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### Radiobiological basis of fractionated and hypofractionated radiotherapy

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### Why do we fractionate?

- ♦ It's because cells are able to repair radiation damage if this is not too great such as when the dose is low
- ♦ Most importantly, the cells of late-reacting normal tissues that are responsible for complications are better able to repair than are cancer cells
  - Hence, at low doses, cell survival of normal tissues will exceed that of cancers

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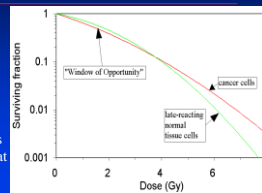
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### Cell survival curve comparison: the "Window of Opportunity"

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



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**So why is this "Window of Opportunity" important?**

- ◆ This is why we typically fractionate radiotherapy at low doses/fraction
- ◆ We have needed to fractionate at doses/fraction within this "Window of Opportunity" i.e. typically about 2 Gy/fraction

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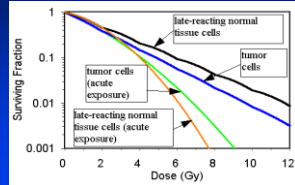
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**Normal vs cancer cells for fractionation at 2 Gy/fraction**



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**For these survival curves we have made an assumption however**

- ◆ We have assumed that the dose to normal tissues is the same as the dose to the cancer cells
- ◆ But is this a reasonable assumption if we are using conformal teletherapy?

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# No!

- 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. Sometimes called the Equivalent Uniform Dose (EUD)

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## 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  $f < 1$

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## 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

Tumor dose (Gy)	Surviving fraction (cancer cells)	Surviving fraction (late-reacting normal tissue cells)
0	1E+00	1E+00
5	~1E-02	~1E-01
10	~1E-04	~1E-02
15	~1E-06	~1E-03
20	~1E-08	~1E-04

**Effect of geometrical sparing,  $f = 0.8$**

Surviving fraction

Tumor dose (Gy)

cancer cells

late-reacting normal tissue cells

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**This means that:**

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

- *hypofractionation*

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**What about overall treatment time?**

- Cancer cells and cells of acutely-reacting normal tissues proliferate during the course of therapy (called "repopulation")
- Cells of late-reacting normal tissues proliferate little
- Hence the shorter the overall treatment time the better
  - *but should not be too short otherwise acute reactions will prevent completion of treatment*

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**Knowing all this, many different fractionation schemes have been investigated**

- ◆ Hyperfractionation
- ◆ Accelerated fractionation
- ◆ Hyperfractionated accelerated fractionation
- ◆ Hypofractionation

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If we change the fractionation scheme, how can we determine what total dose to deliver?

Typically, we use the linear-quadratic model

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

where:

*BED* = biologically effective dose  
*N* = number of fractions  
*d* = dose fraction (in Gy)  
 $\alpha/\beta$  = tissue-specific L-Q model parameter (in Gy)  
*T* = overall treatment time (in days)  
*k* = "lost" BED day due to repopulation

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### Typical values for $\alpha/\beta$

The most common assumptions are:

for late-reacting normal tissues:

$\alpha/\beta = 2 - 3$  Gy

for tumors and acute reactions:

$\alpha/\beta = 10$  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

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### Typical values for *k* assumed for normal tissues

Acutely responding normal tissues:

• 0.2 - 0.3 BED units/day

◆ Late responding normal tissues:

• 0 - 0.1 BED units/day

◆ Note that this is not Gy/day, as you will see in some publications, because BED is not linear in dose (it's linear-quadratic)

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**Typical values for  $k$   
I assume for tumors**

Growth rate of tumor	$k$ (BED units/day)
slow	about 0.1
average	about 0.3 - 0.4
rapid	about 0.6 - 0.7

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- Let's look at different fractionation schemes: conventional fractionation**
- ♦ Dose/fraction: 1.8 - 2 Gy
  - ♦ Fractions/week: 5
  - ♦ Total dose: 50 - 65 Gy
  - ♦ Overall treatment time 5 - 7 weeks
  - ♦ Used for most patients in the past

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- Why might we want to change from this fractionation scheme?**
- ♦ Total dose may be too low for some resistant cancers
    - *We can go to higher doses without exceeding normal-tissue tolerance by giving more fractions at lower dose/fraction i.e. hyperfractionation*
  - ♦ May be too slow for the treatment of fast-growing cancers
    - *We could decrease the overall treatment time i.e. accelerated fractionation*

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### Hyperfractionation

- Dose/fraction: 1.1 - 1.3 Gy
- Fractions/week: 10
  - *otherwise the overall time will be too great and cancer cells will have too much time to repopulate*
- Total dose: 70 - 80 Gy
- Used when we need to go to higher doses to control the tumor but when late normal tissue tolerance is a major problem (low dose/fraction means more repair)

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### Hyperfractionation problems

- ♦ Two fractions/day, with at least six hours between treatments to allow for complete repair, puts extra burden on patients, staff and equipment
- ♦ After many clinical trials, no clear benefit has been demonstrated that would justify these extra burdens

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### Accelerated fractionation

- ♦ Used for rapidly growing cancers
- ♦ Can be achieved by either using two fractions/day or a slightly higher dose/fraction
- ♦ Dose/fraction: about 1.4 (with 2 fractions/day) - 2.5 Gy (with 1 fraction daily)
- ♦ Fractions/week: 5 - 10
- ♦ Total dose: 40 - 50 Gy

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**Accelerated fractionation problems**

- ♦ Early responding normal tissues may not have time to repopulate in the 3 - 4 week course, so acute reactions have been a major problem
  - *This has frequently required patients to be given a rest, which negates the acceleration of the treatment*
- ♦ No clear benefit has been demonstrated in clinical trials

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**Continuous hyperfractionated accelerated fractionation (CHART)**

- ♦ Here we are trying to combine the benefits of hyperfractionation and accelerated fractionation
  - *Dose/fraction: 1.5 Gy*
  - *Fractions/week: 21 i.e. 3 fractions/day*
  - *Total dose: 54 Gy*
  - *Used for rapidly growing cancers*

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**CHART (cont'd.)**

- ♦ Treatment completed in 12 days
- ♦ Acute reactions peak after the completion of treatment
  - *Remember, with accelerated fractionation, patients had to be given a rest due to excessive acute reactions*
- ♦ Very inconvenient since have to treat three fractions per day for 12 consecutive days, including weekends

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**CHARTWEL (continuous hyperfractionated radiotherapy weekend less)**

- ◆ Same as CHART but 5 days/week
- ◆ Treatment completed in 16 days
- ◆ Acute reactions peak after the completion of treatment (but it's close!)

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**CHART and CHARTWEL: problem with late reactions**

- ◆ Initially several patients were treated with as little as three hours between fractions
  - *Late complication rates were excessive with these short inter-fraction times*
  - *A strict minimum of six hours between treatments had to be mandated*
- ◆ This made these treatments highly inconvenient putting a great burden on patients, staff and equipment

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**CHART and CHARTWEL: problem with acute reactions**

- ◆ Acute reactions have been a major concern
  - *Most patients have had to be hospitalized for treatment of excessive acute reactions as soon as they complete therapy*
  - *Results of clinical trials have not been promising enough to justify the inconvenience and extra burdens on patients and staff entailed*

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## Hypofractionation

- ♦ Dose/fraction: above about 2.5 Gy
- ♦ Fractions/week: 1 – 5
- ♦ Total number of fractions: 1 - 20
- ♦ Total dose: 20 – 55 Gy (depends on fractionation used)

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## What we know

- ♦ Clinical trials around the world are beginning to show that, with highly conformal therapy, hypofractionation can be just 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*
  - *See the May 1, 2021 Special HyTEC issue of the IJROBP*

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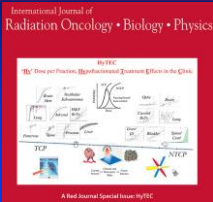
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## Red Journal May 1, 2021



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**Demonstration: how might hypofractionation be better than conventional fractionation?**

- Problem: it is required to change a conventional fractionation scheme of 60 Gy delivered in 30 fractions at 2 Gy/fraction over 42 days to hypofractionation with 10 fractions delivered over 14 days
- What dose/fraction should be used to keep the same effect on cancer cells, and will the new scheme have increased or decreased effect on late-reacting normal tissues?

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**Solution: for tumor**

Assumptions:  
Tumor  $\alpha/\beta = 10$  Gy and  $k = 0.4$  BED units/day

Conventional fractionation;  
 $BED = 60(1 + 2/10) - 0.4(42) = 55.2$

Hypofractionation  
 $BED = 55.2 = 10d(1 + d/10) - 0.4(14)$   
Solution is  $d = 4.26$  Gy

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**For late-reacting normal tissues**

Assumptions:  
Late-reacting normal tissue  $\alpha/\beta = 3$  Gy and tissue sparing factor  $f = 0.6$

Conventional fractionation:  
 $BED = 60f(1 + 2/f) = 50.4$

Hypofractionation:  
 $BED = 42.6f(1 + 4.26/f) = 47.3$

It appears that the 10-fraction scheme is now somewhat less damaging to normal tissues (47.3 vs. 50.4)

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## 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 near 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*

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## Summary

- We fractionate because late-reacting normal tissue cells repair better than tumor cells at low doses/fraction (the "Window of Opportunity")
- With highly conformal therapy we can treat at higher doses/fraction (the "Window of Opportunity" widens)
- There have been numerous clinical trials of fractionation schemes to replace conventional fractionation, often designed using the L-Q model
- In the future we are likely to increasingly use hypofractionation

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