was commonly seen (Dose in Bone could be 10X Higher)
- Still seen not Uncommonly in Ribs
- Mandibular Circulation
- Nature of Head and Neck Radiation
- Results of Head and Neck Irradiation

Additional Authors have Duplicated these Results

- Prophylactic HBO2 has(d) become a standard treatment
- Recall though that Marx study enrolled only patient with at least 6800 cGy to a portion of the mandible

Soft Tissue Necrosis of Head and Neck Including Larynx

- 7 publications discovered
- 3 Larynx
- 4 Miscellaneous

Laryngeal Necrosis

- Standard Textbook Recommendation is for Laryngectomy if Symptoms persist for 6 months or more
- Experience shows that the majority harbor an occult/persistence of cancer
- Biopsy often difficult since recurrence is submucosal
- Biopsy may further traumatize injured tissue and inhibit healing

Three Studies: Laryngeal Necrosis

- Ferguson (1987), Feldmeier (1993) and Filintisis (2000)
- All are uncontrolled case reports (AHA level 5; NCI level 3ii)
- All had severe necrosis (Chandler III or IV)
- In total of 35 patients and 29 were able to avoid laryngectomy and most had good quality of voice with closure of tracheostomy
- Since the review one additional successful case report (Hsu 2005)

Other Soft Tissue Necrosis of Head and Neck

- Four Papers Discussed in our Review
- 1 (Marx) controlled but not strictly randomized trial (AHA 3; NCI 3)
- Report by Neovius historic control group (AHA 4; NCI 3)
- Davis and Narozny Case Reports

Hyperbaric Oxygen as Treatment for Soft Tissue Radiation Injury of the Head and Neck

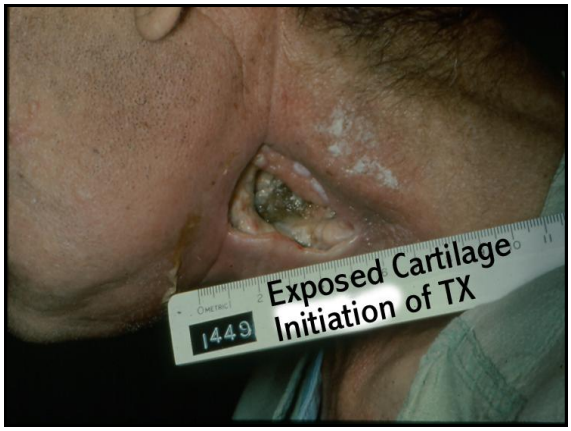
Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Davis (1979)[19]	Case Series-16 patients	5	3ii	Likely to be Beneficial	15 of 16 resolved
Ferguson (1987)[28]	Case Series-8 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	Dramatic improvement in 7 of 8
Feldmeier (1993)[29]	Case Series-9 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	Resolution in all 9 patients
Marx (1999)[30]	Prospective controlled but not randomized study of 160 patients	3	2	Likely to be Beneficial	Statistically significant reduction in wound infection, dehiscience and delayed healing in HBO group
Filintisis (2000)[31]	Case Series-18 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	13 of 18 had major improvement
Narozny (2001)[32]	Case Series-2 patients soft tissue necrosis including larynx and pharynx	5	3ii	Likely to be Beneficial	Resolution in both patients

Neovius H&N Study

- 15 patients in each group
- HBO Group:
- Matched pair historic controls
  - Healing in 12/15; 2 improved; 1 non-healing
- Non-HBO Group:
  - Only 7/15 Healed; 1 fatal bleed

Marx Soft Tissue H&N Trial

- 160 patients: 50% with;50% without HBO
- In terms of following outcome parameters outcome is highly significant statistically:
  - Wound Infection 6% vs 24%
  - Wound dehiscence 11%% vs 48%
  - Delayed Healing 11 vs 55%



Hyperbaric Oxygen as Treatment for Radiation Injury of the Chest Wall and Breast

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Hart (1976)[16]	Case Series-6 patients	5	3ii	Likely to be Beneficial	HBO2 as adjunct to skin graft all 6 grafts successful
Feldmeier (1995)[23]	Case Series-23 patients-8 soft tissue-15 bone+ soft tissue necrosis of chest wall	5	3ii	Likely to be Beneficial	6 of 8 soft tissue resolved 8 of 15 soft tissue+bone resolved
Carl (1998)[54]	Case Report Single positive case	5	3ii	No category for single case report	Resolution of breast edema and pain
Carl (2001)[55]	Case Series-44 patients 32 received HBO;12 control	4	2	Likely to be Beneficial	Statistically significant improvement in pain, erythema and edema of breast in HBO group compared to control

Chest Wall Necrosis

- Feldmeier et al (Undersea Hyper Med 1995;22:383-393) report experience in chest wall necrosis
  - 75% (6/8) Success if only soft tissue involved
  - 53% (8/15) Success if bone involved and all successful interventions required adequate debridement of bone

Radiation Cystitis

- This can be a life threatening disorder
- Usual initial treatment for hemorrhagic cystitis is chemical or electro cautery
- Adds another noxious insult to already injured tissues
- Sometimes requires cystecytomy and ileal loop

Cystitis Update

- 19 papers in the review
- Only 1 negative trial
- 2 additional case reports
- The Virginia Mason Group now with the largest series-60 pts.
- 18 resolved; 26 partial response; 8 unchanged; 2 progressive

Mini Meta-analysis

- All publications of 257 reported
- 196 or 76.3% improved

European Consensus Conference in Lisbon October 2001

Considered Radiation Cystitis Second only to Mandibular ORN in terms of strength of evidence

Radiation Cystitis without HBO

- Sun and Chao 1995 378 pts 3.7% mortality
- Cheng and Foo 1992 reported 9 patients
  - 6 percutaneous nephrostomies
  - 3 with ileal loop diversions
  - 44% died

Proctitis and Enteritis

- Combined for the purpose of this review
- The small bowel has inherently lower tolerance to radiation compared to large bowel
- Clinical incidence of proctitis is higher due to relative increased frequency of radiating pelvic tumors (GYN, prostate, rectum)

Enteritis and proctitis Feldmeier-Hampson Review

- 14 papers found
- 12 are case series (AHA 5; NCI 3)
- 2 animal studies by Feldmeier et al

Proctitis and Enteritis Update

- Gnius at U of Cinncinati 9 patients with hemorrhagic proctitis: 7/9 complete resolution with median f/u 17 months
- Virginia Mason: 65 pts (54 rectum)
- Complete and partial response rates of 43 and 25%

Radiation Enteritis

- Bredfeldt and Hampson in abstract (Am J Gastroentero 1998;93:9) report 19 patients with chronic radiation enteritis: 47% resolution; 37% improvement and 16% no improvement
- Animal study by Feldmeier et al(Radiother Oncol 1995;35:138-144) successful prevention of enteritis

2 Animal papers by Feldmeier: AHA Level 6 Evidence

- This study in a controlled murine model showed less fibrosis and better compliance in animals who received prophylactic hyperbaric oxygen

Prevention Of Enteritis

- Animal Study by Feldmeier et al 1995 Radiotherapy and Oncology 35;138-44
- Fifty animal (25 in each group) received 30 Gy Abdominopelvic radiation; ½ received a prophylactic course of hyperbaric oxygen 7 weeks after completing radiation
- Several assays as well as gross and microscopic morphometry done

Results by Every Assay showed Protective Effect

- Stretch assay showed better compliance
- Histologic staining showed more collagen in the bowel wall of animals not receiving HBO
- Morphometry showed gross changes in radiation only animals and almost none in HBO animals

At last Level 1 Evidence Radiation Proctitis

- Baromedical Research Trial
- Randomized and Double Blinded
- 150 patients enrolled 120 evaluable
- Severity of injury quantified by Soma/LENT standards
- Active arm vs. control improvement in SOMA/LENT score 5.00 vs. 2.61
- Number needed to treat 3

Other Abdominopelvic Injuries

- In a variety of injuries (6 soft tissue groin, 5 necrosis vagina, 8 skin necrosis of perineum or buttocks and 2 ORN of pelvic bones) Feldmeier et al (Undersea and Hyper Med 1996;23:205-213) 57% complete resolution of injury at 2.4 ATA

Hyperbaric Oxygen as Treatment for Delayed Miscellaneous Radiation Injuries of the Abdomen and Pelvis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Farmer (1978)[17]	Single Case Report	5	3ii	Unknown Effectiveness	Single case of vaginal necrosis resolved
Williams (1992)[68]	Case Series-15 patients	5	3ii	Likely to be Beneficial	13/14 patients with vaginal necrosis resolved
Feldmeier (1996)[57]	Case Series-37 patients	5	3ii	Likely to be Beneficial	26/31 who received at least 20 HBO sessions resolved including 1of 2 with pelvic osteoradionecrosis

Extremity Necrosis

- 2 papers discovered
- Farmer single case report which failed to resolve
- Feldmeier et al 17 patients
- Both studies AHA Level 5; NCI level 3

Extremity Necrosis Results

- In the review by Feldmeier:
  - 11/17 patients resolved
  - 11/13 resolved if we exclude 2 with persistent cancer and 2 who were improved but not resolved at completion of treatment and were lost to follow-up

At Initiation

Hyperbaric Oxygen as Treatment for Radiation Injuries of the Nervous System

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Hart (1976)[46]	***Case Series-5 myelitis pa- tients and 1 with brain necrosis***	***5***	***3ii***	***Unknown Effectiveness (mixed result)***	***Sensory but no motor improvement for myelitis patients; brain patient improved***
Glassburn (1977)[47]	Case Series-9 patients with Myelitis	5	3ii	Likely to be Beneficial	6 of 9 improved
Guy (1986)[48]	Case Series-4 patients optic nerve	5	3ii	Likely to be Beneficial (if initiated within 72hrs)	2 of 2 improved if started within 72 hrs; if beyond 72 hrs, neither responded
Roden (1990)[49]	***Case Series-13 patients optic nerve injury***	***5***	***3ii***	***Not likely to be Beneficial***	***No patient had improvement in vision***
Fontanesi (1991)[50]	Single Case Report optic nerve	5	3ii	Unknown Effectiveness Single Positive Case	Visual acuity significantly improved in spite of persistent tumor
Feldmeier (1993)[51]	Animal Study of Myelitis	6	Not Clinical	Not Clinical but Positive Study	Onset of myelitis delayed for 9 weeks in a statistically significant fashion for animals treated prophylactically

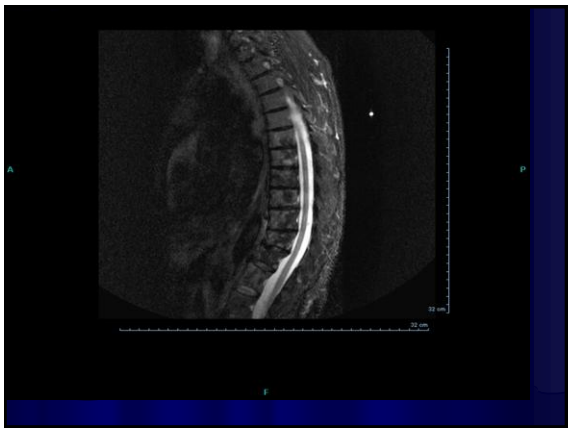
Borruat (1993)[72]	Single Case Report	5	3i	Unknown Effectiveness	Single patient with bilateral optic neuritis; resolution in more recently affected eye; slight improvement in earlier affected eye
Chuba (1997)[73]	Case Series-10 patients brain necrosis	5	3i	Likely to be Beneficial	All ten initially improved; 4 died from tumor; 5 of remaining 6 still improved
Leber (1998)[74]	Case Series-2 patients brain necrosis	5	3i	Likely to be Beneficial	One lesion disappeared; the other was reduced in size
Calabro (2000)[75]	Single Case report of radiation myelitis	5	3i	Unknown Effectiveness Single Positive Case	Progressive improvement following HBO
Cirafisi (2000)[76]	***Single Case Report of rhombencephalopathy***	***5***	***3ii***	***Unknown Effectiveness Single Negative Case***	***No improvement with HBO, steroids or anticoagulants***
Pritchard (2001)[77]	***RCT: Brachial Plexopathy***	***1B***	***1ii***	***A Negative Study: No Benefit***	***No improvement in brachial plexopathy 6 patients with lymphedema had significant reduction***

Central Nervous System: Brain

- Report by Chuba et al (Cancer 1997;80: 2005 -2012) 10 children with brain necrosis; improvement or stabilization seen in all; 4 died of tumor;1 alive with tumor;5 alive with clinical and imaging evidence of improvement (20-30txs)
- Fontanesi et al (J Hyper Med 1991;20:245-248) reported successful tx of radiation optic neuritis in a 13 yr old

Central Nervous System: Spinal Cord

- Dr Hart et al reported the tx of a small group of patients with radiation myelitis with slight and temporary improvement (Cancer 1976;37:2580-2585)
- Feldmeier and associates reported delay in onset of myelitis in heavily irradiated mice (Undersea Hyper Med 1993;20:249-255)



NCI Conference 9/2000

Modifying Normal Tissue Damage Postirradiation

Radiation Research 157:204-223

- A number of strategies were discussed:
  - Use of SOMA/LENT Scores
  - Use of pro-inflammatory cytokines and chemokines
  - Look at growth factors TGF-B, FGF2,FGF7
  - Proteases to avoid fibrosis
  - Blocking renin-angiotensin system
  - Trental and Vitamin E

Strategies of NCI Conference

- For the most part no clinical trials
- Based on pre-clinical work
- FGF7, Inhibition of Renin angiotensin system and Trental all subject of preliminary clinical reports
- No large RCT's

Strategies for Treating Radiation Complications

- Alum or Formalin for Cysitis, Proctitis
- Rotation of vascularized flaps such as omental or myocutaneous flaps with vascular supply originating outside radiation field
- These are not supported by RCT's
- Level of support based on case series or "common sense"

Strategies contd

- Non-HBO tx of brain necrosis is craniotomy and resection of necrotic focus
- Steroid enemas for proctitis
- Elemental diets for enteritis
- Artificial saliva for xerostomia
- Trental for soft tissue necrosis

Evidence for Interventions other than Hyperbaric Oxygen for Radiation Injuries

- These are limited to case series and individual institutional reports
- Often involve radical surgery (Bypass or Removal of Affected organ) and risks inherent in patient previously treated
- No other therapies are consistently effective

Strategies for Preventing Radiation Injuries

- Targeted Therapy avoiding critical structures-IMRT
- Radioprotectors-recent use of Ethyol routinely to protect salivary glands and prevent xerostomia in head and neck irradiation-very expensive amounting to about $20K per treatment course-must be applied to all patients
- RCT's have shown decreased complication rates with these strategies

Hyperbaric Oxygen for Prophylaxis of Radiation Injury:Clinical Experience

- Marx's RCT (J Am Dent Assoc 1985;11:49-54) of HBO Prior to Dental Extractions (5%vs30% Incidence of ORN)
- Pomeroy and Associates (J Uro 1998; 159: 1630-1632) 5 patients preop HBO prior to surgical intervention for radiation injury in pelvis
- Feldmeier et al in abstract (Undersea Hyper Med 1998;Supl:10 reported 87.5% prompt wound healing in patients operated for salvage of H&N Ca after XRT

Hyperbaric Oxygen Prophylaxis of Radiation Injury: Animal Research

- Feldmeier et al (Radiother Oncol 1995;35:138-144) demonstrated success in applying HBO to reduce radiation enteropathy in murine model of small bowel and subsequently reduction of fibrosis in rectum abstract (Undersea Hyper Med 2000;26 Supl)
- Feldmeier et al(Undersea Hyper Med 1993;20:249-255) demonstrated ***delay*** of onset of myelitis in a murine model

Issues of Treatment

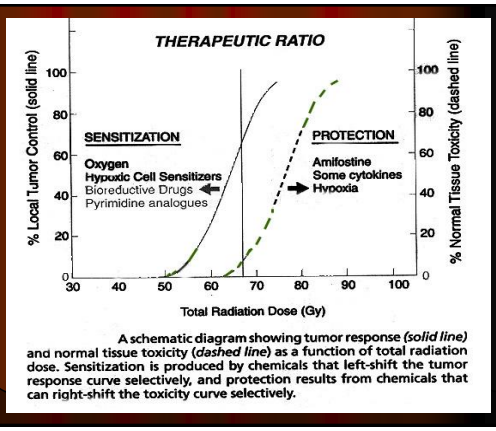
- Dose:
  - Pressure: Marx has shown dose response in animal model for increasing pressure
  - Number of treatments: Often 40 or more are required
- Carcinogenesis: No convincing evidence in either animal studies or clinical reports

Conclusions

- Results in Soft Radiation Necrosis are consistently positive
- Various protocols used
- Several of positive studies delivered too few treatments
- In my experience and review, 40 treatments should be utilized
- Animal studies by Marx suggest an advantage for 2.4 ATA though many + results have been obtained at 2.0 ATA

Hyperbaric Oxygen Radiosensitization: A Lost Indication Worth Another Good Look

John J. Feldmeier, D.O.
Toledo Radiation Oncology
Professor and Chairman
Radiation Oncology
Medical College of Ohio



A schematic diagram showing tumor response *(solid line)* and normal tissue toxicity (*dashed line*) as a function of total radiation dose. Sensitization is produced by chemicals that left-shift the tumor response curve selectively, and protection results from chemicals that can right-shift the toxicity curve selectively.

First Indications Of O2 Sensitization

Radiation Oncologists in the early 1900's observed that there was a less pronounced skin reaction when pressure was applied to a surface applicator temporarily making the skin ischemic

Classic Work Establishing the "Oxygen Effect"

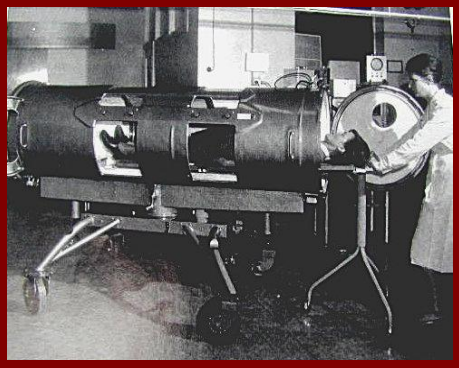
In 1953, Gray and associates demonstrated in several in vitro and 1 animal transplanted tumor models that cell kill and tumor control were drastically enhanced in oxygenated circumstances compared to hypoxic conditions

Demonstration of Practical Clinical Application

- This work was accomplished by Dr. Churchill-Davidson and his collaborators in 1955.
- Eight patients (4 with breast and 4 with lung cancer) were irradiated at 3.0 ATA through the "perspex" port of a British Navy HBO chamber.
- Patients were anesthetized to prevent seizure and "discomfort".

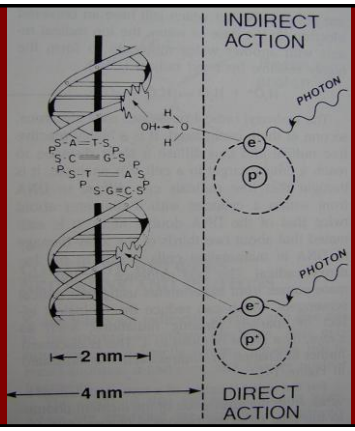
In Churchill-Davidson's Classic Work

- One half of each patients tumor was treated in oxygen at pressure and one half in air with the same dose (1000-1500r)
- Tumors were then biopsied or removed.
- In 6 of 8 cases the response was deemed to be more pronounced in the HBO part
- The study showed the practicality of the approach and served as the model for the next 20 yrs.



Biology of the "Oxygen Effect"

- Radiation effects cell death through free radical formation in H20 molecules in the body
- These free radicals if of adequate energy can interact with chemical bonds joining the molecules of the DNA strand effecting breaks in these bonds
- If not repaired, these breaks will prevent successful cell reproduction
- The goal is a double strand break because these are not generally repaired

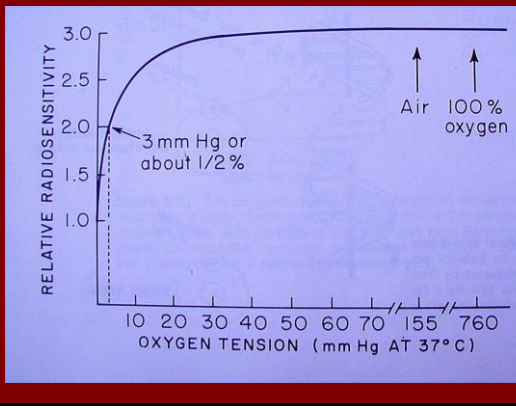


Biology of the Oxygen Effect Contd.

- The presence of molecular oxygen is likely to increase the production of oxygen radicals
- More importantly oxygen combines with the free radical and the molecule with which it has interacted to form a more stable chemical moiety (an organic peroxide)
- In this way, oxygen "fixes" or sets the damage and prevents repair

Magnitude of Oxygen Effect

- The OER (Oxygen Enhancement Ratio) for low LET (Typical xray or electron beam therapy) shows that cell killing is increased by a factor of 2.5 to 3.0 compared to 1.8 to 2.0 for chemical sensitizers
- Most of this enhancement occurs between oxygen tensions from 0 to 20mmHg

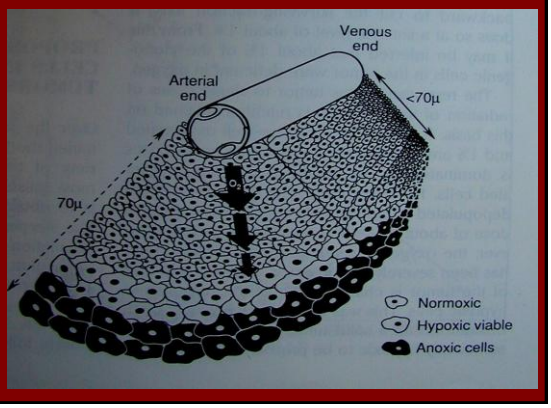


Timing of Radiation Relative to Oxygen Administration

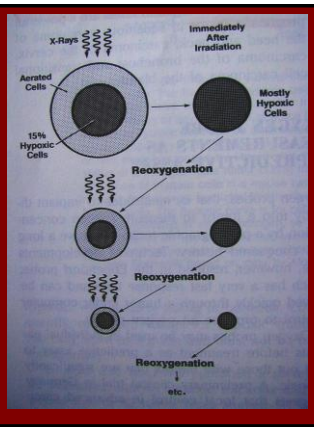
- Very sophisticated experiments were designed and demonstrated by Gray that oxygen must be present within milliseconds of the radiation
- These experiments exposed mammalian cells and bacteria to radiation with blasts of oxygen given at various times before or after the radiation

Fractionated Radiation

- This principle exploits several aspects of tumor biology (the 4 R's of Radiobiology:Reoxygenaton, Repair, Reassortment, Repopulation)
- Prominently these include re-oxygenation
- Between radiation doses, the tumor shrinks and cells which were hypoxic are now well oxygenated-physically they become close to the available vasculature



A classic study showed that the proportion of hypoxic cells not the absolute number remain constant



Experience with HBO Sensitization Head and Neck Cancer

- Henk reported the 2 Cardiff Trials in 1977
- First Cardiff Trial:
  - 10 identical fractions in air vs. HBO-significant advantage in local control; no advantage survival; higher complication rate (laryngeal necrosis)

Head and Neck (contd)

- Second Trial:
  - 10 fractions HBO(10% reduction) vs. standard fractionation in air (30 treatments)
  - Complication rate the same
  - Survival and local control improved in HBO Group
  - Magnitude of survival increase from 27% in air to 56% in HBO at 4 years

Figure 2 Photograph of hyperbaric vessel.

The Medical Research Council

- **Review done by Dische in 1979 reported the results in all the MRC trials**:
  1. No improvement in bladder cancer, a single trial positive in bronchogenic cancer
  2. In cervical cancer an advantage for HBO group especially Stage III and women less than 55

Other Trials in Cervical Cancer

- Studies from MD Anderson and Cape Town failed to reproduce MRC results
- Cape Town study is valuable in that standard fractionation in air compared to HBO failed to show a difference whereas if treatment was given in 10 fractions for both HBO was superior
- HBO for ten treatments had similar results as air for 27 treatments

Meta-analysis of Hyperbaric Oxygen Sensitization

- Done by Overgaard and Horsman in 1996
- 17 Trials with 2026 patients were reviewed
- Tumors included cervical, head and neck, bladder and lung cancers
- Results showed an improvement in local control from 48.2% to 54.9% (P=.003) for all sites

Why Lost Interest

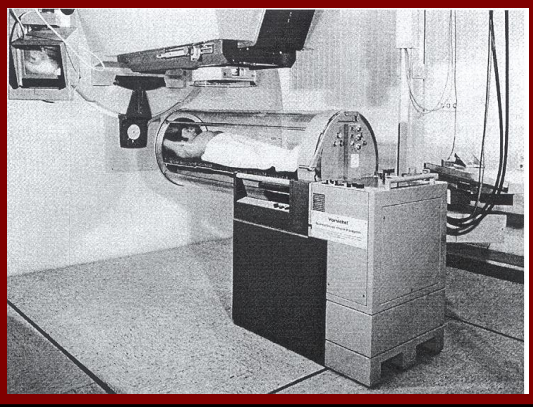
1. Risk of Damage to Acrylic Chamber Hull and Fatal Decompression
2. Slowed through-put in busy radiation oncology departments (30 minute soak)
3. Inability to lay hands on patient to position for complex targeted radiation techniques such as IMRT
4. Possibility of increased complications seen in Cardiff I trial

Results of Phase I Study

- Abstract submitted to the ASCO Meeting
- 10 of 12 pts completed study
- 2 left the study: 1 non-compliance and 1 for distant metastases (liver and bone)
- No dose limiting toxicity from HBO
- 25% required myringotomies
- Average time between HBO and rads 10.2 minutes
- Initial complete tumor response seen in all 10 pts.
- Plan is to complete a Phase III trial

"Irrational Exuberance"

- Various reports including proceedings of HBO International Conference reveal an attitude of extreme confidence
  - "**CANCER IS CURED !!!**."



Why are there no Current Trials?

- Some trials showed higher complication rates (not clear whether dose or HBO effect)
- Most trials showed no survival advantage (problem of selection-very advanced cancers)
- Modern conformal radiation effects not possible (requires precise localization)
- HBO slowed the throughput in a busy dept
- Interest in Chemical Sensitizers

Why no Trials (contd)?

- Outcome differences were not clearly due to HBO-could be non-standard dosing scheme (not likely)
- Radiation weakened acrylic hull/ports and at least 1 accident with fatalities(4megarad limit)
- Oxygen mimetic sensitizers became available (nitroimidazoles)
- Perflurocarbons and Carbogen Trials
- High LET Radiation (neutrons) (2 ctrs)

Problems with these Strategies

- Nitroimidazoles toxic especially neurotoxic in doses required to sensitize
- Perflurocarbons and increase in Hgb not impressive in their results
- Similar for Carbogen Breathing (95% O2 and 5% CO2)
- High LET radiation not widely available and expensive; complications may be higher in some circumstances

In spite of Problems

- Oxygen is a potent sensitizer with most other agents having enhancement ratios less than 2.0
- Most other sensitizers have toxicities that are not insignificant
- Most sensitizers in use in the clinic are chemotherapeutic agents that sensitize as well as exert their own cytotoxicity and lead to higher complication rates

Radiation just after HBO

- A finite time is required before O_2 return to baseline pre-HBO levels
- Dr Kohshi group has reported in 2 papers (9 and 29 patients) results in radiating patients with high grade astrocytomas just after HBO
- In 1st study 4/9 had CR 5/9 PR compared to 0/12 with CR and 4/12 with PR in retrospectively matched group (Kohshi 1996)

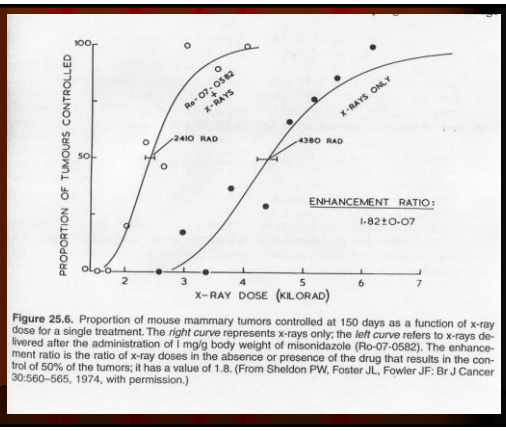


Figure 25.6. Proportion of mouse mammary tumors controlled at 150 days as a function of x-ray dose for a single treatment. The *right curve* represents x-rays only; the *left curve* refers to x-rays delivered after the administration of 1 mg/g body weight of misonidazole (Ro-07-0582). The enhancement ratio is the ratio of x-ray doses in the absence or presence of the drug that results in the control of 50% of the tumors; it has a value of 1.8. (From Sheldon PW, Foster JL, Fowler JF: Br J Cancer 30:560–565, 1974, with permission.)

Innovative New Approaches

- Don't give external radiation through the chamber hull or acrylic ports
- Consider brachytherapy (implant) or radioisotope therapy
- Consider radiation just after HBO while O_2 levels are still elevated-must determine the window of opportunity

MIBG and Hyperbaric Oxygen

- MIBG (meta-iodobenzylguanidine) with I-131 as the iodine moiety is selectively taken up in Neuroblastomas (analogue of norepinepherine)
- At the Netherlands Cancer Institute 27 children with Stage IV treated with HBO after injection and compared to 36 without HBO
- 28 month survival increased from 12% to 32%

Considerations with MIBG or other Injected Isotope

- With this isotope or others radiation safety principles must be adhered to
- In a decay scheme of an injected isotope requiring days or weeks to give dose, daily HBO treatments will sensitize for only a small part of the overall dose

Radiation after HBO (contd)

- In 2nd report, 15 patients treated at 2 centers: One center XRT within 15 mins (11)-other center XRT within 30 mins (4)
- Results were compared to 14 others without HBO
- (Kohshi et al 1998)

Radiation after HBO (contd)

- 11 HBO to XRT in 15min: 3 CR; 8PR
- 4 HBO to XRT 30 min: 0 CR or PR
- In non-HBO group: 4/14 had PR

Survival

- All 14 patients in non-HBO group were dead in 36 months (median survival 16 months)
- In HBO group, 6 patients were still alive at the time of the report and median survival was 24 months

Experience by 2 Additional Authors

- Ogawa et al 2003 Okinawa were able to irradiate 21 patients with high grade astrocytoma within 15 mins with chemotherapy (ACNU and Vincristine)
- Out of 16 evaluable patients: 3 CR and 8 PR
- No unexpected toxicities
- 3 had ottic barotrauma; 48% hematologic complications

Additional Experience

- Beppu et al 2003 Morioka Japan
- 39 patients (29 GBM, 10 AA) radiation, HBO and ACNU and interferon-beta
- 39 patients enrolled; 35 completed full therapy
- Response rates GBM, AA, overall: 50, 30 and 43%
- Time to tumor progression: 38, 56 and 43 weeks

Beppu's Experience

- Radiation within 15 minutes of HBO (2.8 ATA)
- Chemotherapy at least 2 hrs after HBO
- No unexpected toxicity except one with severe ottic barotrauma

The Issue with XRT after HBO is Mechanism of Sensitization

- **Kohshi has suggested that malignant astrocytomas do not use oxygen for metabolism; and O_2 levels are maintained**
- **Previous washout measurements with transcutaneous suggest return to baseline within few minutes-may stay elevated for hour**
- **Possible that vasoconstriction of HBO reduces edema and improves blood flow; this would maintain increased O2 for some time**

Issue of Time element in Maintaining Elevated Levels of O2

- Beppu's group investigated O2 levels with implanted Clark electrodes in brain tumor patients subjected to 100% O2, osmotic diuretics (mannitol) and HBO both asleep and awake
- Diuretics and HBO led to increased measured O2 levels
- In HBO exposure increased levels were maintained for at least 15 mins

German Experience in Head and Neck Cancer

- Becker et al 2002 in 7 patients with Eppendorf electrodes measured O2 levels in H&N Ca's
- Patients given HBO at 2.4 ATA
- O2 levels increased from median of 8.6 mmHg to 550 mmHg during HBO
- Elevated O2 maintained up to 25 mins

High Dose Rate Brachytherapy with HBO Sensitization

- High Dose Rate Brachytherapy involves the computer controlled movement of a high activity radioactive source through a target volume defined by an applicator
- This high intensity source usually Ir192 dwells along the path of the applicator at various points to deliver the desired dose
- The movement and dwell times and positions are controlled by sophisticated planning computers

Important for Future Studies

- Determine by direct measurement or by functional imaging the interval during which oxygen levels are elevated

Potential Advantages of HDR

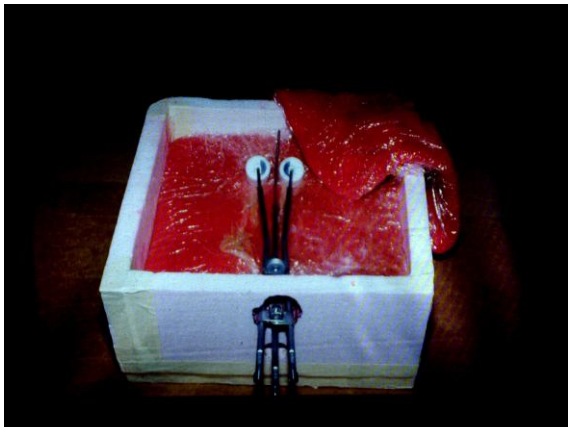
- Positioning of the patient is not an issue
- Dose per treatment is high (typically 500cGy or more)
- Normal tissue effects are minimized by the precise targeting of the Implant
- The source can move through penetrations in a steel chamber or the steel door of an acrylic chamber

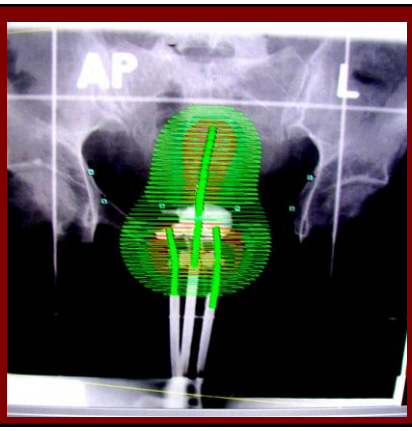
Problems with Acrylics and XRT

- Recall that at least one fatal accident previously occurred
- ASME Safety Standards for pressure vessels for human occupancy limit cumulative dose to 4 megarads
- HDR would avoid virtually all dose to acrylic

HDR in HBO: A Feasibility Study

- Feldmeier et al 1996 demonstrated the successful passage of HDR source through a hull penetrator with the successful programmed movement of source through a Fletcher-Suit gynecologic implant device





What about HBO with Seed Implants?

- Prostate Cancer is most common tumor in men-about 250,000 new cases and 40,000 deaths
- Estimated that 1/3 of patients will receive permanent seed implants in near future
- Hyperbaric sensitization attractive and easy but daily HBO for several weeks would only sensitize small portion of dose which takes 1 yr. with I-125.

Current Status of HBO Radiosensitization Trials

- No active trials currently for external radiation and HBO Simultaneously
- Interesting Reports from Japan in treating GBM
- Laurie Gesell M.D. while at U of Cincinnati had initiated a trial XRT post HBO in GBM

Current Status (contd)

- Dick Clarke and his collaborators have just completed a Phase I trial in Head and Neck Squamous Cell Cancer
- Patients received combined Cisplatin and IMRT radiation to a dose of 7000 Cgy
- HBO was given just before rads (radiation started within 15 minutes)
- Began HBO 2X weekly then increasing in groups of 3 stepwise to 3X,4X and 5X weekly

Summary Contd

- Current state of art in the clinic is to use certain cytotoxic agents simultaneously with radiation for sensitization including 5FU, Taxol, Cisplatin, Xeloda and Gemzar
- Also use Protectors such as Amifostine
- In both cases must increase therapeutic advantage, i.e have selective sensitization of tumor or selective protection of normal tissues
- No chemical sensitizer is as potent or as safe as oxygen sensitization

Summary Contd 2

- Radioresistance is not the only reason that hypoxic tumors fail treatment; loss of apoptosis, proclivity for metastases genetic instability and development of resistance
- Intriguing observation in our work with melanoma cells in culture which would not adhere to culture plate after HBO; ? Effect on metastases