Phase II Trial of Hyperbaric Oxygenation in Conjunction with Radiotherapy and Temozolomide in Adults with Newly Diagnosed Glioblastomas

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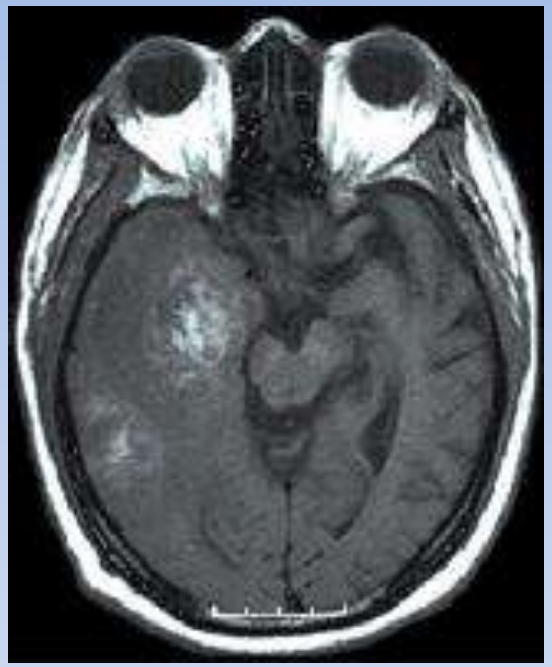


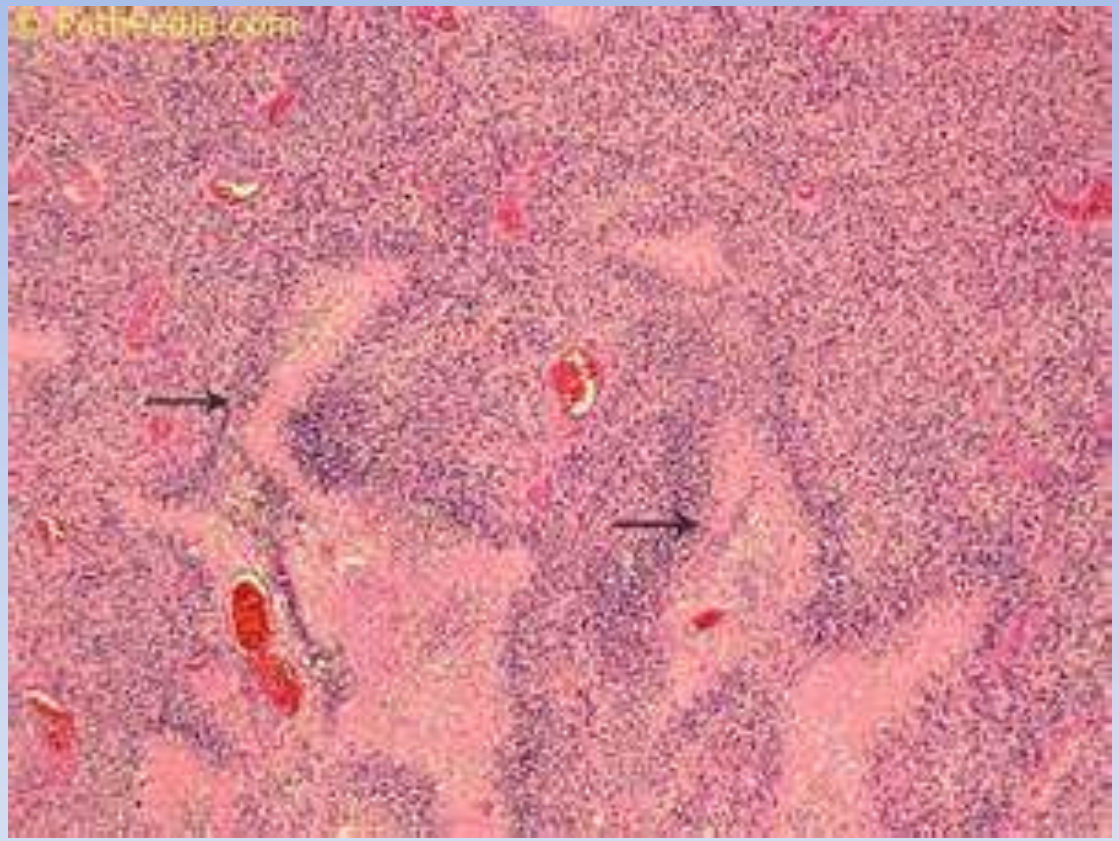
Glioblastoma

1. heterogenous mixture of poorly differentiated neoplastic astrocytes
2. GBM accounts for 15% of all intracranial neoplasm
3. Incidence of 4-5/100,00
4. Second leading cause of cancer deaths in patients under 35 and fourth in patients under 54
5. Mean survival 12-14 months and 2 year survival is approximately 26%
6. Statistics have not changed despite new advances in surgery, radiation and chemotherapy

Glioblastoma

1. Due to diffusely infiltrative nature, surgical resection is not curative
2. Radiation therapy in combination with Temozolide is standard of care for newly diagnosed disease
3. No standard of care for recurrent disease
4. Severe hypoxia within GBM is thought to play a role in their refractoriness to treatment
5. Ogawa et al published data indicating some improvement in survival with hyperbaric oxygen, prior to radiation with ACNU(nimustine) chemotherapy (17.3 month median survival)

Histopathology of a Glioblasoma



Particulate Radiation

Electrons-small, negatively charged particles that can be accelerated to high energy. Have a finite range.

Protons-positively charged particles. Relatively massive with a mass almost 2000X greater than an electron. Deliver energy by a phenomenon called the *BRAGG Peak.* Because of their mass, they require more complex and more expensive equipment to accelerate them to useful energies.

Neutrons-particles with a mass similar to that of a proton but with no electric charge. Because they are electrically neutral, they cannot be accelerated in an electric device.

General Points about Radiosensitivity and the Cell Cycle

1. Cells are most sensitive at or close to mitosis
2. Resistance is usually greatest in the latter part of S phase
3. If G_1 has an appreciable length, a resistant period is evident early in G_1 followed by a sensitive period toward the end of G_1
4. G_2 is usually sensitive, perhaps as sensitive as M phase

Radiation Damage

1)Lethal Damage-irreversible, irreparable, and by definition leads irrevocably to cell death

2)Sublethal Damage-damage which, under normal circumstances can be repaired unless additional sublethal damage is added

3)Potentially Lethal Damage-the component of radiation damage that can be modified by post irradiation environmental conditions

Oxygen Effect

First noted in 1912 *Swartz* (*Germany*) who noted

that the skin reaction produced on his arm

was reduced if applicator was pressed hard onto the skin-interruption of blood flow

1921-*Holthusen* notes that *Ascaris* eggs were relatively radioresistant in the absence of oxygen

1930's -*Mottram* (UK) looks at survival of tumor

slices irradiated +/- oxygen

Oxygen Effect

Oxygen Enhancement Ratio-The ratio of hypoxic to aerated doses needed to achieve the same biologic effect.

Typically about 2-3 for x-rays.

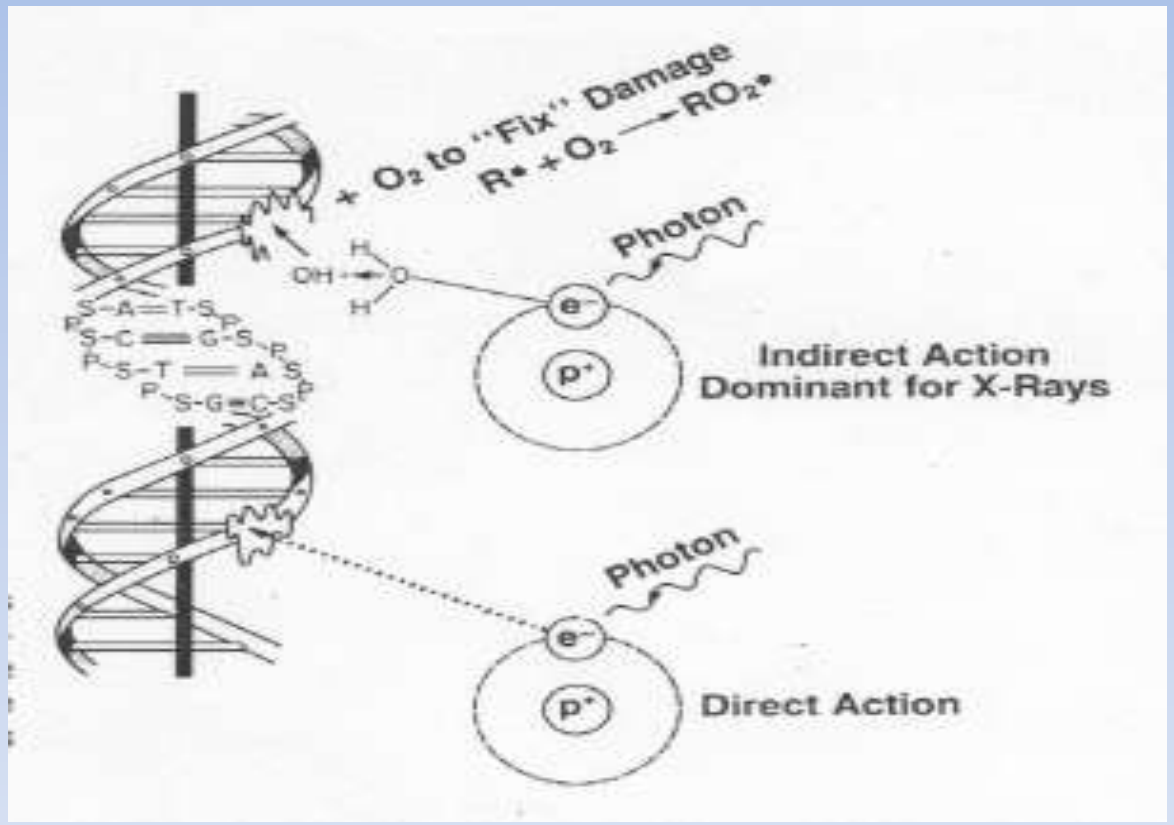
Dependent of phase of the cell cycle.

Cells in G1 have a lower OER than cells in S phase.

Oxygen Effect

1) Absorption of radiation leads to production of fast charged particles (e-)
2) Charged particles ultimately produce free radicals which are highly reactive due to unpaired e-
3) Free radicals break chemical bonds, produce chemical changes and initiate the chain of events that result in the final expression of biological damage
4) If oxygen is present, it reacts with the free radical R and produce RO_2 a nonrestorable form of the target material. This results in a change in the chemical composition of the material exposed to radiation.

Oxygen effect

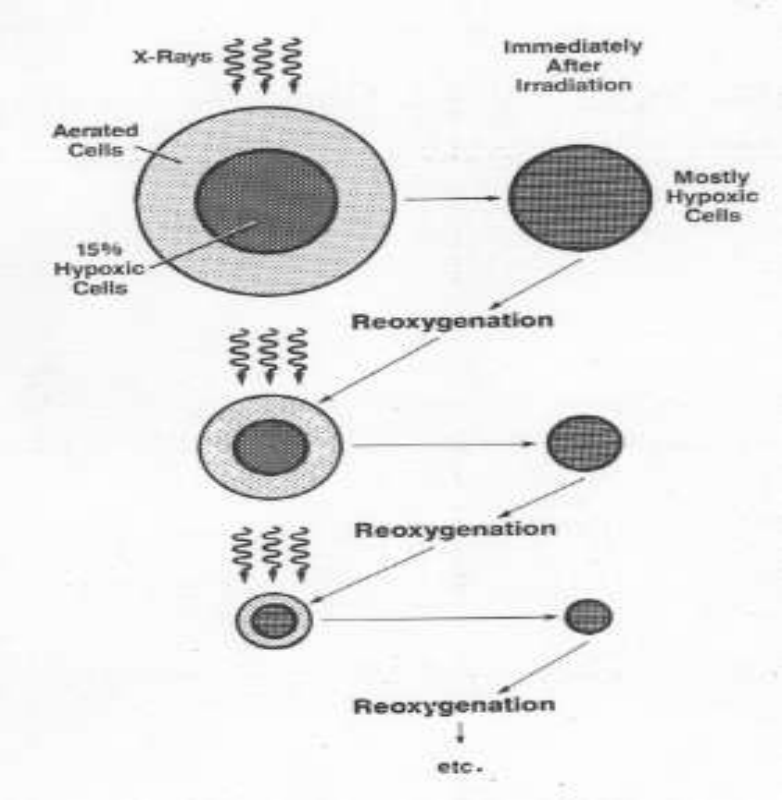


REOXYGENATION

The oxygen status of cell in a tumor is not static; it is dynamic and constantly changing.

As well oxygenated cells die off after a dose of radiation (more than hypoxic cells due to ^OER) hypoxic cells more closer to oxygen source (blood vessels) and become reoxygenated.

Reoxygenation



Introduction to Fractionation

4 R's of Radiobiology

1) Repair of sublethal damage
2) Reassortment of cells w/i the cell cycle
3) Repopulation
4) Reoxygenation

Dividing a dose into a number of fractions ***spares*** normal tissue because of repair of sublethal damage between fractions and repopulation of cells and ***increases*** damage to the tumor because of reoxygenation and reassortment of cells into the radiosensitive phases of the cell cycle

Clincal Protocol

- Inclusion Criteria
  - Age greater than or equal to 18
  - Histology confirmed newly diagnosed GBM
  - Karnofsky score >= 60
  - No significant comorbidities or prior/concurrent antitumor therapy
  - No Contraindications for Hyperbaric Oxygen Treatment

Clinical Protocol

- Temozolomide 75mg/m2/day for 42 consecutive days
- Radiotherapy over 30 days for total dose of 6000cGy in (30) 200cGy fractions
- Hyperbaric Oxygen at 3.0 ATA prior to each session of radiotherapy
- No more than 15 minute delay from exiting chamber to receiving radiation

Study Population Demographics

- 32 Patients enrolled beginning 6/2009
- 19 Male
- 13 Female
- Age Range 28-80
- Mean Age 62.5
- 25/32 completed HCRT
- 23 subjects evaluated

23 Evaluable patients

- Median survival 14.9 months
- Longest survival time to date 31.9 months
- 12 month survival=82.6%
- 18 month survival=43.4%
- 24 month survivial=34.8%

Adverse Events

- 4 patients had otic barotrauma
- 2 patients had focal seizure activity during HBO
- One unexpected death

Conclusions

- Hyperbaric therapy in conjunction with radiation and chemotherapy is well tolerated without significant increased risk to adults with glioblastomas over current standard of care. Due to the small sample size of this study larger randomized trials are needed.

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