Radiobiological Aspects of Radiotherapy and the Potential for Hypofractionation

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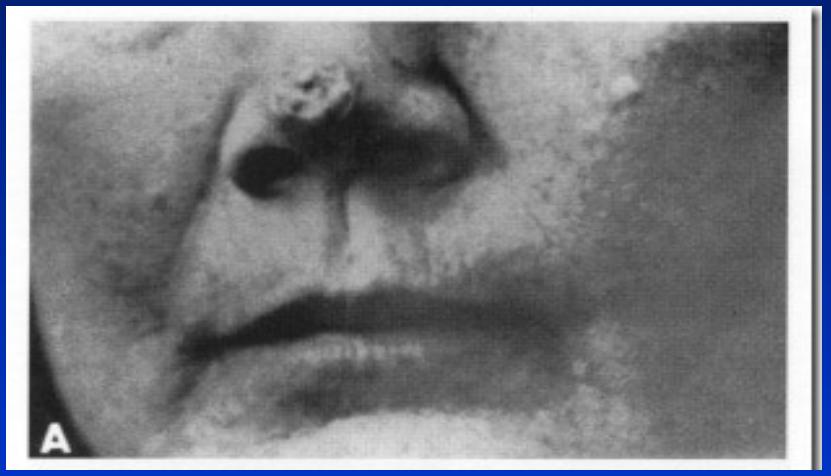
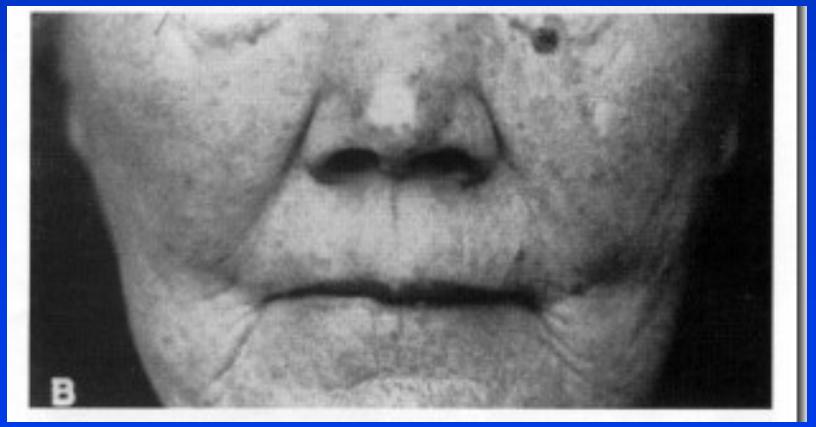
1st (documented) successfully treated patient

Patient in Sweden treated for basal cell carcinoma in 1899 using a total of 99 fractions



Follow up 30 years later



Why were treatments fractionated?

- Very low output
  - *to complete the treatment in one fraction would have taken days*
- Dose was unpredictable
  - *you only found out what dose had been delivered after the completion of each session*
  - *clearly, you couldn't give the full treatment in a single, unpredictable, fraction*

“Doses” were measured for each fraction

Photographic paper dosimeters were placed on the patient’s skin

The degree of blackening was a measure of the “dose”

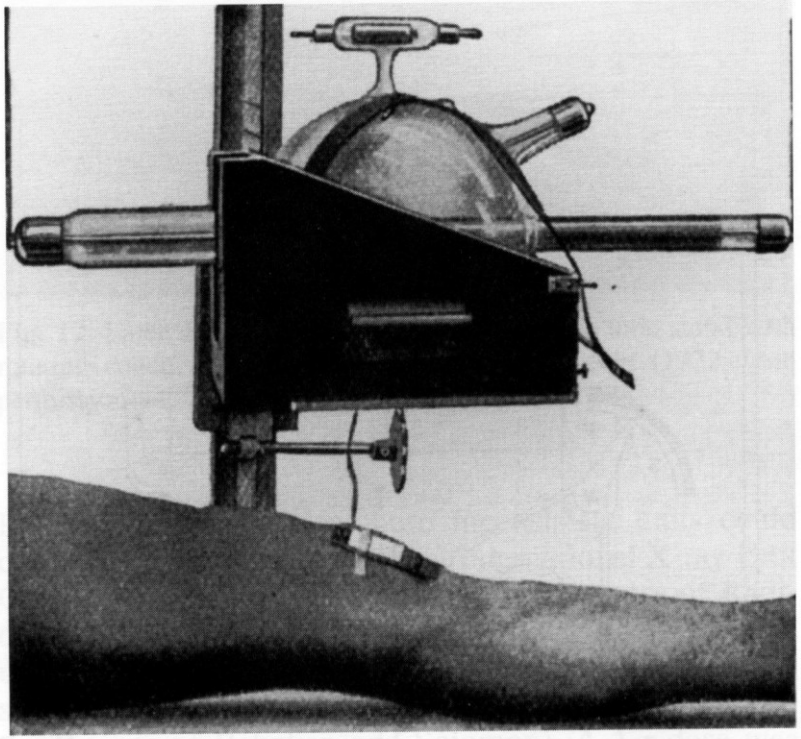
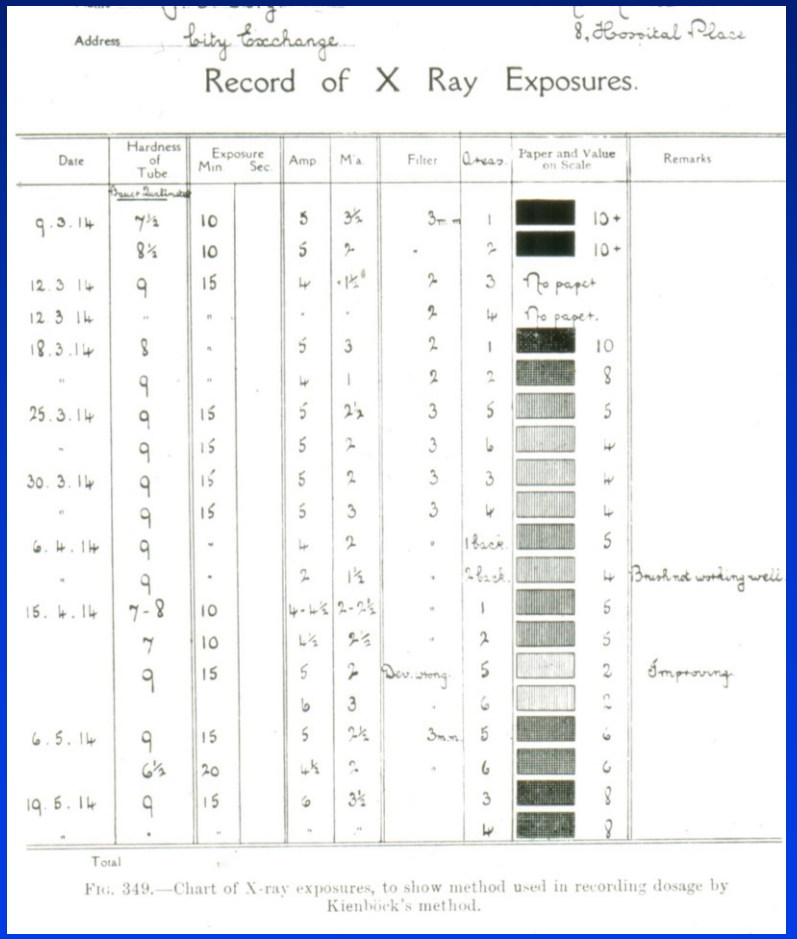


Fig. 7. Photographic paper strips which blacken after development were placed on the patient’s skin during treatments in order to measure the dose received. This was the so-called Kienböck quantimeter. Reproduced from Knox (1916; with permission).

Typical patient's chart

Note that the "dose" (paper blackening) varied enormously day-to-day due to instability of the output



Address City Exchange. 8, Hospital Place

Record of X Ray Exposures.

Date	Hardness of Tube	Exposure Min.	Exposure Sec.	Amp.	M/a.	Filter	Area	Paper and Value on Scale	Remarks
	Spare Radiator								
9.3.14	7½	10		5	3½	3m.m	1	10+	
	8½	10		5	3	"	2	10+	
12.3.14	9	15		4	1½	2	3	No paper	
12.3.14	"	"		"	"	2	4	No paper.	
18.3.14	8	"		5	3	2	1	10	
"	9	"		4	1	2	2	8	
25.3.14	9	15		5	2½	3	5	5	
"	9	15		5	2	3	6	4	
30.3.14	9	15		5	2	3	3	4	
"	9	15		5	3	3	4	4	
6.4.14	9	-		4	2	"	1Back	5	
"	9	-		2	1½	"	2Back	4	Brush not working well
15.4.14	7-8	10		4-4½	2-2½	"	1	5	
	7	10		4½	2½	"	2	5	
	9	15		5	2	Dev. strong	5	2	Improving
				6	3	"	6	2	
6.5.14	9	15		5	2½	3m.m.	5	6	
	6½	20		4½	2	"	6	6	
19.5.14	9	15		6	3½		3	8	
"	"	-		"	"		4	8	
							Total		

FIG. 349.—Chart of X-ray exposures, to show method used in recording dosage by Kienböck's method.

This all changed with the invention of the hot-cathode X-ray unit

- It was not until 1914 with the development of the hot-cathode X-ray tube by William Coolidge that high, predictable, dose rates became possible
- After this, there were two Schools of Thought about fractionation
  - *single fractions are essential*

  or
  - *only with multiple fractions can 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 animal studies which 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 fractionation was essential

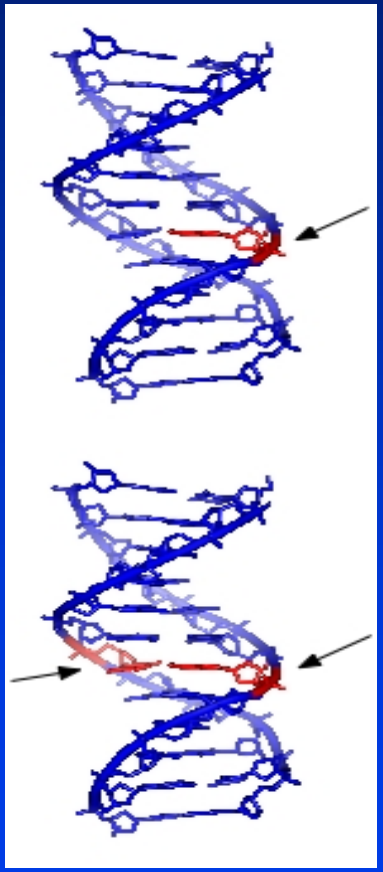
Do we now know, radiobiologically, why fractionation was so important?

- Yes, it's because cells are able to repair radiation damage when low doses or low doses/fraction are used
- So what do we mean by "repair"?

Repair: Single strand and double strand damage

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

Double strand breaks (lower figure) are not usually “repairable” if the breaks are close together, since an intact 2nd strand of the DNA molecule is needed for the repair enzymes to be able to copy the genetic information

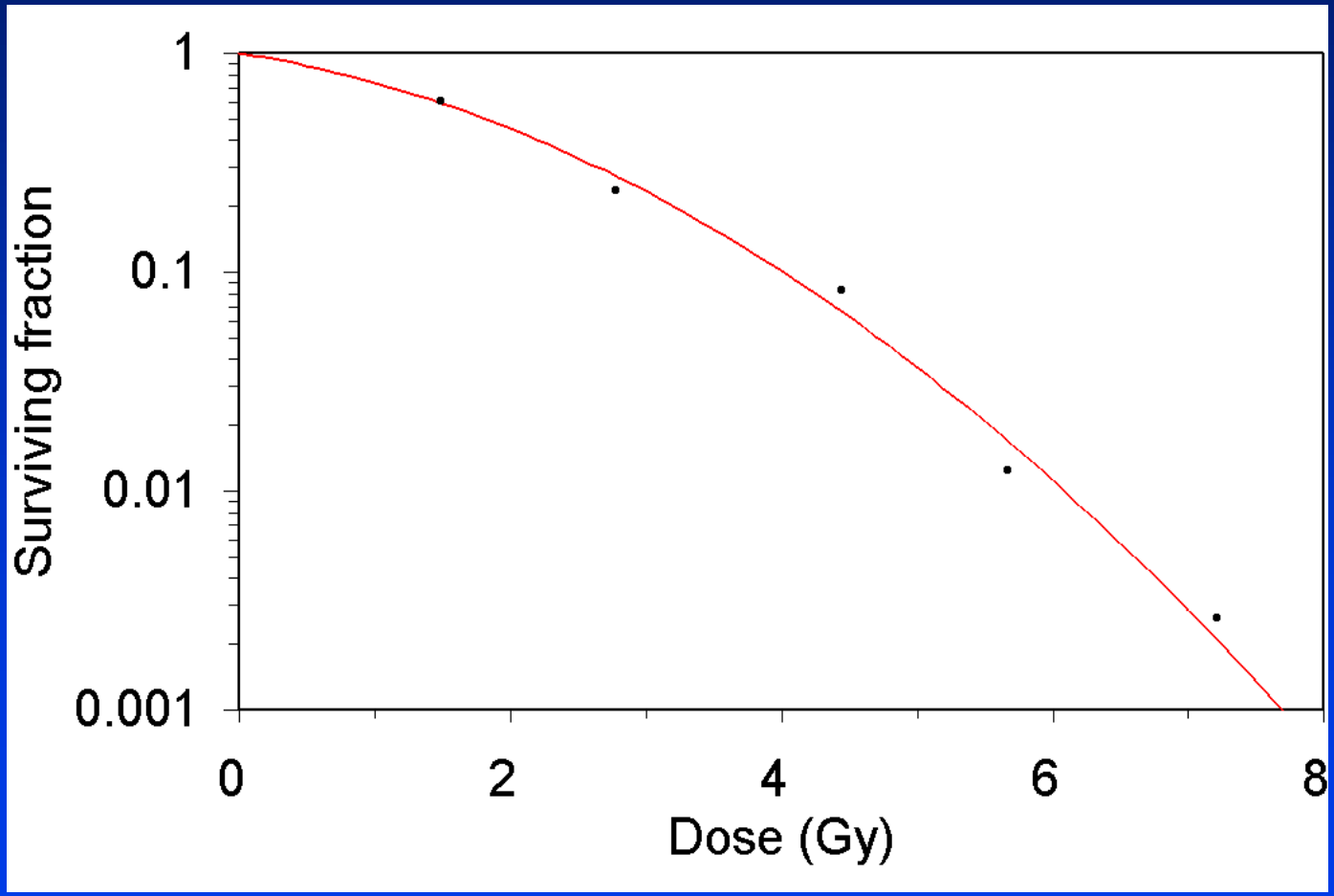


The effect of dose

- At low doses, both DNA strands are unlikely to be hit
  - *so single strand breaks will dominate i.e. repair is common*
- At high doses, double strand breaks will be common i.e. little repair
  - *consequently survival curves get steeper as dose increases*

As dose increases survival curves become steeper

For types of cells that have a high capacity for repair the less steep the curve will be at low doses and hence the curvier the survival curve



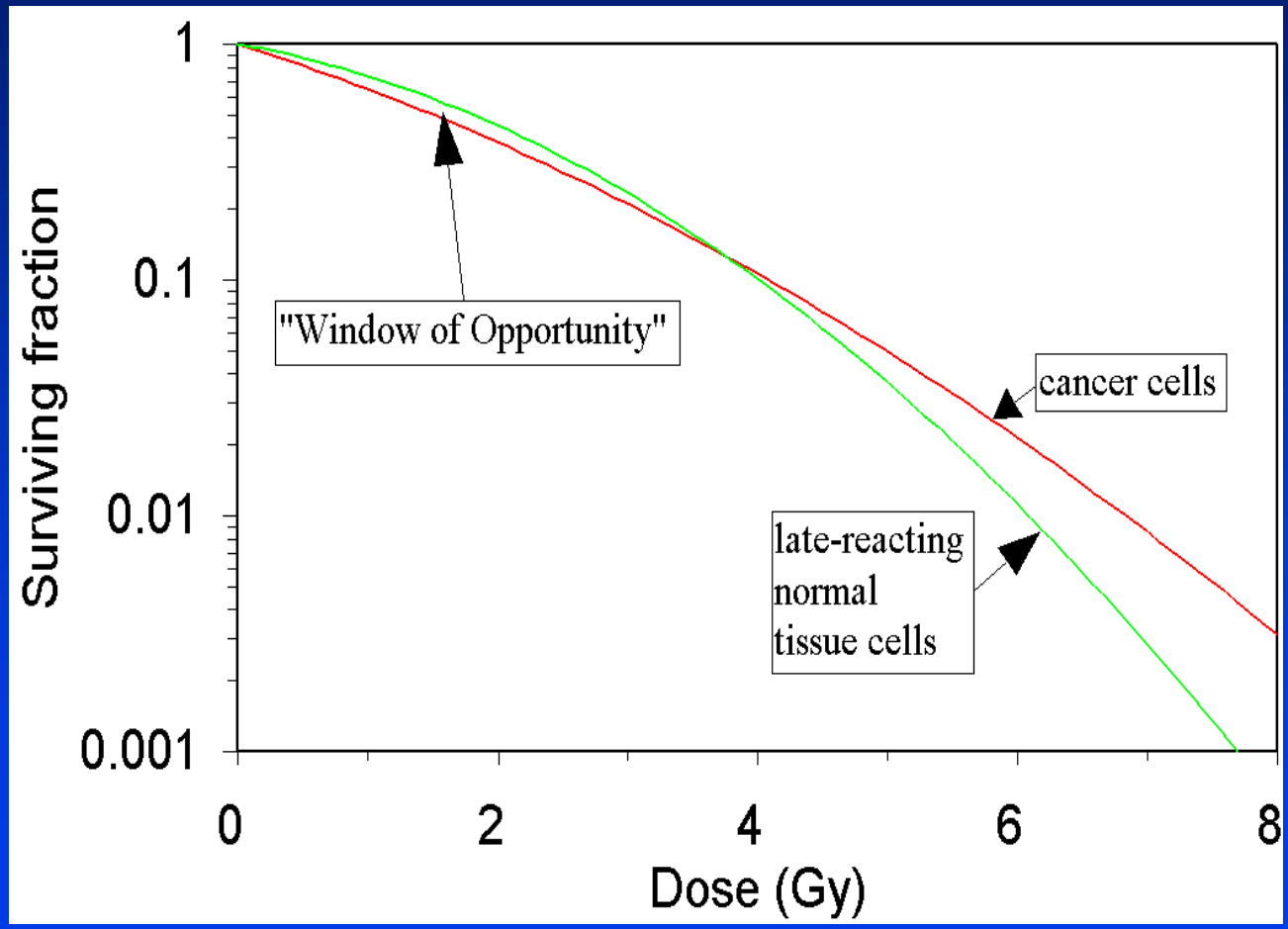
Survival curves: normal *vs* cancer cells

- Cancer cells do not "repair" damage at low doses 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

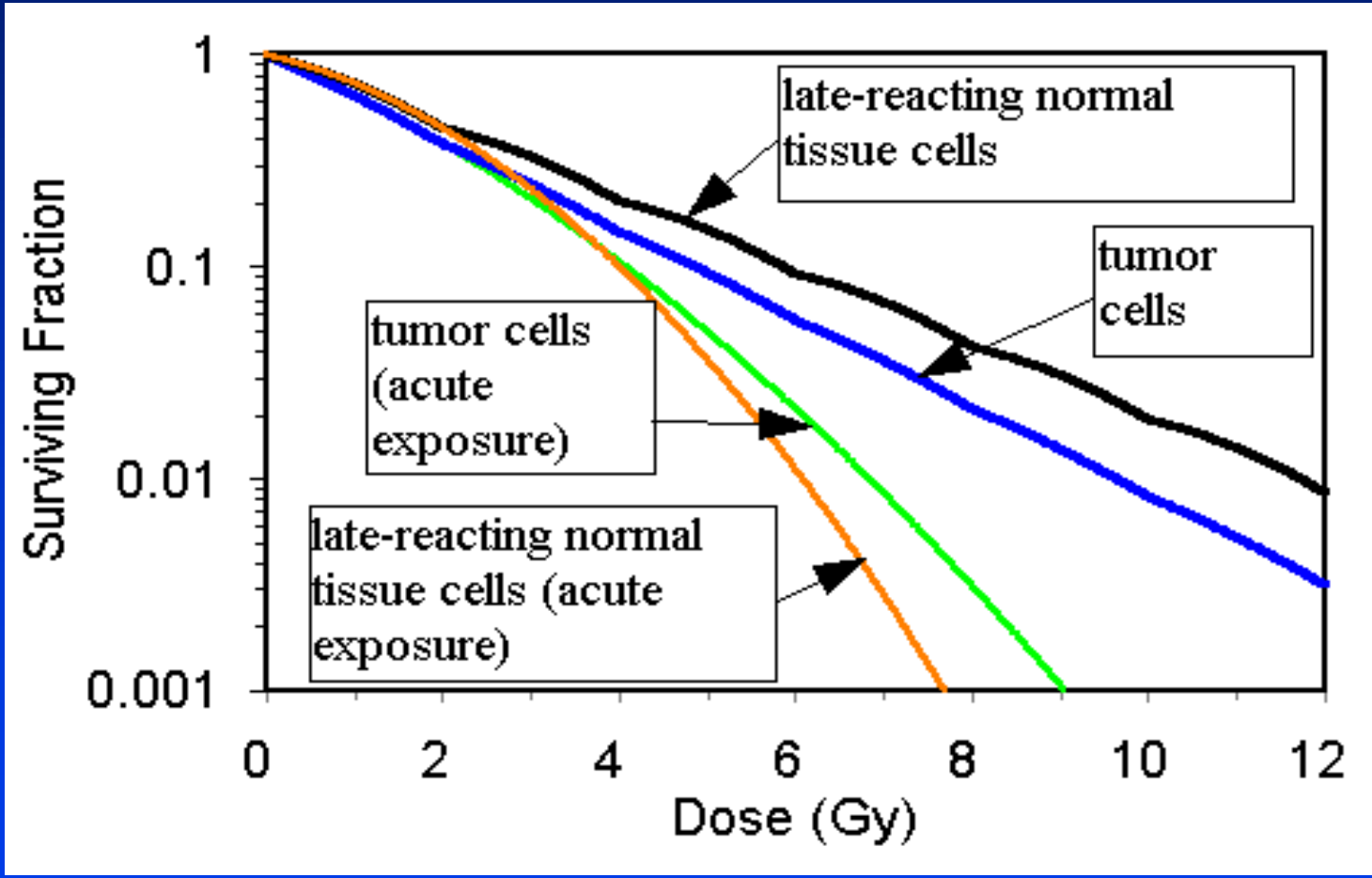
At high doses, the survival of cancer cells (red curve) exceeds that of normal tissues



Fractionation

- This is why we typically fractionate radiotherapy at low doses/fraction
- We need to fractionate at doses/fraction within this “Window of Opportunity” e.g. typically 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, but is this a reasonable assumption if we are using conformal teletherapy?

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 (this is often called the Equivalent Uniform Dose, or EUD)*

Geometrical sparing factor

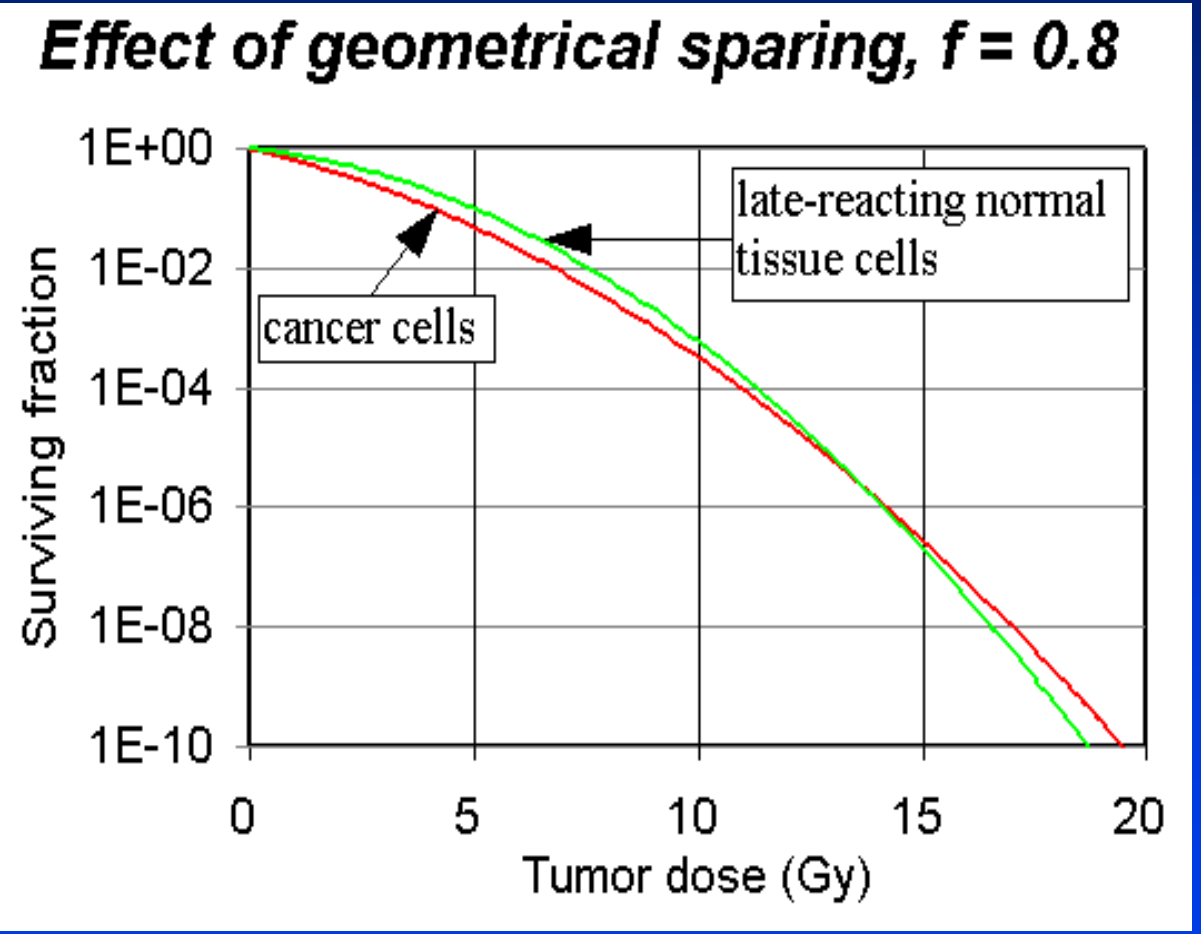
We can define a "geometrical sparing factor", *f*, such that:

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

For highly 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*

What about dose rate and time between fractions?

- Repair takes time (half-time for repair typically 0.5 – 1.5 hours), hence repair decreases as
  - *time between fractions decreases*
  - *dose rate increases*

Importance of time between fractions

- Because repair is more important for normal tissues than for tumors, enough time must be left between fractions for full repair
  - *based on clinical results, this is assumed to be at least six hours*

Importance of dose rate

- Normal tissue cells repair better than cancer cells and low dose rate enhances repair
- This is the basis of low dose rate brachytherapy and, especially, permanent implants at very low dose rate

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*

So how does all this effect the way we treat cancers?

- Different types of fractionation
- Different dose rates for brachytherapy

Different fractionation schemes

- Conventional fractionation
- Hyperfractionation
- Accelerated fractionation
- Hyperfractionated accelerated fractionation
- Hypofractionation

Conventional fractionation

- Dose/fraction: 1.8 -2.2 Gy
- Fractions/week: 5
- Total dose: 50 - 65 Gy
- Used for most patients in the past

Conventional fractionation: potential problems

- May be too slow for the treatment of fast-growing cancers
- Total dose may be too low for some resistant cancers
  - *We can go to higher doses without exceeding normal-tissue tolerance by giving lower dose/fraction*

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 late normal tissue tolerance is a major problem (low dose/fraction means more repair) but we need to go to higher doses to control the tumor

Hyperfractionation problems

- Two fractions/day, with at least six hours between treatments, puts extra burden on patients, staff and equipment
- After many clinical trials, no clear benefit has been demonstrated

Accelerated fractionation

- Used for rapidly growing cancers
- Can be achieved by either using two fractions/day or a 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

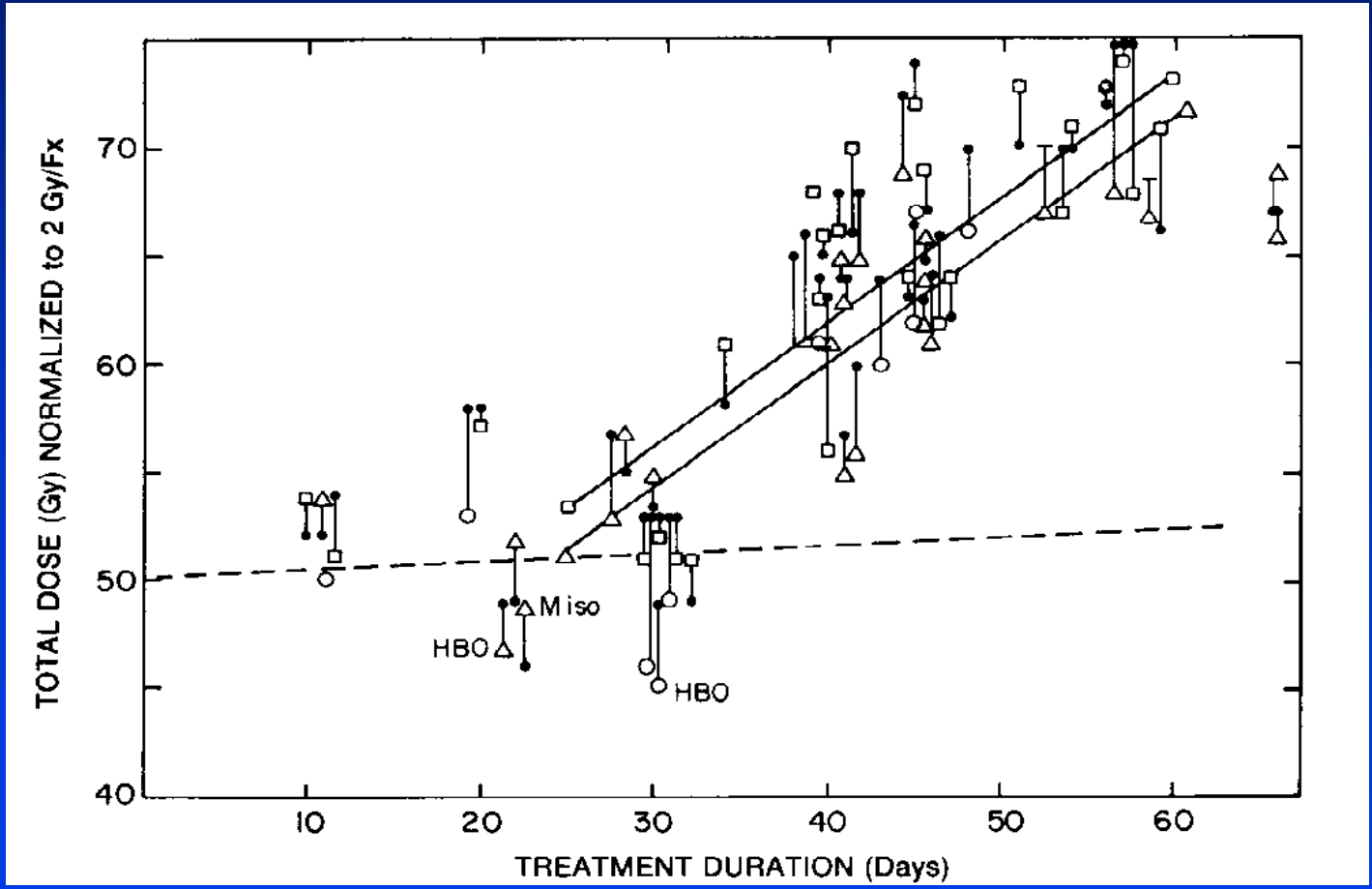
Accelerated fractionation problems

- 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

Accelerated repopulation

Withers' "hockey stick"

The iso-effect dose for local control of H & N cancers increases significantly after 3 - 4 weeks of treatment, showing that even faster treatments might be better



Continuous hyperfractionated accelerated radiation therapy (CHART)

- Dose/fraction: 1.5 Gy
- Fractions/week: 21 i.e. 3 fractions/day
- Total dose: 54 Gy
- Used for rapidly growing cancers, especially if accelerated repopulation is suspected

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 for 12 consecutive days, including weekends

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!)

CHART and CHARTWEL: potential problems

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

CHART and CHARTWEL: potential problems (cont'd.)

- Acute reactions have been a major concern
  - *Most patients have had to be hospitalized as soon as they complete therapy for treatment of excessive acute reactions*
- Results of clinical trials have not been all that promising

Let's look now at hypofractionation

- Hypofractionation is the use of fewer fractions at higher dose/fraction
  - *dose/fraction: about 3 – 20 Gy*
  - *number of fractions: 1 - 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, it is now being used for cure with highly conformal therapy*

What do 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*

My prediction

- With even more conformation of dose distributions using more sophisticated imaging, image guidance, motion tracking, etc., we'll be using as few as ten fractions for most cancers in the near future
  - *treatments will cost less*
  - *accelerated regimes will be more prevalent thus reducing cancer cell proliferation during treatment*
  - *cure rates will increase*

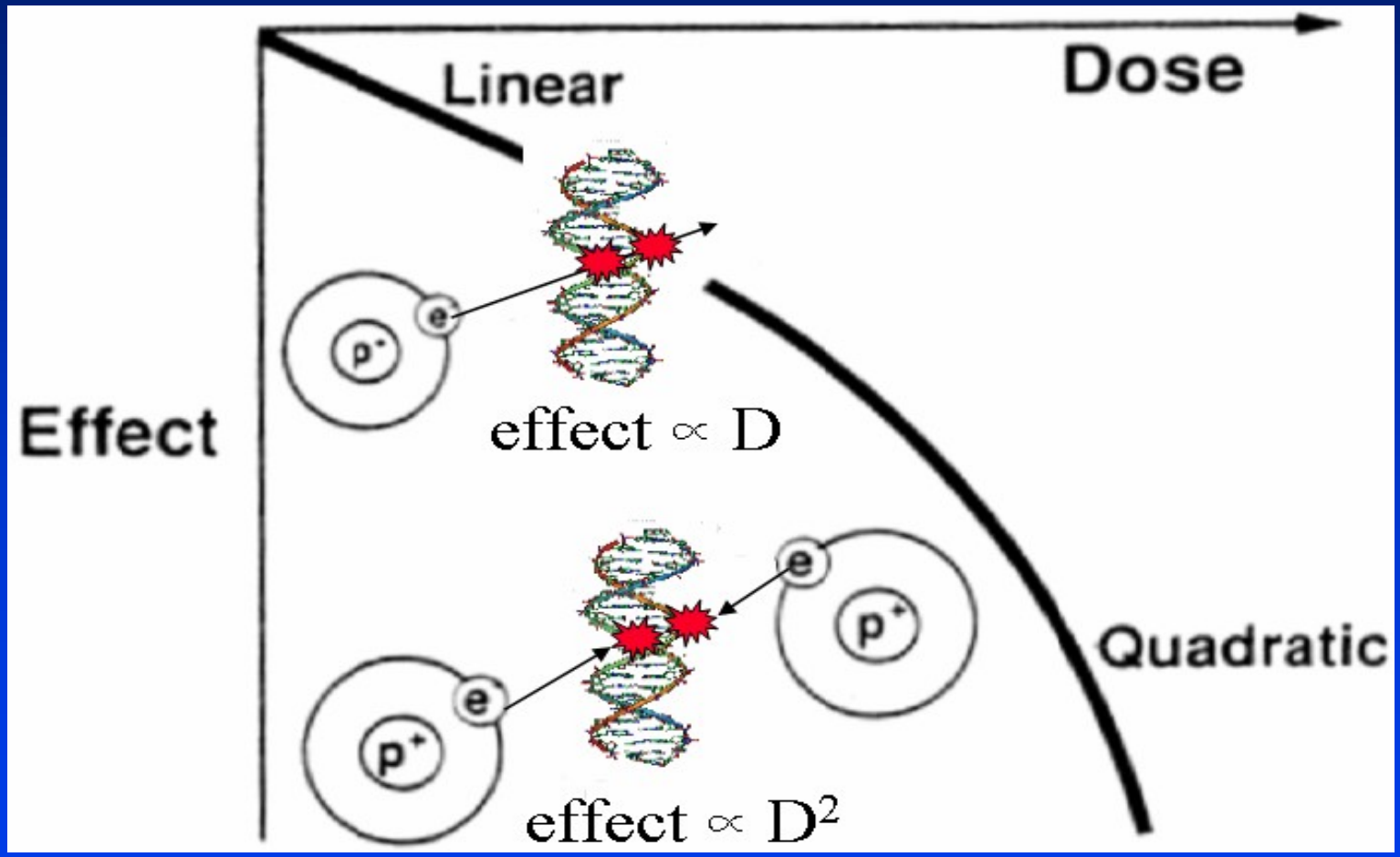
How can we determine the "best" fractionation to use?

- 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 e.g. electron, proton, heavy ion
- Quadratic component:
  - two separate single-strand breaks caused by different charged particles

The linear-quadratic model



The L-Q Model Equation

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

α represents the probability of lethal α-type damage

β represents the probability that independent β-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 (α *and* β) for reliable values to be determined from analysis of clinical data
- These can be reduced to one parameter by dividing *-lnS* by α

The BED equation for fractionated radiotherapy in *N* fractions each of dose *d*

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

or, for *N* fractions:

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

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

The remaining unknown biological parameter is α/β

Typical values for α/β

The most common assumptions are:

for tumors and acute reactions:

α/β = 10 Gy

for late-reacting normal tissues:

α/β = 2 - 3 Gy

* *Note that some recent studies have reported that the α/β value for prostate cancer may be as low as 1.5 Gy and for breast cancer as low as 4 Gy*

What about repopulation?

The BED equation with repopulation is:

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

The remaining unknown biological parameters are α/β and k

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'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)

Growth rate of tumor	*k* (BED units/day)
slow	about 0.1
average	about 0.3
rapid	about 0.6

Example: change in fractionation accounting for repopulation

- 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 with10 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?

Assume that normal tissues receive 60% of the tumor dose and repopulation occurs at a rate of k = 0.3/day

The tumor BED for 30 fractions of 2 Gy is:

$$BED_t = 30 \times 2(1 + 2/10) - 0.3 \times 42 = 55.2$$

Then, for this same BED in 10 fractions of dose d/fraction:

$$55.2 = 10 \times d(1 + d/10) - 0.3 \times 14$$

The solution to this quadratic equation is:

$$d = 4.26 \text{ Gy}$$

What is the effect on late reactions

The dose to normal tissues will be 2 x 0.6 = 1.2 Gy for the 30 fraction treatments but will become 4.26 x 0.6 = 2.56 Gy for the 10 fraction treatments

Then the BEDs for normal tissues will be:

$$BED_n = 30 \times 1.2(1 + 1.2/3) = 50$$

$$BED_n = 10 \times 2.56(1 + 2.56/3) = 47$$

It appears that the 10 fraction scheme is now somewhat less damaging to normal tissues (47 vs. 50)

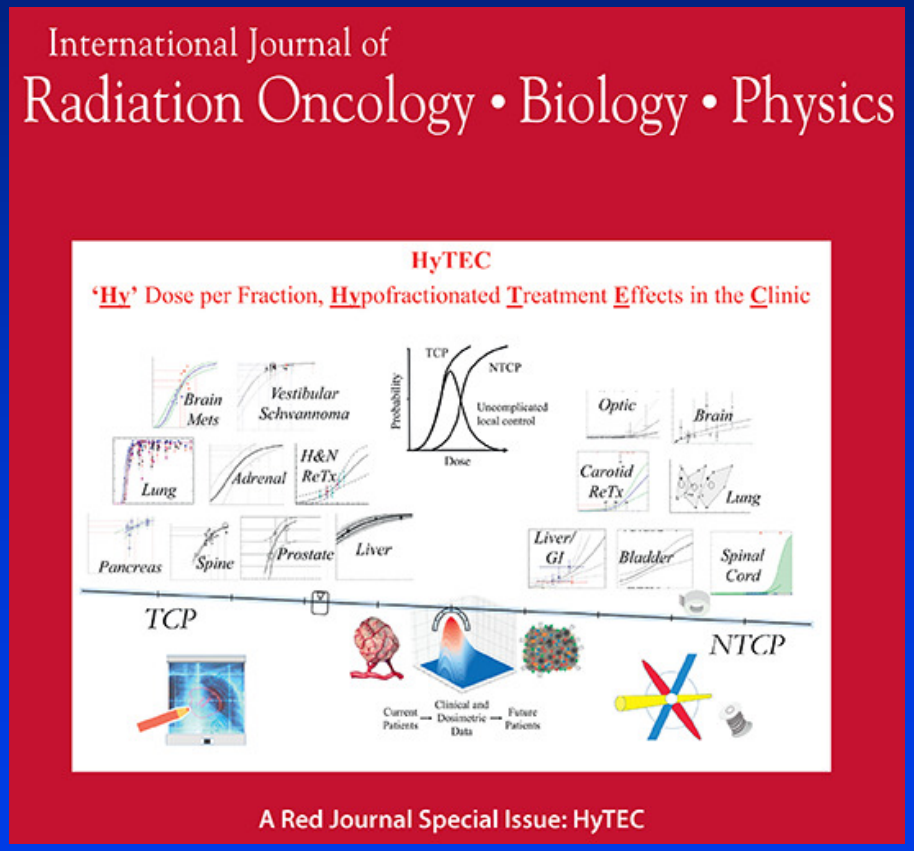
What does this mean?

Decreasing the number of fractions, i.e. hypofractionation, does not necessarily mean increasing the risk of normal tissue damage when keeping the effect on tumor constant

Of course, all these calculations depend on the parameters we use

- But do we know what parameters to use?
- Yes, well, kind of!
- At least we are close for normal tissues due to the QUANTEC initiative stimulated by the AAPM in 2006
- QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic
  - *development of large data bases*
  - *model evaluation and data analysis*
  - *publication of best-fit models and parameters*
- Just beginning to analyze TCP data

Red Journal May 1, 2021



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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)
- In the future we are likely to increasingly use hypofractionation