Biological basis of radiotherapy:
Where do we stand?
Where do we stand?

“I strongly believe that we have not understood the reason for the success of radiotherapy and chemotherapy in treating solid tumours. We have in the text books an abundance of information about [...].”

Juliana Denekamp, Umeå, 2001
Milestones in radiobiology

- 1903 - Radiosensitivity related to mitotic activity
- 1923 - Observation of the oxygen effect
- 1928 - First report on fractionated treatment for human cancer
- 1930 - First survival curve for bacteria exposed to radiation
- 1940 - The LQ formalism for biologic response to radiation
- 1940 - Introduction of the concept of LET
- 1944 - Relation between dose and overall time for skin reaction
- 1956 - The first *in vitro* radiation survival curve for mammalian cells
- 1959 - Repair demonstrated by split-dose experiment with mammalian cells
- 1960 - Survival curve shape change with linear energy transfer
- 1962 - First demonstration of the dose-rate effect in cells in vitro
- 1963 - First observation of variation of radiosensitivity through the cell cycle
- 1963 - Dependence of OER on LET
- 1969 - Accelerated repopulation shown in animal tumours
- 1972 - Discovery of apoptosis
- 1973 - Time course of proliferation in normal tissues following irradiation
- 1975 - First cancer patients treated with heavy ions at Berkeley
- 1976 - Suppressor genes described in cultured cells
- 1980 - Difference in survival curve shape for early and late-responding tissues
- 1980 - First repair gene in human cells
Milestones in radiobiology

• 1982 - Concept of biologically effective dose described
• 1982 - The first human oncogenes described
• 1985 - Estimation of the potential doubling time in patients from a single biopsy
• 1991 - First correlation of surviving fractions at 2 Gy and tumour control
• 1995 - ATM gene sequenced
• 1996 - p53 named as the molecule of the year - the guardian of the genome
• 1996 - A microarray with human genes was first used
• 1996 - Discovery that hypoxia modifies the malignant progression of tumour cells
• 1999 - First application of microarray to radiobiology
• 2000 - Draft sequence of the human genome completed
The response of the tumours to fractionation is described by the 4 Rs of radiobiology:

1. Repair of sublethal damage
2. Redistribution around the cell cycle
3. Repopulation after irradiation
4. Reoxygenation

5. Radiosensitivity (intrinsic)
Biological Effective Dose

$$BED = nd \left(1 + \frac{d}{\alpha/\beta}\right)$$

- BED is clinically used for calculating the isoeffectiveness of fractionated treatments

- Particular applications:
  - Comparisons of full treatments
  - Additions of different fractionations

$$BED_{final} = \sum BED_i$$
Hypoxic Radiosensitization: Adored and Ignored

Jens Overgaard

Abstract

Since observations from the beginning of the last century, it has become well established that

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional control</td>
<td>2,144</td>
<td>4,416</td>
<td>2,465</td>
<td>4,473</td>
</tr>
<tr>
<td>Survival</td>
<td>3,237</td>
<td>4,921</td>
<td>3,405</td>
<td>4,952</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>452</td>
<td>2,332</td>
<td>480</td>
<td>2,339</td>
</tr>
<tr>
<td>Complications</td>
<td>374</td>
<td>2,424</td>
<td>310</td>
<td>2,305</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypoxic modification Better</th>
<th>Odds ratio and 95% CI</th>
<th>Control Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional control</td>
<td>0.77</td>
<td>0.71 to 0.84</td>
</tr>
<tr>
<td>Survival</td>
<td>0.87</td>
<td>0.80 to 0.95</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0.93</td>
<td>0.81 to 1.07</td>
</tr>
<tr>
<td>Complications</td>
<td>1.17</td>
<td>1.00 to 1.38</td>
</tr>
</tbody>
</table>
Tumour hypoxia

Hypoxic Radiosensitization: Adored and Ignored

Jens Overgaard

Since observations from the beginning of the last century, it has become well established that their research application, continuously point toward the sparse clinical results achieved so far. Thus, with the substantial knowledge about hypoxic radioresistance and the means to overcome it, we have reached the point where the situation is almost schizophrenic; the increased research and preclinical interest deeply contrasts with the profession’s resistance toward having the simple drugs or other means implemented to a larger extent. It certainly stresses the fact that there is no strong scientific basis for progress...
Hypoxic Radiosensitization: Adored and Ignored

Jens Overgaard

From the Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark.

Table 2. Methods of Modification of Hypoxic Radioresistance in Clinical Trials

<table>
<thead>
<tr>
<th>Methods of Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased oxygen delivery by the blood</td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>Normobaric oxygen/carbogen breathing</td>
</tr>
<tr>
<td>Nicotinamide</td>
</tr>
<tr>
<td>Blood transfusion, erythropoietin</td>
</tr>
<tr>
<td>Mimic of oxygen in the radiochemical process</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
</tr>
<tr>
<td>Destruction of hypoxic cells</td>
</tr>
<tr>
<td>Hypoxic cytotoxins</td>
</tr>
<tr>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Elimination of OER</td>
</tr>
<tr>
<td>High LET</td>
</tr>
</tbody>
</table>

Abbreviations: OER, oxygen enhancement ratio; LET, linear energy transfer.
Examples of clinical trials focused on tumour and normal tissue response to fractionation:

1. EORTC 22791 – 80.5 Gy in 1.15 Gy/fx, 2 fx per day vs. 70 Gy in 2 Gy/fx
   - Hyperfractionation -> Improvement of locoregional control, no difference in late normal tissue damage

2. CHART – 54 Gy in 1.5 Gy/fx, 3 fx per day vs. 60 Gy in 2 Gy/fx
   - Hyperfractionation and accelerated treatment -> Significant improvement in survival but severe dysphagia in the test arm

3. ARCON – Accelerated radiotherapy with carbogen and nicotinamide vs. AR
   - Improvement of regional control in patients with hypoxic tumours and equal levels of toxicity

3. Swedish HYPOfractionated prostate trial – 42.7 Gy in 6.1 Gy/fx vs. 78 Gy in 2 Gy/fx
Physical optimisation:

- From a desired dose distribution calculate the physically optimised dose distribution based on beam energy, angles, and profiles

Biological optimisation:

- The dose distribution is optimised accounting for the biological characteristics of the target and the OARs
Basic requirements for the biological optimisation:

• Radiobiological models for tumour and normal tissue response

• Clinically relevant mathematical formulations of the objectives and constraints

• Optimisation algorithms
The probability of eradicating a tumour is given by:

\[ P = \exp(-N_0 \cdot SF) \]

- \( N_0 \) is either derived from the slope of the dose-response curve or is assumed to take values between \( 10^5 \)-\( 10^{10} \)/cm\(^3\).
What is the target of radiotherapy?

- What do we have to inactivate/kill/eradicate in the tumour?
- How many such targets do we have in a tumour?
- What do they represent?

☞ Is the TCP model too simplistic?
The probability of eradicating a tumour is given by:

\[ P = \exp(-N_0 \cdot SF) \]

\[ P = \exp(-N_0 \cdot \exp(-n \cdot (\alpha \cdot d + \beta \cdot d^2))) \]

\[ \alpha = \alpha(pO_2, LET, t, genetics, molecular profiles, etc.) \]

\[ \beta = \beta(pO_2, LET, t, genetics, molecular profiles, etc.) \]
TCP and the model for cell killing

- The probability of eradicating a tumour is given by:

\[ P = \exp(-N_0 \cdot SF) \]

\[ P = \exp(-N_0 \cdot \exp(-n \cdot (\alpha \cdot d + \beta \cdot d^2))) \]
• For high dose-rate fractionated treatments, the survival after \( n \) fractions of size \( d \) is:

\[
\ln[SF_n (d, \theta)] = -n(\alpha d + \beta d^2) - n\beta d^2 h_n (\theta)
\]

\[
h_n (\theta) = \frac{2\theta[n - (1 - \theta^n)]}{n(1 - \theta)^2}
\]
• For continuous, low dose-rate exposure, the survival after time $t$ at the given dose-rate is:

$$\ln \left[ SF\left( \dot{D}, t, \theta \right) \right] = -\alpha \left( \dot{D} t \right) - \beta \left( \dot{D} t \right)^2 \cdot g(\mu t)$$

$$g(\mu t) = 2 \frac{\mu t - 1 + \exp(-\mu t)}{(\mu t)^2}$$
LQ corrected for proliferation

- If $T_D$, the overall duration of the treatment, exceeds $T_k$, the kick-of time for accelerated repopulation:

$$BED = nd \left( 1 + \frac{d}{\alpha/\beta} \right) - \frac{(T_D - T_k)}{\alpha T_p} \ln 2$$

- $T_p$, the cell doubling time during treatment, is different from $T_{pot}$, i.e. the kinetic term measured before the start of the treatment.
Are the cell kinetics experiments considered to be obsolete these days?

Are the clonogenic cell survival experiments considered to be obsolete these days?

Very little data is currently published using these techniques…

What are the alternatives?
High dose per fraction – “New biology”

The technical development and the progress in functional imaging and dose delivery complemented by the positive clinical experience of treating lung and liver cancer patients as well as oligometastatic patients using lower number of fractions of high doses lead to the new trend in RT:

Personalised Stereotactic ABlative Radiotherapy

Is there a “new biology” to be considered at high doses per fraction?

- Radiation induced vascular injury
- Abscopal effect and radiation induced immune response
- Tumour microenvironment and hypoxia
- etc.
Normal tissue complication probability

Lyman-Kutcher-Burman Model:

- NTCP can be calculated based on some basic assumptions:
  - Volume dependence: power law relationship for the tolerance doses for different irradiated volumes
  - Dose dependence: described by an integral over a distribution giving a sigmoid-shaped dose response curve
  - A single step of a DVH represents the case of uniform irradiation of a subvolume

\[
NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{t^2}{2}\right) dt
\]

\[
t = \frac{D - D_{50}}{\gamma \cdot D_{50}} \quad D = \sum_i \left(\frac{v_i}{V} D_i^{1/n}\right)^n
\]

\(\gamma\) is the slope of the dose-response curve and \(n\) gives the volume dependence.
Adapting/Replanning

Pre-treatment imaging (morphological image/s)

Pre-treatment imaging (functional image/s)

FDG

FMISO hypoxia

Treatment planning

Dose delivery

On board image acquisition

Treatment evaluation

Functional imaging

Adapting/Replanning

Responsiveness evaluation
**FIGURE 1: Areas of Research Specialization**

<table>
<thead>
<tr>
<th>Area</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Microenvironment</td>
<td>18%</td>
</tr>
<tr>
<td>Normal Tissue</td>
<td>15%</td>
</tr>
<tr>
<td>Radiosensitizer</td>
<td>15%</td>
</tr>
<tr>
<td>Cell Cycle/Signaling</td>
<td>12%</td>
</tr>
<tr>
<td>Radiolmmuno Therapy</td>
<td>10%</td>
</tr>
<tr>
<td>Systemic Therapy-Targeted</td>
<td>5%</td>
</tr>
<tr>
<td>DNA Damage</td>
<td>5%</td>
</tr>
<tr>
<td>Carcinogenesis</td>
<td>3%</td>
</tr>
<tr>
<td>Cancer Stem Cells</td>
<td>3%</td>
</tr>
<tr>
<td>Biomarkers/Radiogenomics</td>
<td>3%</td>
</tr>
<tr>
<td>Immunology</td>
<td>3%</td>
</tr>
<tr>
<td>Radioprotectors</td>
<td>2%</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperthermia RT</td>
<td>1%</td>
</tr>
<tr>
<td>Protons</td>
<td>1%</td>
</tr>
<tr>
<td>Nanotherapeutics</td>
<td>1%</td>
</tr>
<tr>
<td>Radiochemistry</td>
<td>1%</td>
</tr>
</tbody>
</table>
Where do we stand and future research...

- The most funded subgroups are: radiosensitisers, normal tissue and tumour microenvironment.

  ⇒ Is this the way to go now in Radiobiology?

- Where do we stand now in Radiobiology?

  ⇒ On solid rock or quick sand?
Biological basis of radiotherapy:
Where do we stand?