Hypofractionation 1\textsuperscript{st} became possible in 1914

- It was not until 1914, with the development of the hot-cathode X-ray tube by William Coolidge, that high enough dose rates could be delivered in order to use high doses/fraction

- After this, there were two Schools of Thought about fractionation
  - *single fractions were essential*  
  - or  
  - *only with multiple fractions could you cure cancers without exceeding normal tissue tolerance*
The Single Fraction School

- They believed that fractionated treatments were inferior because they allowed cancer cells to proliferate during the course of treatment.
  - To overcome this would require higher doses to be delivered and these would not be tolerated by the normal tissues.
The Multiple Fractions School

- They believed radiobiological (animal) studies that seemed to indicate that, only with fractionation, could high enough doses be delivered to cancers for cure without exceeding normal tissue tolerance.

- It was not until 1932 when Coutard in Paris published his excellent results with fractionated therapy that the world realized that single fraction radiotherapy was a bad idea.

  *At least, then it was!*
Radiobiologically, why is fractionation so important?

Repair!
Repair: Single strand and double strand breaks

Single strand breaks (upper figure) are usually considered “repairable”

Double strand breaks (lower figure) are usually lethal (not “repairable”) if the breaks are close together, such as when caused by transit of a single high-LET charged particle (such as a slow electron), since an intact 2nd strand of the DNA molecule is needed for the repair enzymes to be able to copy the genetic information.
The effect of dose: low doses

- At low doses, interactions with DNA molecules by low-LET charged particles in the beam are unlikely to be close enough together to cause single strand breaks in close enough proximity to become lethal double strand breaks
  - so repair is common

- Any single strand breaks in close proximity that occur will likely be caused by high-LET charged particles in the beam
  - so the initial slope of the survival curve will be due to these single high-LET particle interactions
The effect of dose: high doses

- At high doses, the density of single strand breaks will be high, so single strand breaks in close proximity caused by different low-LET interactions will be common i.e. repair will be reduced as dose is increased

  - *consequently survival curves get steeper as dose increases and continue to curve downwards*
Low- and high- LET components

At low doses, DNA double strand breaks caused by high-LET (e.g. slow electron) interactions will dominate. These increase linearly with dose.

At high doses, double strand breaks by separate, low-LET interactions will dominate. The probability of each single strand break is a linear function of dose, so the probability that both DNA strands will be hit will be a function of $D^2$. 

![Diagram showing linear and quadratic effects with dose](image)
Review: as dose increases survival curves become steeper.

The initial slope of the survival curve at low doses is due to single event interactions with the high-LET component of the beam. At higher doses, cell killing by two event (low-LET) processes will dominate and survival curves should continue to curve downwards. The “curvature” of the survival curve is due to the ability of cells to repair.
Survival curves: normal vs cancer cells

- Cancer cells do not "repair" damage as well as do normal tissue cells
  - survival curves will be straighter
- There is a "Window of Opportunity" at low doses where the survival of late-reacting normal tissue cells exceeds that of cancer cells
Cell survival curve comparison: the “Window of Opportunity”

At low doses, the survival of normal tissue cells (green curve) exceeds that of cancer cells.

At high doses, the survival of cancer cells (red curve) exceeds that of normal tissues.
This is why we have typically fractionated radiotherapy at low doses/fraction.

We have needed to fractionate at doses/fraction within this “Window of Opportunity” e.g. at about 2 Gy/fraction.
Normal vs cancer cells for fractionation at 2 Gy/fraction
Cell survival curve comparison: the “Window of Opportunity”

- Note that we have assumed that the dose to normal tissues is the same as the dose to the cancer cells.
- Is this a reasonable assumption if we are using conformal teletherapy such as SBRT?
Because the major advantage of conformal radiotherapy is that the dose to normal tissues is kept less than the tumor dose.

Hence the effective dose* to normal tissues will usually be less than the effective dose to tumor.

*the effective dose is the dose which, if delivered uniformly to the organ or tumor, will give the same complication or cure rate as the actual inhomogeneous dose distribution. A good example is the Equivalent Uniform Dose (EUD)
Geometrical sparing factor

We can define a “geometrical sparing factor”, $f$, such that:

$$f = \frac{\text{effective dose to normal tissues}}{\text{effective dose to tumor}}$$

For conformal radiotherapy $f < 1$
The “Window of Opportunity” widens with geometrical sparing.

Even with a modest geometrical sparing of only 20%, the “Window of Opportunity” extends to over 10 Gy.
This means that:

With highly conformal therapy we can safely use much higher doses per fraction

• for teletherapy i.e. hypofractionation
• for brachytherapy i.e. HDR
How can we determine the “best” fractionation to use?

- We need a mathematical model that describes the effects of radiotherapy on cancer and normal tissue cells
  - *this is the linear-quadratic model*
The linear-quadratic model of cell survival: two components

- **Linear component:**
  - a double-strand break caused by the passage of a single charged particle

- **Quadratic component:**
  - two separate single-strand breaks in close proximity caused by different charged particles, where the 1st break is not repaired before the 2nd break occurs
The L-Q Model Equation

\[ \ln S = -(\alpha D + \beta D^2) \]

Or, for \( N \) equal fractions

\[ -\ln S = -N(\alpha d + \beta d^2) \]

\( \alpha \) represents the probability of lethal \( \alpha \)-type damage

\( \beta \) represents the probability that independent \( \beta \)-type events have combined to produce lethal events e.g. double-strand breaks
Problem with the L-Q model

- There are too many unknown biological parameters in the basic L-Q equation ($\alpha$ and $\beta$) for reliable values to be determined from analysis of clinical data.

- These can be reduced to one parameter by dividing $-\ln S$ by $\alpha$ to give the Biologically Effective Dose (BED) equation.
The BED equation for fractionated radiotherapy in $N$ fractions each of dose $d$

$$-\ln S = N(\alpha d + \beta d^2)$$

Hence:

$$\text{BED} = \frac{-\ln S}{\alpha} = Nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

The remaining unknown biological parameter is $\alpha/\beta$
Typical values for $\alpha/\beta$

The most common assumptions are:
for tumors and acute reactions:
\[ \alpha/\beta = 10 \text{ Gy} \]
for late-reacting normal tissues:
\[ \alpha/\beta = 2 - 3 \text{ Gy} \]

*Note that some recent studies have reported that the $\alpha/\beta$ value for prostate cancer may be as low as 1.5 Gy and for breast cancer as low as 4 Gy*
Controversial issue: does this model hold up for very high doses/fraction?

- Many believe that cell-survival curves begin to straighten out at very high doses so cell survival will be greater than predicted by the L-Q model.
- Others believe that vascular damage after high doses increases the effectiveness of radiation and hence cell survival will be less than predicted by the L-Q model.
- Maybe both of these are correct and the L-Q model is a good compromise since the two “errors” tend to cancel each other out.
What about repopulation?

The BED equation with repopulation is:

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

The unknown biological parameters are \( \alpha / \beta \) and \( k \).
Typical values for $k$ assumed for normal tissues

Acutely responding normal tissues:
- $0.2 - 0.3 \text{ BED units/day}$

Late responding normal tissues:
- $0 - 0.1 \text{ BED units/day}$

Note that this is not Gy/day, as you’ll see in some publications, because BED is not linear in dose (it’s linear-quadratic)
Typical values for $k$ assumed for tumors (assuming no accelerated repopulation)

<table>
<thead>
<tr>
<th>Growth rate of tumor</th>
<th>$k$ (BED units/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>slow</td>
<td>about 0.1</td>
</tr>
<tr>
<td>average</td>
<td>about 0.3</td>
</tr>
<tr>
<td>rapid</td>
<td>about 0.6</td>
</tr>
</tbody>
</table>
Let’s look now at hypofractionation

- Hypofractionation is the use of fewer fractions at higher dose/fraction
  - \textit{dose/fraction: from 2.5 up to >30 Gy}
  - \textit{number of fractions: 1 to 20}
Hypofractionation: potential problems

- Historically, because of the risk of late complications, the total dose was kept considerably less than that needed to cure cancers, and hypofractionation was used for palliation only
  - however, with highly conformal therapy, it is now being used for cure
What we know

- Clinical trials around the world are beginning to show that, with highly conformal therapy, hypofractionation can be at least as effective as conventional fractionation (both for cure and avoidance of normal tissue complications)
  - we already knew this from stereotactic radiosurgery in the brain, but now know it for other sites
My prediction

- With even more conformation of dose distributions using more sophisticated imaging, image guidance, motion tracking, protons, etc., we’ll be using as few as five fractions for most cancers in the not too distant future
  - treatments will cost less and be more convenient
  - accelerated regimes will be more prevalent thus reducing cancer cell proliferation during treatment
  - cure rates will increase
There are some caveats however e.g. hypoxic cells

- Oxygen “fixes” the damage (the “oxygen fixation hypothesis”) and prevents repair
  - hypoxic cells are more radioresistant

- However, hypoxic cells may reoxygenate between fractions
Importance of reoxygenation

- Hence spreading irradiation over many fractions ought to be beneficial
  - *hyper*fractionation might be the way to go, not *hypofractionation*
Hypofractionation Results in Reduced Tumor Cell Kill Compared to Conventional Fractionation for Tumors With Regions of Hypoxia

David J. Carlson, Ph.D., Paul J. Keall, Ph.D., Billy W. Loo, M.D., Ph.D., Zhe J. Chen, Ph.D. and J. Martin Brown, Ph.D.

Total surviving fraction of tumor cells assuming daily fractionation and full reoxygenation between fractions
What happens if we add repopulation of tumor cells (with $f_{hyp} = 0.2$)?
What does all this mean?

- If there is a significant hypoxic fraction and $\alpha/\beta$ for cancer cells is higher than that for normal cells, hypofractionation should:
  - be a good option for rapidly growing cancers but with an optimum dose/fraction and number of fractions

- But what if $\alpha/\beta$ for cancer cells is lower than that for normal cells e.g. prostate cancer?
Prostate cancer

If the $\alpha/\beta$ for prostate cancer is lower than that for late-reacting normal tissues, as has been suggested, prostate cancer cells will repair sublethal damage better than normal cells, so hypofractionation ought to be better than conventional fractionation if we can ignore the effect of hypoxia.
Local control rates (bNED) for intermediate-risk prostate cancer (if $\alpha/\beta = 1.5$ Gy): conservative treatments

Equivalent to 66 Gy at 2 Gy/fraction as far as late-reactions ($\alpha/\beta = 3$ Gy) are concerned

<table>
<thead>
<tr>
<th>No. Frs</th>
<th>Dose per Fr</th>
<th>Total dose (Gy)</th>
<th>NTD (Gy)</th>
<th>bNED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>2.00</td>
<td>66.00</td>
<td>66.0</td>
<td>51.6</td>
</tr>
<tr>
<td>25</td>
<td>2.43</td>
<td>60.77</td>
<td>68.3</td>
<td>58.5</td>
</tr>
<tr>
<td>20</td>
<td>2.83</td>
<td>56.60</td>
<td>70.2</td>
<td>64.4</td>
</tr>
<tr>
<td>15</td>
<td>3.42</td>
<td>51.37</td>
<td>72.3</td>
<td>69.9</td>
</tr>
<tr>
<td>10</td>
<td>4.44</td>
<td>44.37</td>
<td>75.3</td>
<td>77.1</td>
</tr>
<tr>
<td>5</td>
<td>6.76</td>
<td>33.81</td>
<td>79.8</td>
<td>85.5</td>
</tr>
</tbody>
</table>

Hypoxia and repopulation assumed negligible

Highly aggressive treatments (equivalent to 78 Gy at 2 Gy/fraction)

<table>
<thead>
<tr>
<th>No. Frs</th>
<th>Dose per Fr</th>
<th>Total dose (Gy)</th>
<th>NTD (Gy)</th>
<th>bNED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>2.00</td>
<td>78.00</td>
<td>78.0</td>
<td>82.6</td>
</tr>
<tr>
<td>25</td>
<td>2.73</td>
<td>68.13</td>
<td>82.2</td>
<td>88.9</td>
</tr>
<tr>
<td>20</td>
<td>3.16</td>
<td>63.28</td>
<td>84.3</td>
<td>91.2</td>
</tr>
<tr>
<td>15</td>
<td>3.82</td>
<td>57.23</td>
<td>86.9</td>
<td>93.5</td>
</tr>
<tr>
<td>10</td>
<td>4.92</td>
<td>49.23</td>
<td>90.3</td>
<td>95.7</td>
</tr>
<tr>
<td>5</td>
<td>7.46</td>
<td>37.29</td>
<td>95.4</td>
<td>97.6</td>
</tr>
</tbody>
</table>

Fowler, 2003
Fowler’s conclusions

Hypofractionation will increase the therapeutic ratio between tumor control and late sequelae, provided that the $\alpha/\beta$ ratio for prostate tumors is lower than those for complications, including late rectal, late bladder, and any acute reactions.
Fowler’s conclusions (cont’d.)

- It is obvious that too-modest hypofractionation will not yield enough gain in cure rates to be detectable with a practical number of patients in a clinical trial.
- Fewer than about 20 fractions will probably be necessary for a significant gain.
We caution against the hasty adoption of extreme hypofractionation using very small numbers of larger fractions, given in an unusually short overall time, without proper Phase I testing of the toxic effect of shortening the overall treatment time.
Another caveat: Repair *during* each fraction

- With higher doses/fraction the time to deliver each fraction increases
- If this time gets too long the cancer cells might repair significantly *during* the treatment
- This might be OK if normal cells repair at the same rate but some believe that cancer cells tend to repair faster than normal cells
Potential effects of long treatment times with IMRT for prostate cancer

- Because of the potentially low $\alpha/\beta$ for prostate cancer, some concern has been expressed about the possibility that longer treatment times associated with the delivery of IMRT might allow prostate cancer cells to repair more during each session of treatment than normal tissue cells.
- This might be a problem for other cancers if late-responding normal tissue cells repair slower than tumor cells, as has been suggested.
Potential effects of long treatment times for prostate treatments

The prescription dose was 81 Gy in 1.8 Gy fractions. Except where explicitly noted otherwise, the following cancer-cell LQ parameters were used in this study:

\[ \alpha = 0.15 \text{ Gy}^{-1}, \quad \alpha/\beta = 3.1 \text{ Gy}, \quad \text{repair half time} = 16 \text{ min}, \]

and the initial number of cancer cells = \(3.0 \times 10^6\)

*Jian Z. Wang, Ph.D.,* X. Allen Li, Ph.D., *Warren D. D’Souza, Ph.D.,* and Robert D. Stewart, Ph.D.†

EUD and TCP for an intermediate-risk patient group as a function of IMRT fraction delivery time for prostate cancer

EUD as a function of $\alpha/\beta$ ratio and repair half-time for prostate cancer

--- 2 min. delivery time

— 30 min. delivery time

Wang et al conclusions

- Our calculations indicate that fraction delivery times in the range of 15 - 45 min may significantly decrease cell killing.
- The total time to deliver a single fraction may have a significant impact on IMRT treatment outcome for tumors with a low $\alpha/\beta$ ratio and a short repair half-time, such as prostate cancer.

Is repair during each fraction likely to be a real problem?

- Probably not, since we can now significantly reduce the time/fraction by using flattening-filter free linacs and rotational techniques such as IMAT, both of which reduce treatment times.

- Also, the biggest effect of long treatment times is for low $\alpha/\beta$ cancers, for which hypofractionation ought to be most beneficial.
So we need to be careful when we decide to use hypofractionation

- Hypofractionation might not be appropriate if:
  - the fraction of hypoxic cells is significant
  - treatment times get so long that cancer cells repair during treatments, especially for tumors with short cancer cell repair half times and low $\alpha/\beta$

- Only carefully controlled clinical trials will give us the answers
Modest hypofractionation: Breast (START) trial
Lancet Oncology 14, 1086-1094 (2013)

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the START Trialists’ Group†

In START-B, a regimen of 50 Gy in 25 fractions over 5 weeks was compared with 40 Gy in 15 fractions over 3 weeks
Relapse rates

Adapted from Haviland, et al

- conventional fractionation to 50 Gy
- hypofractionation to 40 Gy

40 Gy vs 50 Gy HR 0.77, 95% CI 0.51-1.16; p=0.21
Late side effects

- Ischemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis were rare and occurred in much the same proportions with each treatment schedule.
- Moderate or marked breast shrinkage, telangiectasia, and breast edema were significantly lower with the hypofractionated regime (the hazard ratios were significantly less than 1).
Hazard ratios for late normal tissue effects

Hazard ratio (95% CI)

40 Gy vs 50 Gy
Breast shrinkage
Breast induration
Breast oedema
Telangiectasia
Shoulder stiffness
Arm oedema

Favors hypofractionation
Favors 2 Gy/fraction

Adapted from Haviland, et al
• The 10-year START trial results presented here...confirm the earlier findings and strengthen the evidence in favour of using hypofractionated schedules for breast cancer radiotherapy

• They support the continued use of 40 Gy in 15 fractions as the UK standard of care ...and contribute further to the worldwide debate about breast cancer radiotherapy hypofractionation
Extreme hypofractionation: RTOG 0915

- A randomized Phase II study comparing two SBRT schedules for medically inoperable patients with Stage I peripheral cell lung cancer
- Arm 1: 34 Gy in 1 fraction
- Arm 2: 48 Gy in 4 once-daily consecutive fractions
- **Objective**: To select the most favorable treatment regimen based on the rate of grade 3 or higher protocol-specified adverse events at 1 year
RTOG 0915 Report at ASTRO 2013
(Videtic, et al)

Results: At one year, 34 Gy in one fraction met pre-specified criteria with respect to adverse events and primary control, and therefore is selected as the experimental arm for a planned phase III trial.
Summary

- We fractionate because late-reacting normal tissue cells repair better than tumor cells at low doses/fraction (the “Window of Opportunity”)
- With SBRT we can treat at higher doses/fraction (the “Window of Opportunity” widens)
- In the future we are likely to increasingly use hypofractionation with SBRT
- But clinical trials are essential to find the proper doses to use