

# Radiobiological Principles of Fractionated Radiotherapy and the Potential for Hypofractionation

---

Colin G. Orton, Ph.D.  
Professor Emeritus,  
Wayne State University,  
Detroit, Michigan, USA

# History of fractionation: 1<sup>st</sup> (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?

---

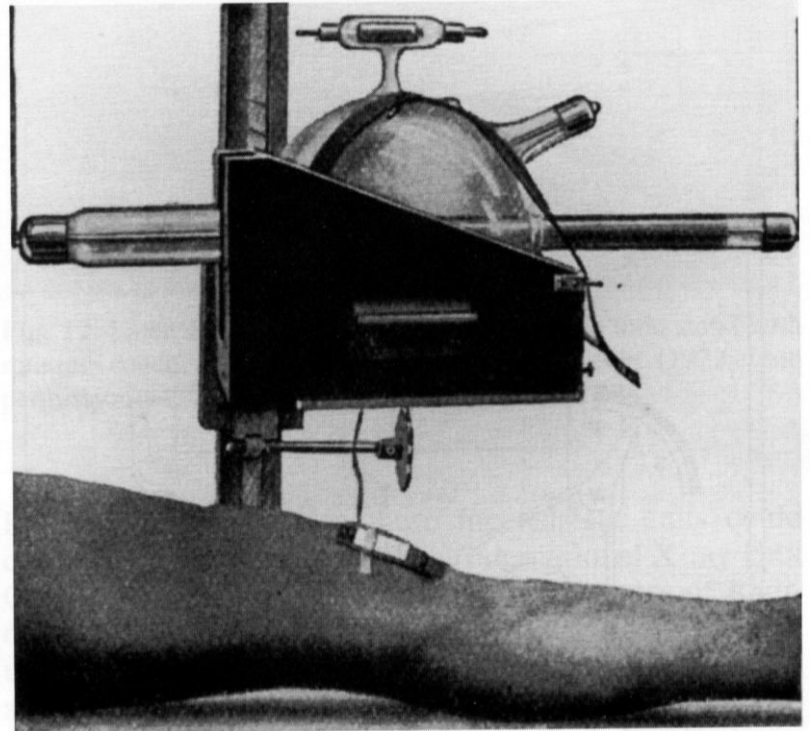
- ◆ Very low output
  - *to complete the treatment in one fraction would have taken hours, even days*
- ◆ Dose was unpredictable
  - *at first there were no dosimeters so treatments were designed individually dependent on skin reactions between fractions*
  - *you only found out what dose had been delivered after the completion of each session*
  - *clearly, you couldn't give the full treatment in a single, unpredictable, fraction*

# Later “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	Sec	Amp	Ma	Filter	Area	Paper and Value on Scale	Remarks
9.3.14	7½	10		5	3½	3mm	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	"	1 Back	5	
"	9	"		2	1½	"	2 Back	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	3mm	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.

# 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 radiobiological 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 fractionation was essential



Radiobiologically, why is  
fractionation so important?

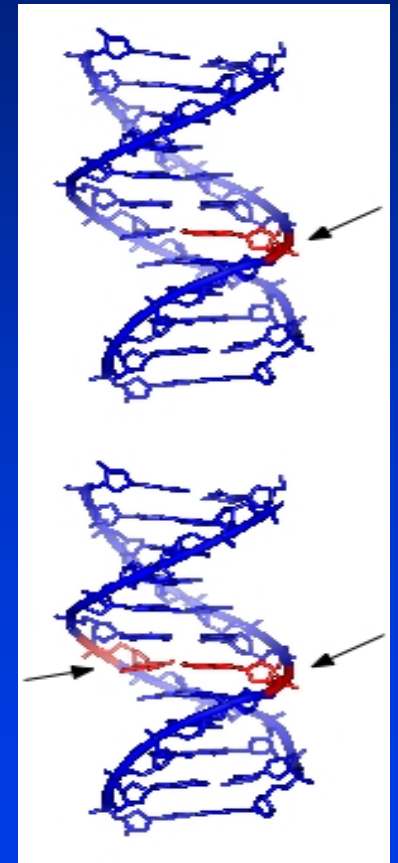
Repair!

# 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 2<sup>nd</sup> strand of the DNA molecule is needed for the repair enzymes to be able to copy the genetic information



# The effect of dose

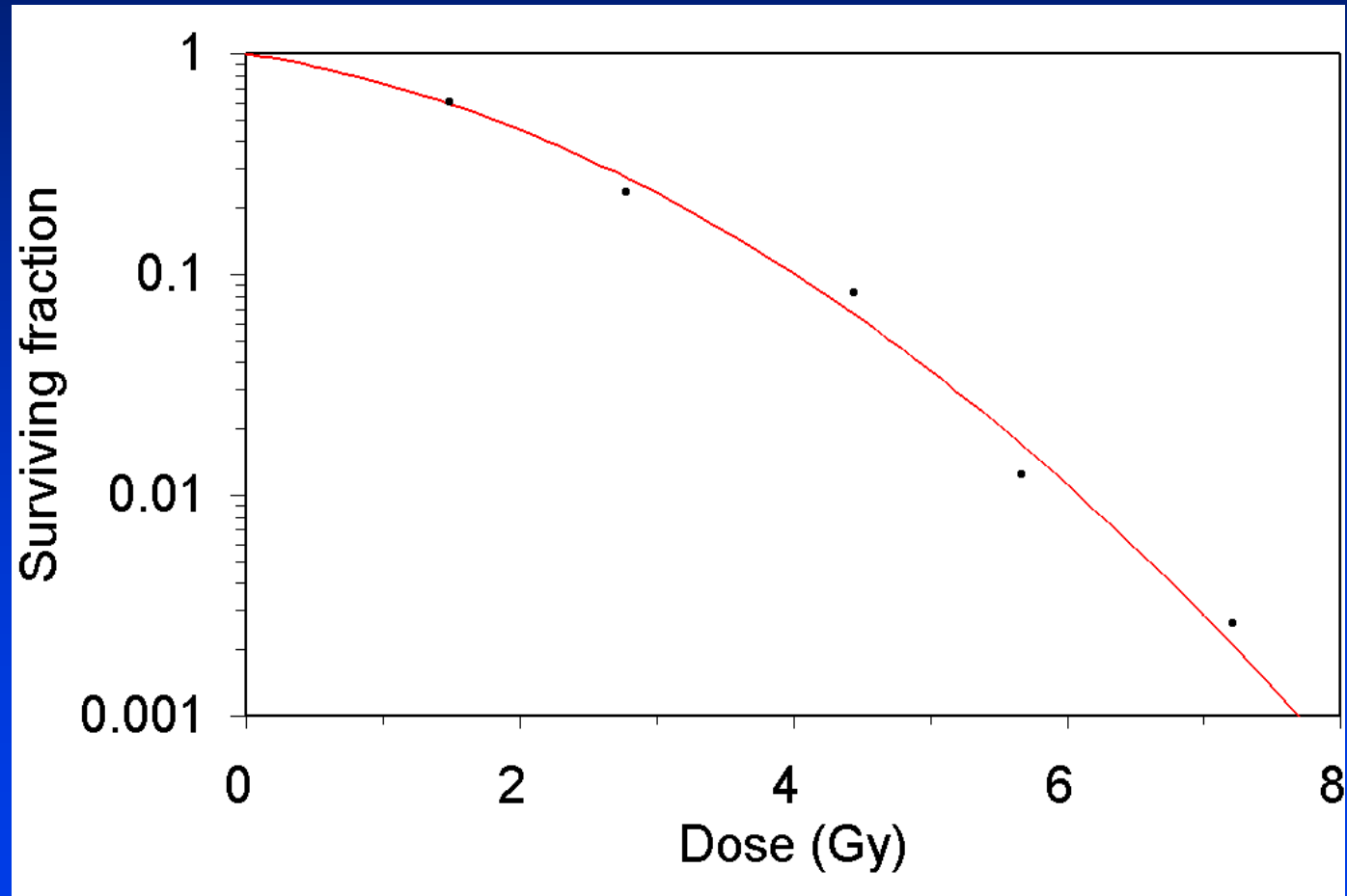
---

- ◆ 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



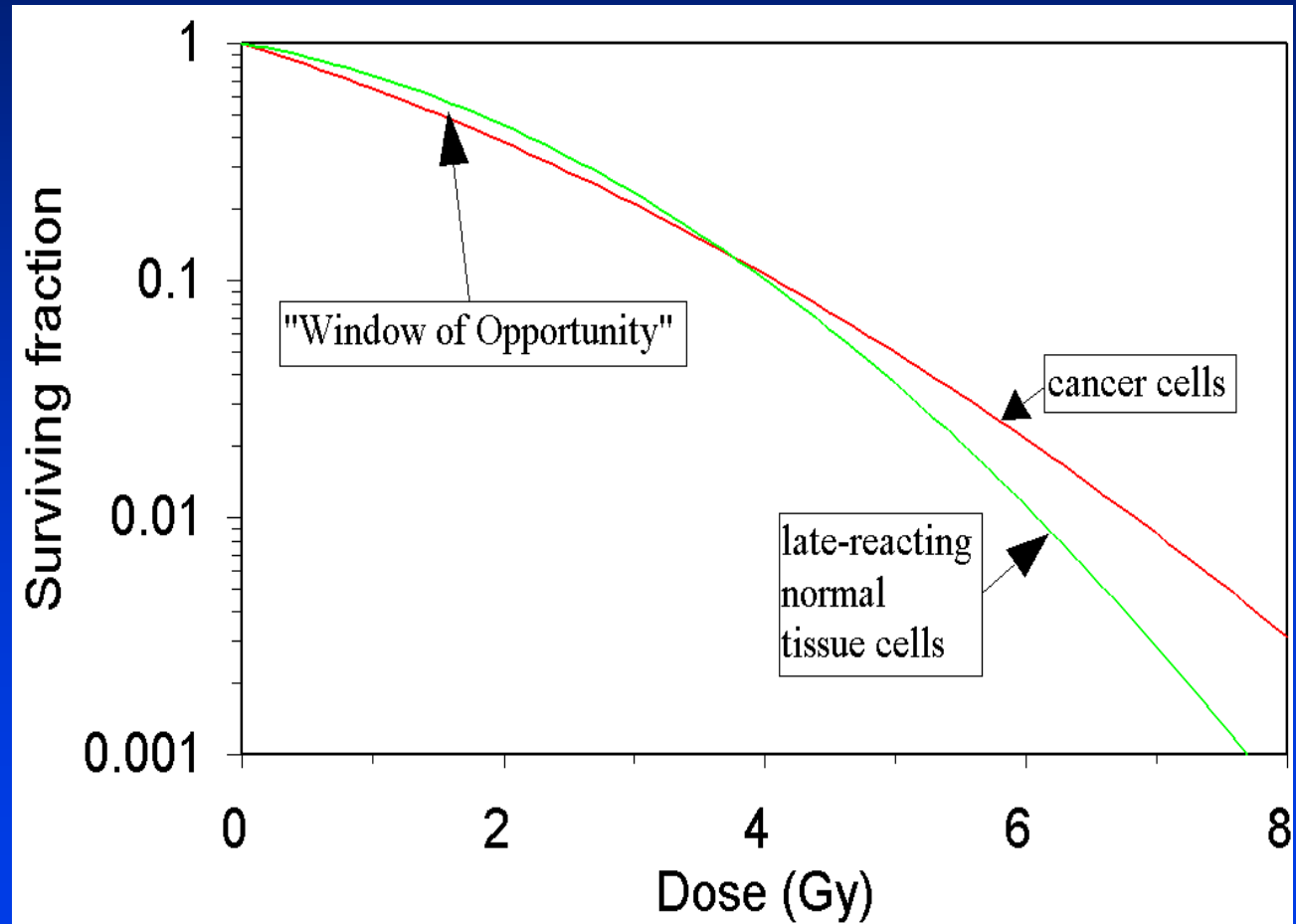
# Survival curves: normal vs cancer cells

- ◆ 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

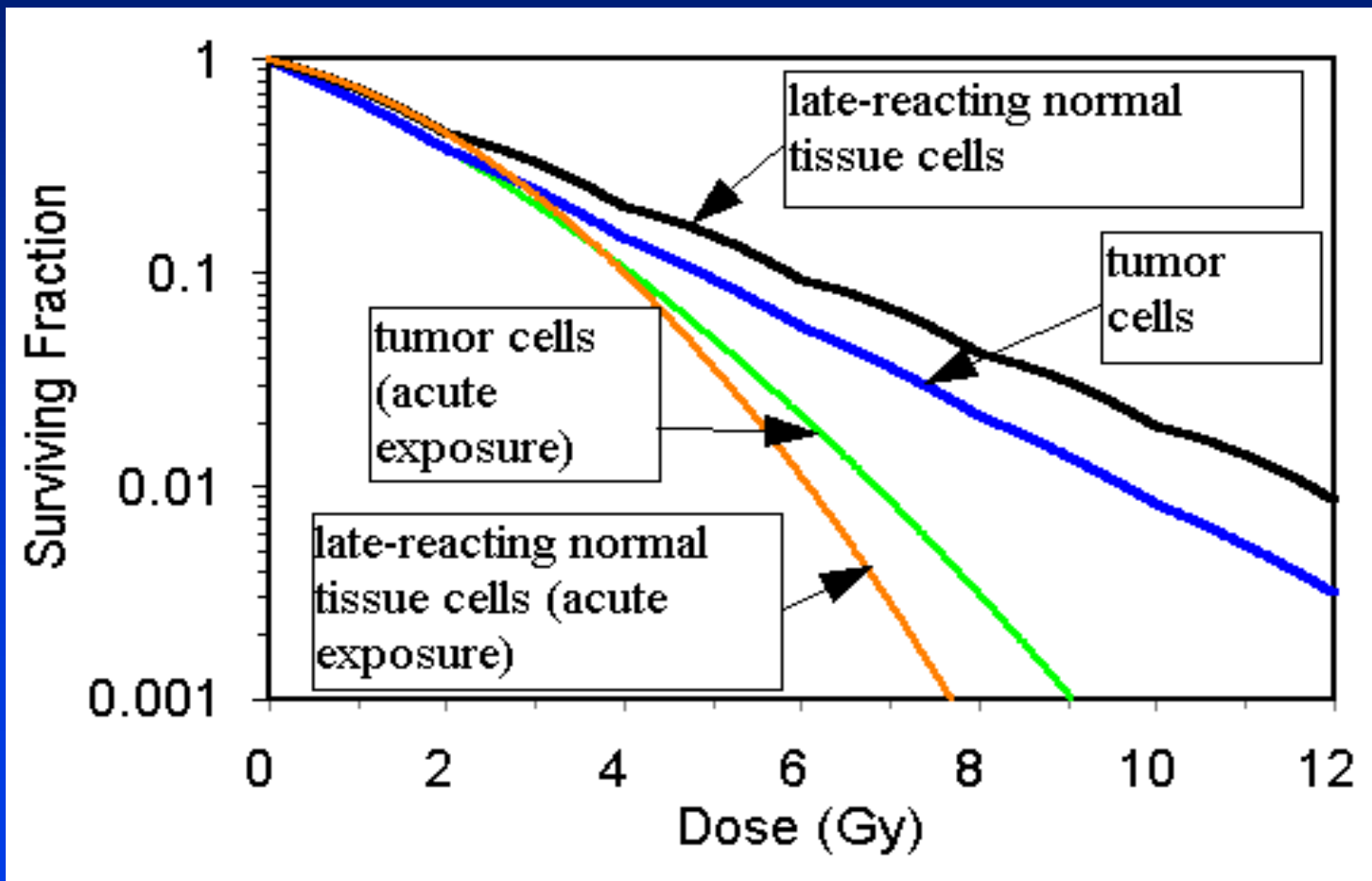


# Fractionation

---

- ◆ 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
- ◆ 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. Sometimes called the Equivalent Uniform Dose (EUD)*

# Geometrical sparing factor

---

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

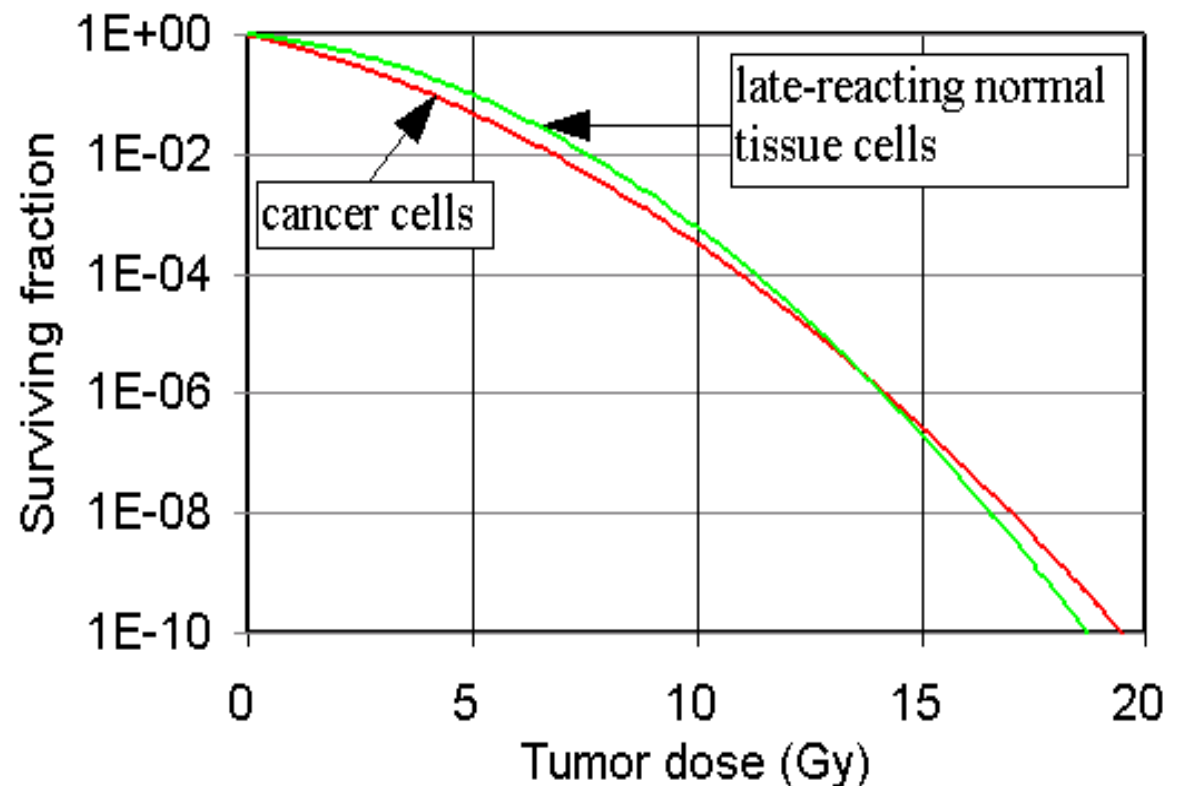
$$f = \frac{\text{effective dose to normal tissues}}{\text{effective dose to tumor}}$$

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

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



# 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*

# Radiobiologically important parameters we can control

## ◆ Fractionation

- *dose/fraction and number of fractions*
- *time between fractions*

## ◆ Dose rate

## ◆ Overall treatment time

# 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 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*

# How can we determine the “best” fractionation to use?

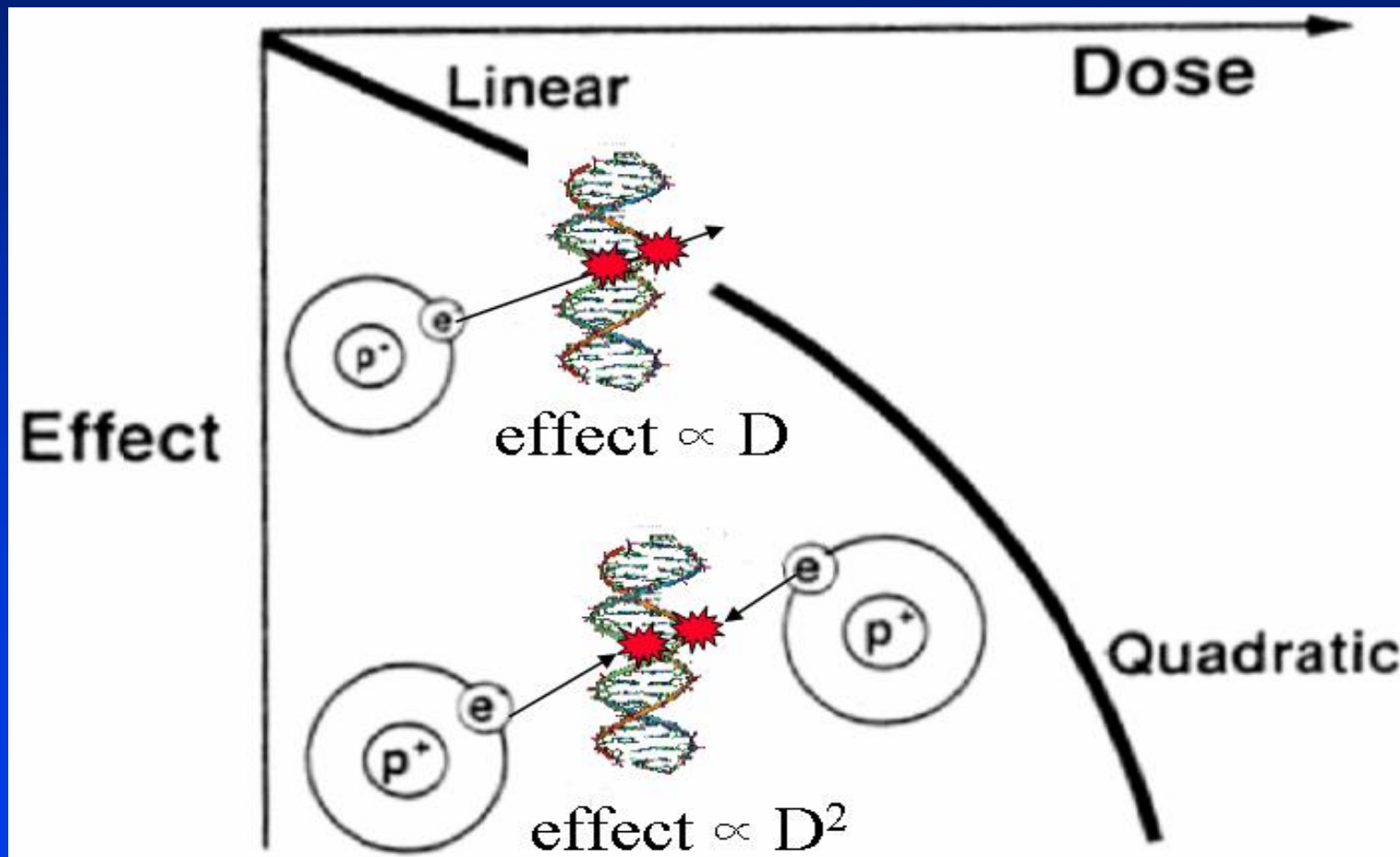
- ◆ We need a mathematical model that describes the effects of radiotherapy on cancer and normal tissue cells
  - *this is the linear-quadratic model*

# 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

---

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

$\alpha$  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  $d$

---

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

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  $\alpha/\beta$



# 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*

# What about repopulation?

---

The BED equation with repopulation is:

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

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 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

# 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 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, 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*



# 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

---

- ◆ Spreading irradiation over many fractions ought to be beneficial
  - *hyperfractionation might be the way to go, not hypofractionation*

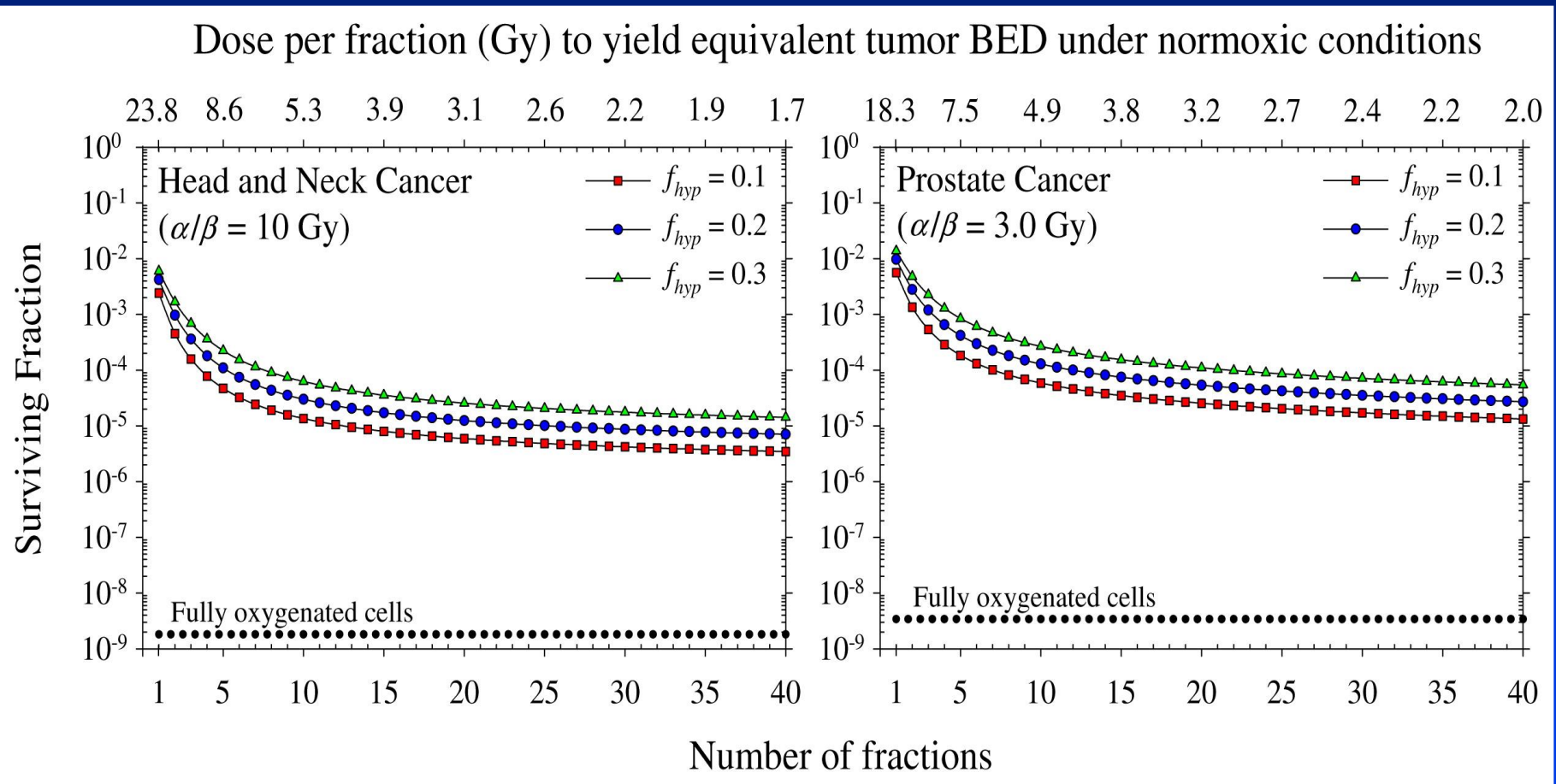
# **Hypofractionation Results in Reduced Tumor Cell Kill Compared to Conventional Fractionation for Tumors With Regions of Hypoxia**

---

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.

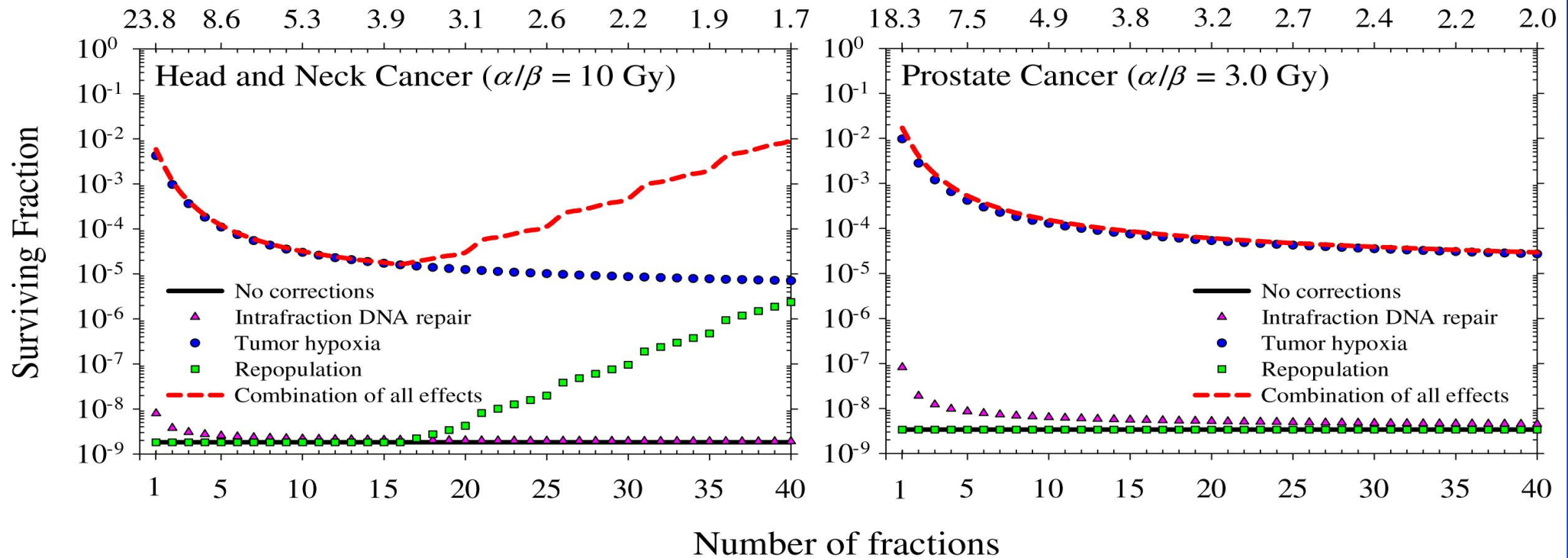
International Journal of Radiation Oncology \* Biology \* Physics  
Volume 79, Issue 4, Pages 1188-1195 (March 2011)

# Total surviving fraction of tumor cells assuming daily fractionation and full reoxygenation between fractions



# What happens if we add repopulation of tumor cells (with $f_{hyp} = 0.2$ )?

Dose per fraction (Gy) to yield equivalent tumor BED under normoxic conditions



# 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?

# 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

NTD = normalized total dose (to 2 Gy fractions)

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

Hypoxia and repopulation assumed negligible



# Estimated increases in bNED (equivalent to 72 Gy at 2 Gy/fraction)

---

No. Frs	Dose per Fr	Total dose (Gy)	NTD (Gy)	bNED (%)
36	2.00	72.00	72.0	69.2
25	2.58	64.51	75.2	77.0
20	3.00	60.00	77.1	81.0
15	3.62	54.35	79.5	85.2
10	4.69	46.85	82.8	89.6
5	7.12	35.58	87.6	94.0

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

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

# 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*

# Fowler's conclusions (cont'd.)

---

*We caution again 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:**

## **low-dose hypersensitivity**

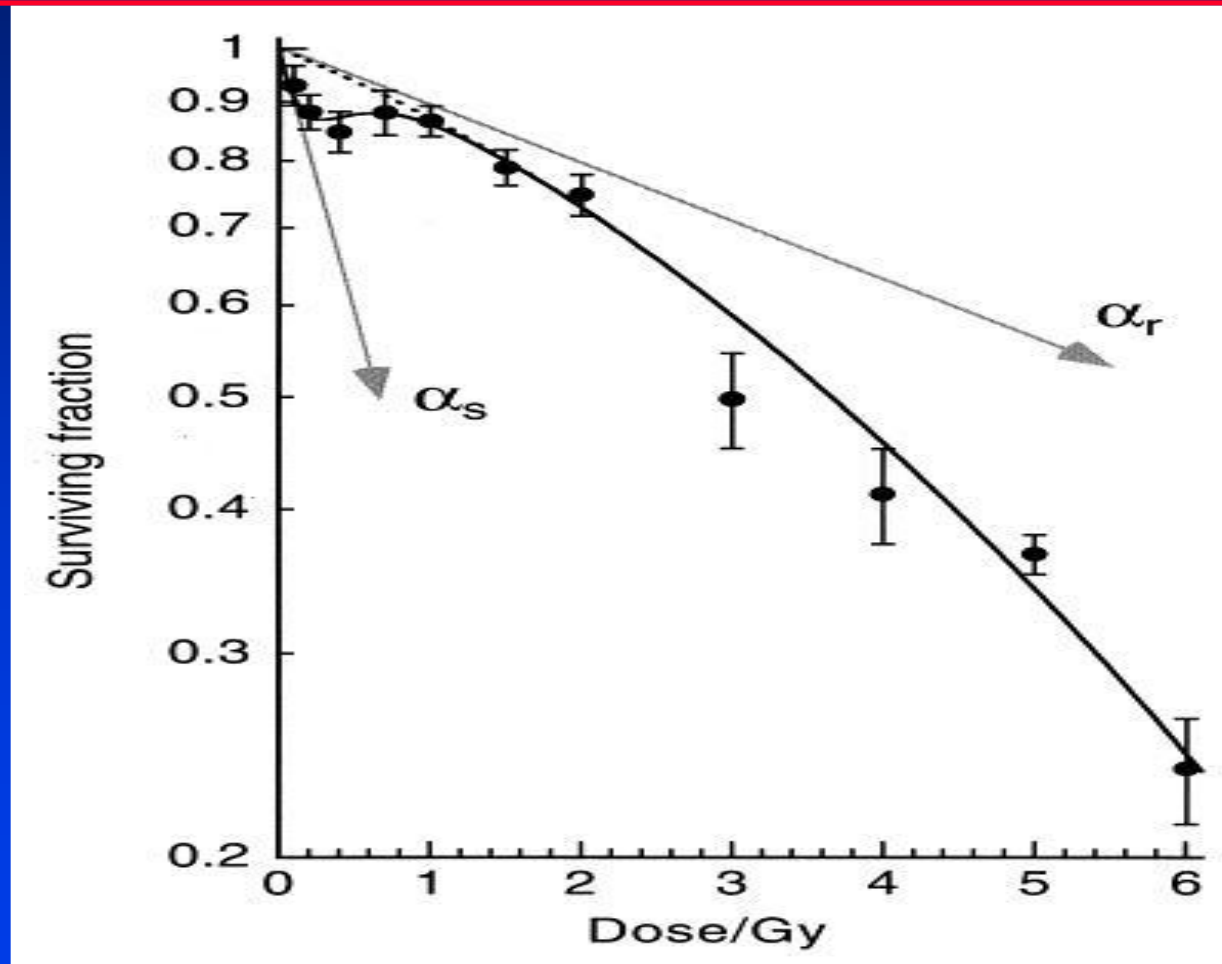
**Low-dose hypersensitivity: current status and possible mechanisms**

Michael C Joiner, Ph.D., Brian Marples, Ph.D., Philippe Lambin, M.D., Ph.D., Susan C Short, Ph.D. and Ingela Turesson, M.D., Ph.D.

International Journal of Radiation Oncology \* Biology \* Physics  
Volume 49, Issue 2, Pages 379-389 (February 2001)



# Low-dose hyper-radiosensitivity (HRS) for human glioma cells



# Why might HRS be a problem for hypofractionation?

---

- ◆ When we demonstrated that hypofractionation might be the treatment of choice because of geometrical sparing of normal tissues we assumed that the lower doses to normal tissues would cause less damage
  - *with HRS, however, this might not be true*



# 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 their half-time for repair is longer than for cancer 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

## IMPACT OF PROLONGED FRACTION DELIVERY TIMES ON TUMOR CONTROL: A NOTE OF CAUTION FOR INTENSITY-MODULATED RADIATION THERAPY (IMRT)

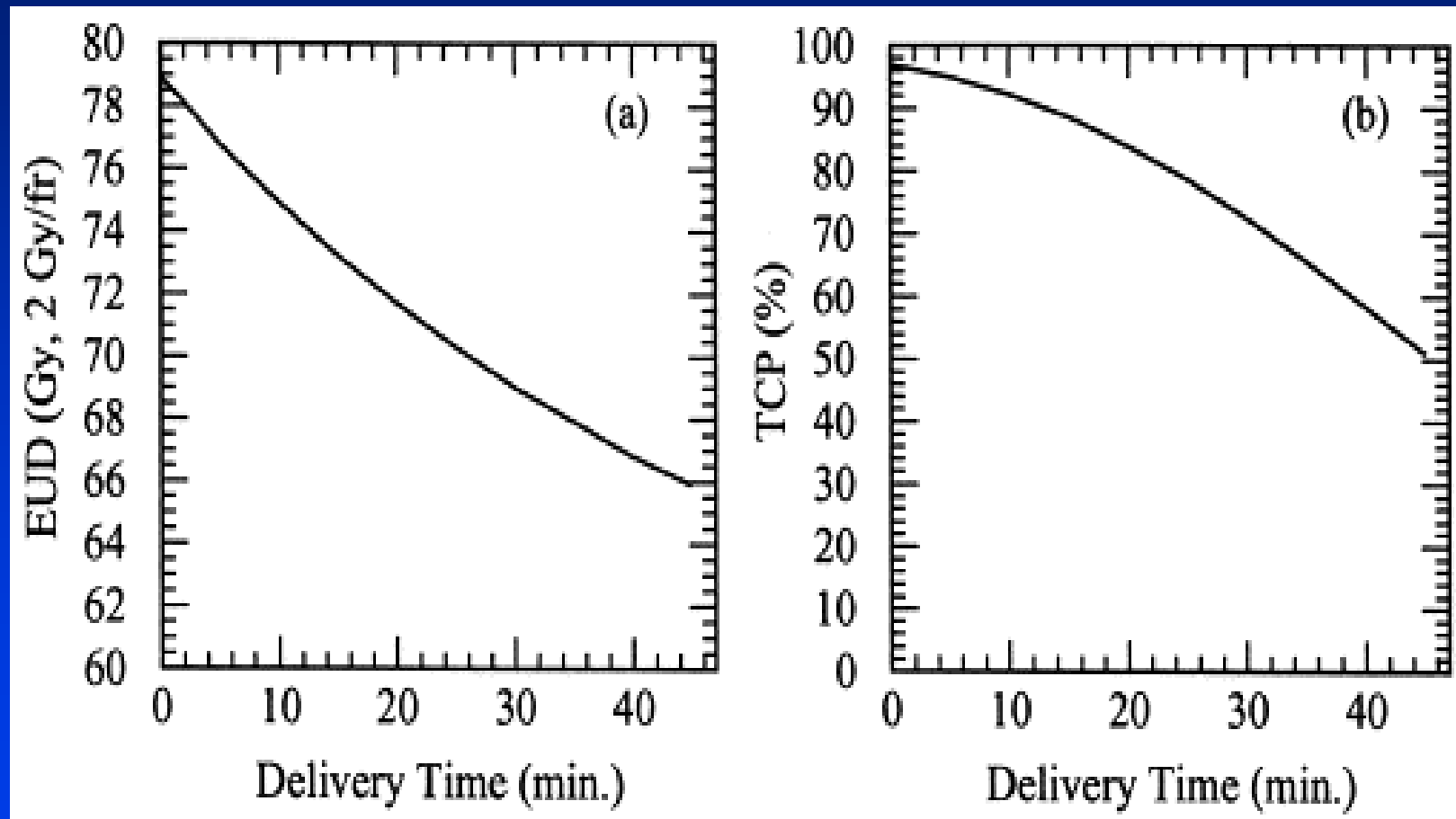
JIAN Z. WANG, PH.D.,\* X. ALLEN LI, PH.D.,\* WARREN D. D'SOUZA, PH.D.,\* AND  
ROBERT D. STEWART, PH.D.†

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:

$\alpha = 0.15 \text{ Gy}^{-1}$ ,  $\alpha/\beta = 3.1 \text{ Gy}$ , repair half time = *16 min*,  
and the initial number of cancer cells =  $3.0 \times 10^6$

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

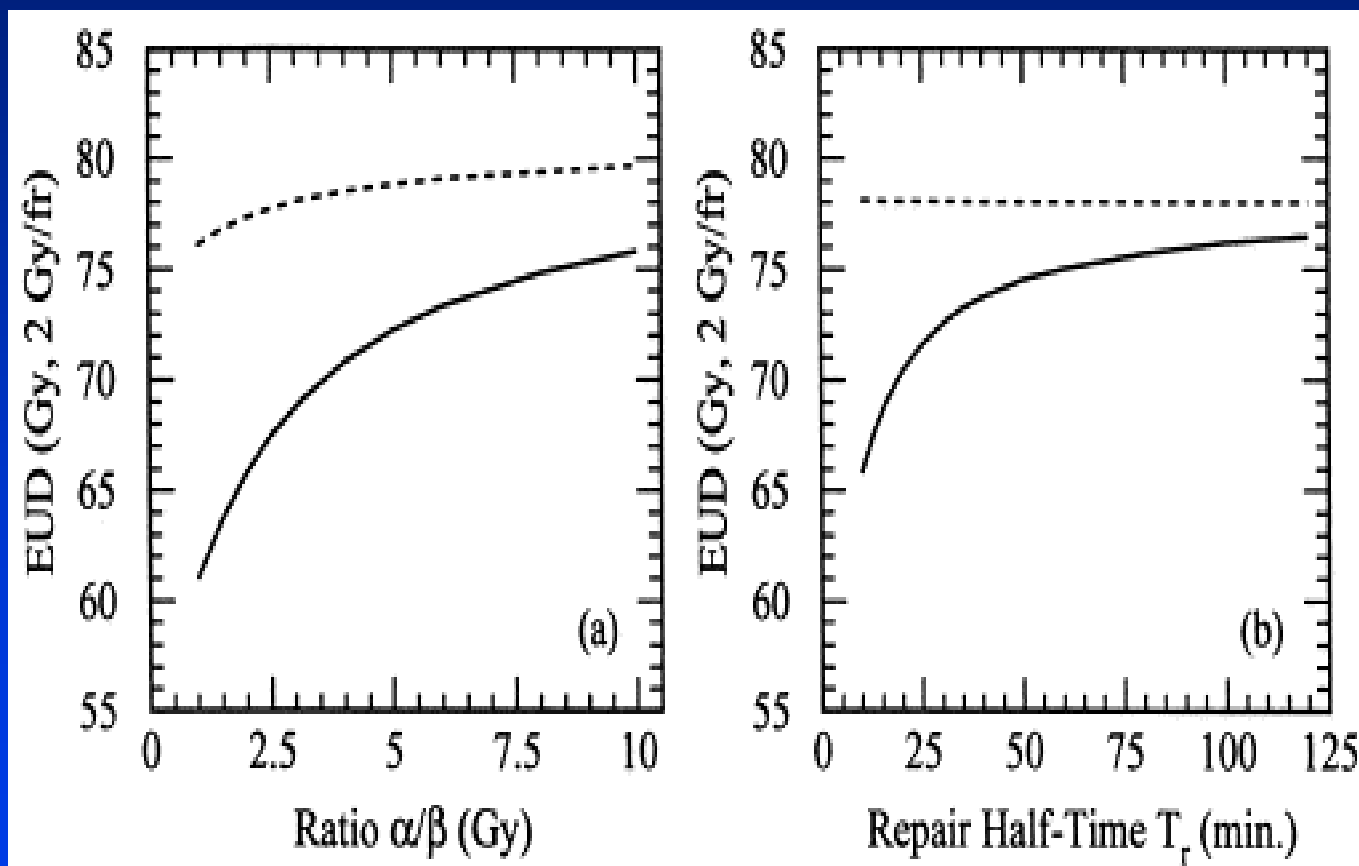


# EUD as a function of $\alpha/\beta$ ratio and repair half-time for prostate cancer

---

--- 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*

# 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

# But we need to be careful

---

- ◆ Hypofractionation might not be appropriate if:
  - *the fraction of hypoxic cells is significant*
  - *low-dose hypersensitivity reduces the effectiveness of highly conformal therapy*
  - *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