Collection of Recorded Radiotherapy Seminars

http://humanhealth.iaea.org
Oxygen effect and Reoxygenation

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Overview

• Radiolysis of water
• Oxygen effect
• Hypoxia in tumours
• Reoxygenation
• Overcoming hypoxia
Radiation interaction with Cells

• Ionizing radiation cause cell death by interacting and damaging DNA

• The effects of radiation on DNA may be:
  – Direct
  – Indirect

• In indirect interaction, x-rays act via radical intermediaries
  – 80% of reactions are indirect
Radiolysis of water

- Photons cause ionization by ejecting electrons from matter.
- Interaction with water cause formation of ions
Interaction Ions / radicals with Oxygen

- Certain reactions during radiolysis of water occurs only in the presence of oxygen

\[
\begin{align*}
H^+ + O_2 & \rightarrow HO_2^* \\
HO_2^* + HO_2^* & \rightarrow H_2O_2 + O_2 \\
H^+ + HO_2^* & \rightarrow H_2O_2 \\
e_{aq}^- + O_2 & \rightarrow O^2^- + H_2O \rightarrow HO_2^* + HO^- 
\end{align*}
\]

- Hydroxyl radicals have a longer lifespan and can diffuse further compared to ion radicals
Process of Radiotherapy

X-rays
  ↓
Free electrons
  ↓
Ion Pairs
  ↓
Free Radicals
  ↓
DNA damage

Life span $10^{-10}s$

Life span $10^{-5}s$
Oxygen Fixation Hypothesis

- **Oxygen fixes** (makes permanent) the damage produced by free radicals.
  - Interacts with damaged DNA and cause peroxidation
  - In the absence of oxygen, damage produced by the indirect action may be repaired.

\[
\begin{align*}
R^\ast + O_2 & \rightarrow ROO^\ast \quad \text{(radical peroxide)} \\
ROO^\ast + R'H & \rightarrow ROOH + R' \quad \text{(hydroxyperoxide)} \\
ROO^\ast + R' & \rightarrow ROOR \quad \text{(peroxide)}
\end{align*}
\]

- Peroxides and hydroxyperoxides are toxic to cells
The Oxygen Effect

- Higher O2 level $\rightarrow$ higher radiosensitivity
- Hypoxic cells $\rightarrow$ radioresistant

- Hypoxic fraction: fraction of clonogenic cells which are hypoxic
  
  $\text{Hypoxic fraction} = \left( \frac{\text{SF air}}{\text{SF anoxic}} \right)$

Cell Survival with radiation in Oxic and anoxic condition
The Oxygen Effect

• Calculating the hypoxic fraction
  \[
  \text{Hypoxic fraction} = \frac{\text{SF}_{\text{air}}}{\text{SF}_{\text{anoxic}}}
  \]
  \[
  \text{Eg.} = \frac{10^{-2}}{10^{-1}} = 10^{-1}
  \]

• Tumours may have high hypoxic fraction (0 - 50%)
  — but average of 15%)

• Normal tissues – well oxygenated (some not so)
Oxygen Enhancement Ratio

- The presence of oxygen dramatically influences the biologic effect of X-rays.
- Oxygen enhancement ratio (OER): The ratio of doses without and with oxygen to produce the same biological effect.
- \[ \text{OER} = \frac{\text{Dose in hypoxia}}{\text{Dose in air}} \]
- Oxygen effect occurs only if \( O_2 \) is present during irradiation or a few msec thereafter.
Oxygen Enhancement ratio (2)

- As a reference, OER under anoxic condition is 1.0

- $\uparrow [O_2] \rightarrow \uparrow$ radiosensitivity $\rightarrow \uparrow$ OER

- OER for x-rays is $\sim 3.0$ for most cells

- OER also depends on LET values
  - As LET increases, OER decreases

\[ \uparrow \text{LET} \quad \rightarrow \quad \downarrow \text{OER} \]
• As LET increases, OER reduces.
• OER values
  - X-rays / electrons = 3
  - Neutrons = 1.6
  - Heavy particles = 1 eg alpha particles, carbon ions
Oxygen and cell survival

Survival of Chinese Hamster cells after irradiation at various oxygen concentration

Adapted From Hall 2009
OER and Oxygen pressure

- Relationship between OER and paO₂ is shown by the curve:
  - Curve starts at OER=1.0 (hypoxic condition)
  - Biggest change within pO₂ of 0 – 20 mmHg
  - Near plateau at 30 mmHg
  - Slight but definite increase thereafter even till 100% O₂ (760mmHg)
Hypoxia in tumours

• Tumour growth constantly outstrips its blood supply
  – Growth of solid tumour requires induction of a blood supply - angiogenesis

• The blood supply of spherical tumours are on the outside, oxygen diffuses into the tumour

• The distance oxygen is able to diffuse depends on
  – Partial pressure of $O_2$ in blood
  – Metabolism of oxygen by cells
Hypoxia in tumours

- Central necrosis, with surrounding shell of hypoxic but viable tissues ~ 100 - 180μm: similar to diffusion distance of O₂ in respiring tissues
  - The rim of viable tumour remains the same with increasing tumour size
Development of hypoxia in growing tumors (subcutaneous xenograft)

Hendriksen et al, 2009
First demonstration of hypoxic cells in a tumor: 
~1.5% of the cells were hypoxic

Mouse lymphosarcoma irradiated in vivo
(Powers and Tolmach, 1973)
Tumour microenvironment

- Tumour nodules have 3 rims of cells:
  - Outer rim – well oxygenated
  - Middle - Hypoxic cells
  - Inner - necrotic cells

- There are 2 types of oxygen deprivation in tumours
  - Chronic hypoxia
  - Acute Hypoxia

Modified from Radiobiology for Radiologists 6th Ed Hall E
Chronic Hypoxia

- Is due to limitation of diffusion
- Each patent blood vessel – surrounded by cord of viable oxygenated cells
- Further away from $O_2$ - carrying blood vessels → chronically hypoxic cells at

Modified from Radiobiology for Radiologists 6th Ed Hall E
Chronic Hypoxia (2)

• Delivery of oxygen from blood vessels to tissue is limited by diffusing capacity through tissue.

• This depends on
  – Partial pressure of oxygen in the blood stream
  – Distance of tissue from blood vessel
  – Utilisation of oxygen by cells

• Chronic hypoxia is known as Diffusion Limited Hypoxia
Acute Hypoxia

- Tumours induce angiogenesis as they grow and become hypoxic
- These de-novo vessels are different from normal arteries, veins, and capillaries.
  - Blood flow through these vessels are variable
- Perfusion of blood may be reduced by
  - Plugging of vessels by circulating blood cells or tumour cells
  - Collapse of vessels in regions of high interstitial oncotic pressure
  - Spontaneous vasoconstriction
- Acute hypoxia is not predictable
  - Different regions show hypoxia at different time points.
Evidence for acute hypoxia

- Use hypoxia markers with different colours
  - Pimonidazole (green) & CCI-103F (red)
- Inject sequentially
  - Hypoxic cells stain green with first injection
  - Hypoxic cells stain red with second injection
- If the same cells are hypoxic throughout, they will take both red and green stains and appear yellow

From Basic Clinical Radiobiology 4th Ed
Differences in tumour and normal tissue vasculature

- Increased vessel tortuosity and variable vessel diameter
- Poorly developed and fragile vessel walls
- Variable flow rates leading to micro-regional tumour hypoxia
- Increased interstitial pressure within tumour
- Increased vessel permeability
- Poor connections between pericytes and endothelial cells
- Irregularly shaped endothelial cells and basement membrane
- Lack of lymphatic drainage
- Lack of vascular smooth muscle
Acute vs Chronic Hypoxia

Figure 15.5 Representation of diffusion-limited chronic hypoxia and perfusion-limited acute hypoxia within tumour cords. From Horsman (1998), with permission.
Hypoxia in human tumours

• Difficult to measure hypoxia level in human tumours
• Usually estimated by indirect approaches, by measuring:-
  – Tumour vascularization
    • Vascular density etc.
  – Hb-O₂ saturation
    • MRI Spectroscopy measuring deoxy-haemoglobin
  – Tumour metabolic activity
    • PET etc with 18F-MISO
  – DNA damage
    • Comet assay etc
  – Hypoxic markers
    • IHC or radioactive markers
  – Tumour O₂ partial pressure (pO₂)
    • Oxygen electrodes (esp. Eppendorf)
Clinical evidence of hypoxia in human tumours

On Head & Neck and Cervical cancers

- Direct measurement of tumour pO$_2$ using microelectrodes: poorer pO$_2$ → poorer local tumour control
- Indirect indicator of Hb levels: below 10g/dl → poorer local control
- Hypoxia induces/upregulates many types of genes/proteins – eg. HIF-1, VEGF → influences malignant progression and drug sensitivity (apart from radiosensitivity) → poorer prognosis tumour and chemoresistance
How hypoxic are tumours?

- The proportion of hypoxic cells vary in tumours
- Squamous cell cancers esp of H&N and cervix have high hypoxic fraction
- Measurements of cervical tumours indicate the hypoxic fraction may be as much as 100%

From Basic Clinical Radiobiology 4th Ed
Molecules in tumour hypoxia - HIF

- HIF = Hypoxia-Inducible Factor
- Is a transcription factor
- HIF-1 & HIF-2
  - subunits $\alpha$ & $\beta$
    - HIF-1$\alpha$ & HIF-2$\alpha$
    - HIF-1$\beta$

- **HIF-1$\alpha$ & HIF-2$\alpha$**
  - Levels vary in cells
  - In presence of oxygen, are hydroxlated
    - These protein are then identified for degradation by VHL protein
  - Hypoxia prevent VHL binding leading to increased expression of HIF1 leading to translation of proteins
Control of HIF Protein

• With hypoxia, HIF \( \alpha \) is not degraded

• Binds to HIF- \( \beta \) and acts as transcription factor

• Promotes transcription of many genes
  – Metabolism  - GLUT1-3
  – Angiogenesis  - VEGF
  – Metastases  - CA9
Molecules in tumour hypoxia

• Glucose transporters
  – GLUT 1 -3
  – Hypoxia leads to glycolysis increasing need for glucose.
  – Leads to over-expression of glucose transporters
Molecules in tumour hypoxia

- **uPA (urokinase plasminogen activator)**
  - Catalyse serum plasminogen into plasmin
  - Inhibited by PA-1 and PA-2
  - Poorer prognosis in uPA and Pa-1 positive tumours
  - Approved as marker in breast cancer by ASCO

- **uPA / PAI-1** measured by ELISAs on a minimum of 300 mg of fresh or frozen breast cancer tissue may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer.
Reoxygenation

- Following radiation, the radiosensitive aerobic cells will die; the hypoxic radioresistant cells will tend to survive.
- Hypoxic fraction increases (though number of surviving cells is low).

![Graph showing the life history of a tumour with reoxygenation and irradiation events.](image-url)
Reoxygenation

• The hypoxic cells then become better oxygenated (their oxygen supply improves) and the hypoxic fraction drops
• Rate of reoxygenation is variable
  – Thought to be 24 – 48 hours
Tumours consist of oxic and hypoxic cells.
X-ray preferentially kill oxic cells and therefore the proportion of hypoxic cells increases.
With reoxygenation, the proportion of oxic : hypoxic cell reach equilibrium again.
# Reoxygenation

<table>
<thead>
<tr>
<th>Mechanisms of tumour reoxygenation</th>
<th>Time-scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recirculation through temporarily closed vessels</td>
<td>minutes</td>
</tr>
<tr>
<td>Reduced respiration rate in damaged cells</td>
<td>min to hours</td>
</tr>
<tr>
<td>Ischemic death of cells</td>
<td>hours</td>
</tr>
<tr>
<td>Mitotic death of irradiated cells</td>
<td>hours</td>
</tr>
<tr>
<td>Cord shrinkage as dead cells are resorbed</td>
<td>days</td>
</tr>
</tbody>
</table>
If no reoxygenation

- Without reoxygenation, the proportion of hypoxic tumour cells will increase as the oxic cells are preferentially killed by radiation.
- By 6 fractions, the tumour will be dominated by hypoxic cells.
Without reoxygenation, survival of hypoxic cells exceeds survival of oxic cells after just four 2 Gy fractions.
Improving oxygenation improves survival

Tumor oxygenation and locoregional tumor control in Head & Neck

Eppendorf $pO_2$ Histogram, stratified by the median (22%) HP$_{2.5}$

Hypothesis generated

Hypothesis tested

Nordsmark & Overgaard et al 2000
Overcoming tumour radioresistance due to hypoxia

Strategies (tested/undergoing clinical trials):

1. Increase $O_2$ availability
   - Breathe high $O_2$ (hyperbaric oxygen)
   - Carbogen
   - Increase $O_2$-carrying capacity
     • eg. perfluorochemical emulsions, stop smoking
   - Modifying Hb
     • eg. blood transfusion, EPO (under trial)
   - Improve blood flow (overcome acute hypoxia)
     • eg. Nicotinamide
Hyperbaric oxygen

• Hemoglobin is fully oxygenised under normal condition
  – Hyperbaric oxygen increased plasma \([\text{O}_2]\)

• Use \(\text{O}_2\) up to 3 atm. highest without anest
Hyperbaric oxygen

- Result of MRC randomised trial comparing Stage III cervical cancer treated with Hyperbaric Oxygen (HBO)

Hyperbaric oxygen

• Issues
  – Uncertainty if dissolve O$_2$ reaches tumour due to poor perfusion + vasoconstriction by increased O$_2$ tension
  – Sensitization of hypoxic normal tissue eg cartilage
  – Convulsions due to oxygen
  – High pressure complications to lungs and ears
  – Danger of explosion
  – Difficulty in beam alignment

Carbogen breathing

- Breathing pure oxygen leads to vasoconstriction

- Carbogen is 95% oxygen and 5% carbon dioxide

- \( \text{CO}_2 \) acts as vasodilator
  - Adding \( \text{CO}_2 \) improves perfusion
  - Higher concentrations of \( \text{CO}_2 \) is toxic

Figure 2. Effects of Inhalation of carbogen shown by a double hypoxia-marker technique. The two markers were injected in mice bearing a xenografted human squamous-cell carcinoma (SCCN)[3]. CCI-103F was injected under ambient conditions followed 2 h later by pimonidazole injection while the animal was inhaling carbogen. Consecutive sections of the tumour were stained by immunofluorescence and scanned on an automated image analysis system, yielding composite binary images of the complete tumour section. (a) Blood vessels (9F1, red) and hypoxic areas before carbogen breathing as identified by CCI-103F (green). (b) Blood vessels and residual hypoxia (pimonidazole, green) under inhalation of carbogen. The areas with hypoxic-marker binding are reduced as a result of greater oxygen diffusion distance. N, necrosis.
Effect on tumour oxygenation of methods of increasing oxygen delivery

![Graph showing effect of different methods on tumour oxygenation](image-url)
Carbogen and $pO_2$ in GBM and Ca larvnx

It takes several minutes of carbogen breathing before there is increase in $pO_2$.

Figure 4. Continuous $pO_2$ measurements by use of a fibreoptic probe with luminescence-based optical $O_2$ sensor. Measurements in two human tumours xenografted in nude mice during inhalation of carbogen: squamous-cell carcinoma of the larynx (red) and glioblastoma (blue). Triangle indicates start of carbogen breathing. Several minutes are required before highest $pO_2$ values are reached. After 1 h of inhalation of carbogen, there is a decrease in tumour oxygenation.
ARCON – Accelerated Radiotherapy with Carbogen and Nicotinamide

- **Rationale**
  - Acceleration to prevent repopulation
  - Hyperfractionation to reduce normal tissue damage
  - Carbogen to overcome chronic hypoxia
  - Nicotinamide as vasodilator to overcome acute hypoxia

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**Figure 6.** Kaplan-Meier estimates for rates of local control of bladder carcinomas after treatment with ARCON or ARCO (accelerated radiotherapy with only carbogen). Comparison with previous British trials of radiotherapy with the hypoxic sensitizer misonidazole and radiotherapy in hyperbaric oxygen.
Local control with ARCON

- Patients with advanced squamous carcinomas of H&N were put on ARCON therapy
- Good local control was reported for advanced disease

Table 3. Three-year actuarial local and regional control rates by site and T and N-stage

<table>
<thead>
<tr>
<th>Site</th>
<th>T-stage</th>
<th>Local control (%)</th>
<th>N-stage</th>
<th>Regional control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td>T1</td>
<td>2/3*</td>
<td>N0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>80</td>
<td>N1</td>
<td>100</td>
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<tr>
<td></td>
<td>T3</td>
<td>79</td>
<td>N2</td>
<td>84</td>
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<tr>
<td></td>
<td>T4</td>
<td>84</td>
<td>N3</td>
<td>0.1*</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>80</td>
<td>all</td>
<td>95</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>T1</td>
<td>2/2*</td>
<td>N0</td>
<td>8/8*</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>72</td>
<td>N1</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>7.9*</td>
<td>N2</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>54</td>
<td>N3</td>
<td>1/1*</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>69</td>
<td>all</td>
<td>72</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>T1</td>
<td>1/1*</td>
<td>N0</td>
<td>5/5*</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>6/7*</td>
<td>N1</td>
<td>86</td>
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<tr>
<td></td>
<td>T3</td>
<td>100</td>
<td>N2</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>75</td>
<td>N3</td>
<td>1/3*</td>
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<tr>
<td></td>
<td>All</td>
<td>88</td>
<td>all</td>
<td>85</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>T1</td>
<td>—</td>
<td>N0</td>
<td>3/3*</td>
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<td>—</td>
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</tr>
<tr>
<td></td>
<td>T4</td>
<td>29</td>
<td>N3</td>
<td>—</td>
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<tr>
<td></td>
<td>All</td>
<td>37</td>
<td>all</td>
<td>68</td>
</tr>
</tbody>
</table>

* Absolute rates; actuarial values not calculated because of low patient numbers.
ARCON therapy
Blood transfusion and survival

- Easiest to correct low Hb by transfusion
- Should improve Hb level and oxygen delivery

Hemoglobin level during RT

**Females**

**Males**

![Graph showing hemoglobin levels over weeks from RT start for females and males with transfusion and no transfusion ranges.]
Survival in H&N cancer with blood transfusions

Locoregional control

- High vs Low -t p=0.03
- Low -t vs Low +t p=0.9
- Low all vs High p=0.01
- 44% High
- 38% Low +t
- 35% Low -t

Overall survival

- High vs Low -t p=0.01
- Low -t vs Low +t p=0.6
- Low all vs High p=0.0005
- 39% High
- 29% Low -t
- 26% Low +t
Maybe Erythropoietin Better?

Forest plot of comparison: EPO plus RT versus RT alone, outcome: overall survival (proportion alive at end of study period).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RT + EPO</th>
<th>RT</th>
<th>Total</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
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<tr>
<td>Henke 2003</td>
<td>71/180</td>
<td>82</td>
<td>171</td>
<td>27.5%</td>
<td>0.71 [0.46, 1.08]</td>
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<tr>
<td>Hoskin 2004</td>
<td>122/151</td>
<td>127</td>
<td>149</td>
<td>13.5%</td>
<td>0.73 [0.40, 1.33]</td>
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<tr>
<td>Machray 2007</td>
<td>37/72</td>
<td>37</td>
<td>69</td>
<td>11.3%</td>
<td>0.91 [0.47, 1.77]</td>
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<tr>
<td>Overgaard 2007</td>
<td>97/255</td>
<td>133</td>
<td>260</td>
<td>40.5%</td>
<td>0.59 [0.42, 0.83]</td>
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<tr>
<td>Rosen 2003</td>
<td>28/47</td>
<td>19</td>
<td>43</td>
<td>7.2%</td>
<td>1.84 [0.81, 4.19]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>705/398</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.73 [0.58, 0.91]</td>
</tr>
<tr>
<td>Total events</td>
<td>355</td>
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<td>398</td>
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<tr>
<td>Heterogeneity: Chi² = 6.79, df = 4 (P = 0.15); I² = 41%</td>
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<tr>
<td>Test for overall effect: Z = 2.82 (P = 0.005)</td>
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</table>

1.1.2 Without studies supplementing iron to intervention group only

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>RT</th>
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<td>149</td>
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<tr>
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<td>133</td>
<td>260</td>
<td>49.7%</td>
<td>0.59 [0.42, 0.83]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>586/342</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.65 [0.51, 0.83]</td>
</tr>
<tr>
<td>Total events</td>
<td>290</td>
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<td>342</td>
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<tr>
<td>Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 3.46 (P = 0.0005)</td>
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<td></td>
</tr>
</tbody>
</table>

Lambin P et al Cochrane review 2009
Overcoming radioresistance due to hypoxia (2)

Strategies (tested/undergoing clinical trials):

1. Radiosensitizing the hypoxic cells
   – Drugs eg. metronidazole, misonidazole (potent but neurotoxic), nimorazole
     • Hypoxic cell radiosensitizers mimic O₂
       – (electron affinic, ‘fixes’ the free radicals)
     • DAHANCA 2, DAHANCA 5 trials – nimorazole is standard in RT for H&N Ca in Denmark
   – Hyperthermia
     • Sensitizer Enhancement Ratio (SER)
Nimorazole in H&N Cancer

- Conventional RT with or without Nimorazole as radiation sensitizer

Fig. 4. Actuarial estimated loco-regional tumor control in patients randomized to receive nimorazole or placebo in conjunction with conventional radiotherapy for carcinoma of the pharynx and supraglottic larynx.

Overgaard J et al Radiotherapy and Oncology 46 (1998) 135–146
Overcoming radioresistance due to hypoxia (3)

Strategies (tested/undergoing clinical trials):

1. Preferential hypoxic cell killing
   - Bioreductive drugs eg. mitomycin C, tirapazamine
   - Hyperthermia
     • More toxic to hypoxic compared to oxic cells

2. Targeting tumour vasculature
   - antiangiogenic drugs, etc.

3. High LET radiation
   - No difference in cell kill between hypoxic and non-hypoxic cells
Targeting tumour vasculature

• Disrupting tumour vasculature sounds counter productive
  – Tumours become more hypoxic when blood vessels are damaged.

• However by hypoxic necrosis, tumours become smaller and with reoxygenation may become more radiosensitive

• Inhibitors of tumour vessels include
  – VEGF inhibitors eg bevacizumab
  – TKI eg sorafenib, Sunitinib
Vascular Disrupting Agents

• Flavinoids
  – Act by causing partial dissolution of actin cytoskeleton, resulting in DNA strand breaks and endothelial cell apoptosis

• Tubulin-binding agents.
  – act by binding to a different site on the tubulin molecule causing subsequent tubulin depolymerisation and disorganisation of actin and tubulin
  – subsequent change in endothelial shape leads to vessel blockage, reduced blood flow and disruption of the endothelial cell layer
## Meta Analysis - Hypoxic modification of radiotherapy in head and neck cancer

**Endpoint: Loco-regional tumor control**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events / Total</th>
<th>Hypoxic modification</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1970 Evans 1</td>
<td>O2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1975 Evans 2</td>
<td>O2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1979 RTOG 7002</td>
<td>Carbogen</td>
</tr>
<tr>
<td></td>
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<td>2005 Mendelhall</td>
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### Hypoxic sensitizers

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### Odds ratio and 95% CI

- **Normobaric oxygen**
  - OR: 0.72 [0.54-0.97]
  - OR: 0.47 [0.34-0.64]
- **Hyperbaric oxygen**
  - OR: 0.77 [0.67-0.88]
  - OR: 0.73 [0.66-0.82]

Survival and Hypoxia

- Studies have shown that survival of patients with hypoxic tumours are poorer.
- Graph shows survival of 47 patients with cervical cancer treated with radiotherapy.
- This would be “expected” as hypoxic cells are radioresistant.
- Therefore surgery may be a better option for these patients.
Surgery and Hypoxia

- Later studies showed that even with surgery, patients with hypoxic tumours have poorer survival.
- Graph shows survival of patients with ovarian cancer after surgery according to expression of HIF protein.
- Why should this be?
Hypoxia as a prognostic factor

• Hypoxic tumour have adapted to their environment
  – May undergone gene / protein alteration to adapt
  – Mutations in genes regulating apoptosis
  – Selection to resist hypoxic stress may also confer resistant to other stresses eg drugs

• Hypoxia increases genetic instability
  – Increase mutation rate, selection of “stronger” clones
Summary

• X-rays cause DNA damage mostly by indirect action through radiolysis of water
• Oxygen acts to “fix” repairable radiation damage to make it permanent and unrepairable
• Tumour may be hypoxic due to limitation of diffusion or disrupted blood flow
• The Oxygen Enhancement Ratio (OER) is about 3 for low LET radiation
• No oxygen effect is seen with high LET radiation.
• Oxygen needs to be present during or soon after radiation for its effect
Summary

- Hypoxia in tumours is important
  - Promotes radiation resistance
  - Promotes malignant progression
  - May be a bad prognostic factor independent of intervention
- Hypoxia may be modulated by several methods
  - Some of the methods may bring 10-15% survival advantage
  - At present, there is no universally accepted method of overcoming hypoxia in tumours