Hypofractionation:
Biological rationale and clinical application

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Radiobiology is of great importance for radiotherapy.

It allows the optimization of a radiotherapy schedule for individual patients in regards to:

- Total dose and number of fractions
- Overall time of the radiotherapy course
- Tumour control probability (TCP) and normal tissue complication probability (NTCP)
The aim of radiotherapy is to kill tumour cells. (they may be in a bulk tumor, in draining lymph nodes and/or in small microscopic spread)

Tumour radiobiology is complex.

The response depends not only on dose but also on individual radiosensitivity, timing, fraction size, other agents given concurrently (e.g. chemotherapy).
Dose-Response relationship

Radiation dose-response curves have a sigmoid shape.
Local tumour control

The eradication of every clonogenic tumour cell must lead to tumour cure.

- Tumour (1 cm³) = $10^9$ cells !!!

- Large mass (1 kg) = $10^{12}$ cells - need three orders of magnitude more cell kill

- Microscopic tumour, micrometastasis = around $10^6$ cell - need less dose

Whiters RH et al - IJROBP - 2004
Survival of tumor stem cells after Radiotherapy

Table 1
Average number of surviving clonogenic tumour cells calculated using Poisson statistics for different tumour control probabilities in the “curative” dose range

<table>
<thead>
<tr>
<th>Tumour control probability</th>
<th>Surviving clonogenic cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>2.3</td>
</tr>
<tr>
<td>37%</td>
<td>1</td>
</tr>
<tr>
<td>50%</td>
<td>0.69</td>
</tr>
<tr>
<td>90%</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Krause, Radiother Oncol 2006
‘The name of the game’ : Therapeutic Ratio

The principle of radiotherapy is usually illustrated by plotting two sigmoid curves

- For tumour control probability (TCP)
- For normal tissue complication probability (NTCP)
The optimum choice of radiation dose delivery technique in the treatment of a given tumour is such that it maximizes the TCP and simultaneously minimizes the NTCP.
Sparing of normal tissues is essential for a good therapeutic outcome.

The radiobiology of normal tissues is complex:

- different organs respond differently
- there is a response of a cell organization not just of a single cell
- repair of damage is important
Tissue architecture

- **Serial organs**
  The organ behaves *like a chain*:
  if one link breaks chain breaks.

  A loss of function in one part equals a total loss of function.

- **Parallel organs**
  The organ behaves *like a rope*:
  if a fraction of strands breaks, the rope still holds if sufficiently many strands remain.

  A partial loss of function is tolerable.

Effect of radiation on the organs is different
Dose fractionation

- Early 1900’s: radiotherapy initially delivered in single/few fractions
  Increased toxicity, limited tumor control

- 1920-1930: experience in France with multiple fractions over longer duration in H&N cancer
  Less toxicity, increased tumor control

- Fractionation of radiation adopted based on empiric observation

- Before the era of randomized trials
The five “R”s of radiotherapy

The biological factors that influence the response of normal and neoplastic tissues to fractionated radiotherapy

- Repair
- Redistribution
- Repopulation
- Reoxygenation

Radiosensitivity

Withers HR (1975), Adv Radiat Biol 5:241-7
Radiosensitivity

Division of dose into multiple fractions spares normal tissues through repair of sublethal damage between dose fractions and repopulation of cells.

The repair of sublethal damage is greater for late responding tissues, the repopulation of cells is greater for early responding tissues.

Fractionation increases tumour damage through reoxygenation and redistribution of tumour cells.
Conventional fractionation

It is the application of daily doses of **1.8 - 2 Gy** and 5 fractions per week.

Total dose depends on:

- tumour histology,
- tumour size and localization,
- macroscopic/microscopic disease.

Fletcher GH (1988), Radiother Oncol 12: 253-71
Conventional fractionation
1.8 – 2.0 d/fx, 9-10 Gy per week (5 fractions/week)

Non-conventional/modified fractionation

Hyperfractionation: d/fx < 1.8 Gy
Hypofractionation: d/fx > 2 Gy
Protraction: < 9 – 10 Gy/ week
Acceleration: > 10 Gy per week
Hypofractionation…the first thing that comes to mind when considering large dose per fraction radiation treatment is the concern for “late effects”.

Hypofractionation radiation therapy has become of increasing interest with the recognition of a potential improvement in therapeutic ratio with treatment delivered in larger-sized fractions.

Cell survival curves

Cell surviving fractions are determined with in vitro or in vivo techniques. Several mathematical methods of varying degrees of complexity have been developed to define the shape of cell survival curves, all based on the concept of the random nature of energy deposition by radiation.
There are many models.

Based on clinical experience, cell experiments, or simply the beauty or simplicity of the mathematics.

One of the simplest and most used is the so-called "linear quadratic" or "alpha/beta" model developed and modified by Thames, Withers, Dale, Fowler, and many others.
The Linear-Quadratic Model

\[ P_{\text{survival}} = e^{-\alpha D - \beta D^2} \]
The response of different tissues or organs to radiation varies markedly, depending primarily on two factors:

- the inherent sensitivity of the individual cells
- the kinetics of the population.

There is a clear distinction in radiation response between tissues that are early responding (skin, mucosa and intestinal epithelium) and those that are late responding (spinal cord).
“Early” vs “late” responding tissues

![Graph showing surviving fraction vs dose for early and late responding tissues.](image)
The $\alpha$ and $\beta$ components of mammalian cell killing are equal at the following doses:

- **10 Gy** for early responding tissues
- **3 Gy** for late responding tissues
Response to radiation

The response to radiation of tumours and normal proliferative tissues (responsible for acute reactions) substantially differs from that of normal late-responding tissues.

The cell injury mechanism is largely regulated by coefficient $\alpha$ (lethal single-impact injury) in the former, whereas coefficient $\beta$ (lethal injury due to accumulation of sub-lethal injury) predominates in the latter.
“Fraction size is the dominant factor in determining late effects”

A large $\alpha/\beta$ ratio, typical of tumour control, means low sensitivity to changes in fractionation.

A small $\alpha/\beta$ ratio, typical of late sequelae, means large sensitivity to changes in fractionation.
Choise of Fractionation – Therapeutic Ratio

➢ If $\alpha / \beta$ ratio of tumor is the same or less than that of the critical normal tissue, then a larger dose per fraction (hypofractionation) is preferred.
i.e., prostate cancer, breast cancer

Brenner D., IJROBP 57: 912-914, 2003

➢ If $\alpha / \beta$ ratio of tumor is high (often 10 or greater) and $\alpha / \beta$ ratio of normal tissue (often < 5) a lower dose per fraction (hyperfractionation) is preferred.
i.e., squamous cancer of head and neck

Biologically Effective Dose (BED)

The L-Q model states that effect is given by:

$$ E = \alpha D + \beta D^2 $$

For \( n \) equal fractions, each of dose \( d \), with complete repair between fractions:

$$ E = n(\alpha d + \beta d^2) $$

The equation is rearranged to:

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

Dividing both sides of equation by \( \alpha \):

$$ \frac{E}{\alpha} = nd \times \left(1 + \frac{d}{\alpha / \beta}\right) = \text{BED} $$
Use of BED to calculate equivalent doses when changing fractionation

Comparison of equivalent regimens and determination of the isoeffective single dose in groups of tumours with similar kinetics ($\alpha/\beta$ ratio) is possible.

$$(nd/n_1 d_1) = (\alpha/\beta + d_1)/(\alpha/\beta + d)$$

- $n =$ standard number of fractions
- $n_1 =$ equivalent number of fractions in altered schedule
- $d =$ standard dose/fraction
- $d_1 =$ desired dose/fraction
Hypofractionated Radiotherapy in Prostate Cancer

Recent analyses and reviews of clinical tumour control data have argued for a low $\alpha/\beta$ ratio for prostate cancer on the order of 1 to 3 Gy.

Brenner D., IJROBP 43: 1095-1101, 1999
Duchesne GM., IJROBP 44: 747-748, 1999
Fowler J., IJROBP 50: 1021-1031, 2001
Brenner D., IJROBP 52: 6-13, 2002
Williams SG., IJROBP 68: 24-33, 2007
The Theoretical Potential for Hypofractionation to Improve Tumor Control

\[ \text{BED} = D \left(1 + \frac{d}{\alpha / \beta}\right) \]

Therapeutic ratio increases significantly with fraction size

How Best Can Hypofractionation Be Explored in a Clinical Setting?

Two approaches:

1) Normal tissue **de-escalation** of total dose while maintaining constant predicted tumour control.

2) Tumour biological **dose escalation** with constant predicted normal tissue late effects.

Normal tissue **de-escalation** of total dose

Assuming a tumour $\alpha/\beta$ of 1.5 and a late tissue $\alpha/\beta$ of 3 a schema of dose per fraction escalation can be proposed.

The late NTD is the cumulative dose adjusted to its equivalent dose if delivered in 2-Gy fractions to late-responding normal tissues.
Tumour biological “dose escalation”

The equivalent total dose normalized to 2-Gy fractions (NTD₂) increases substantially with hypofractionation, even as the actual total delivered dose decreases.
Hypofractionated Radiotherapy in Breast Cancer

Over the last several years, there has been renewed interest in the use of hypofractionation for whole-breast irradiation.

Research from the irradiation of the cell cultures suggests that certain carcinomas including breast cancer are associated with low $\alpha/\beta$ ratios supporting the idea that hypofractionation is likely to be effective.

Clinical Experience using Hypofractionated Radiation Schedules in Breast Cancer

Recent randomized trials have confirmed that hypofractionated whole-breast irradiation is equivalent to more conventional whole-breast irradiation with respect to local recurrence and cosmetic outcome.

Yarnold J., Radiother Oncol 75: 9-17, 2005
Owen JR, Lancet 7: 467-471, 2006
Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node negative breast cancer.

Node-Negative Post BCS 1234 patients

Standard Whole Breast Irradiation (SWBI)
50 Gy/25 fractions
612 patients

Accelerated Hypofractionated Whole Breast Irradiation (AHWBI)
42.5 Gy/16 fractions
622 patients

Whelan T., Breast Cancer 106: S6, 2007
Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node negative breast cancer.

### Local Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Standard Whole Breast Irradiation (SWBI)</th>
<th>Accelerated Hypofractionated Whole Breast Irradiation (AHWBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>3.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>10 years</td>
<td>6.7%</td>
<td>6.2%</td>
</tr>
</tbody>
</table>

No difference in Overall Survival

Whelan T., Breast Cancer 106: S6, 2007
Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node negative breast cancer.

Cosmetic Outcome by Time and Treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 years</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWBI</td>
<td>83% (604)</td>
<td>77% (496)</td>
<td>79% (423)</td>
<td>71% (216)</td>
</tr>
<tr>
<td>AHWBI</td>
<td>84% (616)</td>
<td>77% (518)</td>
<td>78% (448)</td>
<td>70% (235)</td>
</tr>
</tbody>
</table>

No difference in Cosmetic Outcome (% Excellent or Good)

Whelan T., Breast Cancer 106: S6, 2007
Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node negative breast cancer.

**RTOG/EORTC Late Radiation Morbidity by Time and Treatment**

<table>
<thead>
<tr>
<th></th>
<th>3 years</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWBI</td>
<td>2%</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>AHWBI</td>
<td>2%</td>
<td>3%</td>
<td>9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Subcutaneous fibrosis</strong></th>
<th>3 years</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWBI</td>
<td>5%</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>AHWBI</td>
<td>4%</td>
<td>5%</td>
<td>12%</td>
</tr>
</tbody>
</table>

No difference in late radiation morbidity (% grades 2-3)

Whelan T., Breast Cancer 106: S6, 2007
Hypofractionation for early breast cancer: First results of the UK standardisation of breast radiotherapy (START) trials.

Hypofractionated Radiotherapy in Breast Cancer

- Excellent local control
- No increase in long-term morbidity
- More convenient
- Less costly
Hypofractionated Radiotherapy in Breast Cancer - Research Implications

➢ FAST trial will evaluate 30 Gy/5 fractions (6 Gy) and 28.5 Gy/5 fractions (5.7 Gy).

➢ IMRT to deliver hypofractionation with concurrent boost.

➢ Partial Breast irradiation.
Clinical Experience using Hypofractionated Radiation Schedules in Breast Cancer

Partial Breast Irradiation (PBI) is the delivery of radiation to the surgical cavity plus 1- to 2-cm margin after breast-conserving surgery.

The rationale supporting PBI is that most local recurrences occur at the primary tumour site in the breast.

Numerous techniques have been developed including interstitial brachytherapy, 3-dimensional conformal treatment with external beam, and intraoperative treatment.
Hypofractionated Radiotherapy:

Conclusions

- The use of hypofractionation in the curative management of cancer has been tested before with not so ideal results. Of course, times have changed.

- Major changes in radiotherapy have followed a greater understanding of the biological effects of radiation on tumours and normal tissues.

- The $\alpha/\beta$ ratio is a measure of fractionation response.
Hypofractionated Radiotherapy: Conclusions

➢ Research from the irradiation of cell cultures suggests that certain carcinomas are associated with low $\alpha/\beta$ ratios, supporting the idea that hypofractionation is likely to be effective.

➢ The integration of technology including better machines, planning systems, and radiation quality have to great degree defined the implementation of hypofractionation.

➢ Long-term follow-up from prospective trials will be need to dispel controversy about the feasibility of hypofractionation.