Tumor hypoxia: an obstacle for the radiooncologist

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Influence of tumor hypoxia on radiation therapy

early evidence

1909 Radiation response of skin is markedly decreased if blood flow to the irradiated area is reduced by compression (Schwarz 1909)

1910 Radiation response is more prominent when blood flow is elevated by diathermia (Müller 1910)

1953 The role of oxygen deficiency is described as a major source of radiation resistance in the experimental setting (Gray et al. 1953)
Influence of tumor hypoxia on radiation therapy

**in vitro evidence**

Survival curve illustrating the radiation dose-modifying effect of oxygen.

**OER = oxygen enhancement ratio**

Survival fraction vs. Radiation dose (Gy)
Influence of tumor hypoxia on radiation therapy
Evidence in the clinical setting - 1

• Patients with poorly vascularized tumor show poorer outcome (Horsman 1993, 1998)

• Poorer local control probability in smokers (HbCO!) with advanced head and neck carcinoma (Grau and Overgaard 1997)
Influence of tumor hypoxia on radiation therapy

Evidence in the clinical setting - 2

- Direct measurements with polarographic electrodes show that patients with hypoxic cervix cancers have a poor prognosis.

- Exogenous marker to identify tumor hypoxia (e.g., pimo) are associated with poor outcome after radiation therapy in H&N cancer (Bussink 2003)

Approaches to overcome hypoxia as a source of treatment resistance

1. Reducing hypoxia by increasing oxygen availability
2. Reducing hypoxia by improving tumor blood supply
3. Radiosensitizing hypoxic cells
4. Killing the resistant cell population
   - by drugs
   - by higher dose
(1) Reducing hypoxia by increasing oxygen availability

- **Increase in microvessel O2 content**
  - Normobaric (100% O2, carbogen) or hyperbaric hyperoxia (HBO)
  - Anemia correction (RBC transfusion, rhEPO)
  - Reduction in [HbCO]
  - Modification of O2-hemoglobin affinity
  - Use of artificial O2 carriers (e.g., perfluorocarbons, stroma-free Hb)

- **Decrease in cellular respiration rate**
  - Hypothermia
  - Inhibition of respiratory chain (e.g., Ca-channel blockers)
  - Inhibition of lipid biosynthesis (e.g., lovastatin)
  - Acute hyperglycemia (Crabtree effect)

nach Vaupel et al., IJROBP 1998 (42):843
(2) Reducing hypoxia by improving tumor blood supply

- **Improvement in microcirculation**
  - Vasoactive drugs (e.g. nicotinamide)
  - Modifiers of blood viscosity (rheologically active drugs)
  - Hemodilution (isovolemic, normovolemic)
  - Low-dose hyperthermia
  - Lowering of elevated interstitial fluid pressure

nach Vaupel et al., IJROBP 1998 (42):843
(3) Radiosensitizing hypoxic cells

Radiosensitizer:

- are able to mimic oxygen
- are not metabolized by tumor cells resulting in a higher diffusion distance
- do not increase radiation response of well oxygenated cells / normal tissue as they mimic oxygen

**Examples:** Nitrobenzenes, Nitrofurans, Nitroimidazoles (misonidazole, metronidazole, etanidazole, pimonidazole, doranidazole, nimorazole), Nitrotriazole
Radiosensitizing hypoxic cells

DAHANCA 5 - trial

![Graphs showing loco-regional control and disease-specific survival.]

**Loco-regional control (%)**
- Nimorazole (219 pts) - 49%
- Placebo (195 pts) - 33%

**Disease-specific survival (%)**
- Nimorazole (219 pts) - 52%
- Placebo (195 pts) - 41%

**P-values:**
- Loco-regional control: P=0.002
- Disease-specific survival: P=0.01

**carcinoma of the pharynx and supraglottic larynx**

Overgaard et al. 1998
(4) Killing the resistant cell population by application of higher doses
Maximizing dose to hypoxic subvolume „Dose Painting“

• How to define the hypoxic subvolume?
Definition of the hypoxic volume in “Hypoxia-PET”

• Visually
• Threshold (tumor/background-ratio, tumor/muscle-ratio)
• Dynamic PET-scan (modeling time-activity curves)
Influence of changes in tumor hypoxia on dose-painting treatment plans based on 18F-FMISO PET

<table>
<thead>
<tr>
<th>CT</th>
<th>FMISO 1</th>
<th>FMISO 2</th>
<th>correlation</th>
<th>IMRT</th>
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<td><img src="image8" alt="FMISO 2" /></td>
<td><img src="image9" alt="Tumor/blood ratio of 1.3" /></td>
<td><img src="image10" alt="Lin et al. Int J Rad Onc 2008" /></td>
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</table>
Kinetic modelling for hypoxia

1. **Two-tissue compartment model**
   - a) Reversible model
   - b) Irreversible model

2. **Graphical model**
   - a) Patlak plot
   - b) Logan plot

3. **Thorwarth model** [PMB 2006]

4. **Cho model** [Neoplasia 2009]
Quantitative Assessment of Hypoxia Kinetic models

Principle of 18F-FMISO PET Image Evaluation

18F-FMISO images
Model Assessment by Simulation in Digital Phantoms

Shi et al. 2010

Blood input function

Steps of Simulation
- Physical (Transport)
- Chemical (Transform)
- Physiological (Metabolism)

Assessment

Modeling

Digital Tissue Oxygenation Phantom
(calculated according to Dasu 2003)
Evaluation of Different Kinetic Models

Shi et al. 2010

- Poor perfusion
  - Vascular density: 26 mm²
  - Mean pO₂: 1.36 mmHg
  - Phantom 1

- Moderate perfusion
  - Vascular density: 72 mm²
  - Mean pO₂: 7.36 mmHg
  - Phantom 2

- Good perfusion
  - Vascular density: 164 mm²
  - Mean pO₂: 16.90 mmHg
  - Phantom n

TAC 1
- Activity (Bq/mL)
- Time (s)

TAC 2
- Activity (Bq/mL)
- Time (s)

TAC n
- Activity (Bq/mL)
- Time (s)

Sensitivity Test: Spearman correlation

- Reversible two-compartment
- Irreversible two-compartment
- Thawar
- Patlak
- Logan
- Cho

18F-Fmiso delivery

18F-Fmiso accumulation

Vascular delivery

pO₂
Varying Vascular Density and Hypoxia Distribution by generating 277 Digital Phantoms

Shi et al. 2010

Reversible two-compartment

Irreversible two-compartment

Thorwarth

Patlak

Logan

Cho

Expectation: monotonic inverse correlation
Model Assessment Results  Shi et al. 2010

**pO$_2$ sensitivity**

- Spearman correlation
- Without noise
- With noise

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<th>Cho</th>
<th>Patlak</th>
<th>Logan</th>
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<td>Without noise</td>
<td>-0.5</td>
<td>-0.4</td>
<td>-0.6</td>
<td>-0.8</td>
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<tr>
<td>With noise</td>
<td>-0.4</td>
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<td>-0.5</td>
<td>-0.7</td>
<td>-0.5</td>
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**Vascular density sensitivity**

- Spearman correlation
- Without noise
- With noise

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<tr>
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<td>0.8</td>
<td>1.0</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>With noise</td>
<td>0.7</td>
<td>0.9</td>
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<td>0.7</td>
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Summary

• Evidence for the negative role of tumor hypoxia in radiation therapy

• Approaches to overcome hypoxia in clinical routine were not convincing

• Modern techniques allow to apply higher doses to tumor subvolumes

• Problems:
  How to assess 3-D-images of hypoxia?
  Which subtypes are relevant (chronic/acute)?
  How to account for changes over time?
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