Linear Quadratic (LQ) Model & Biological based treatment planning

Prof Manoj Gupta

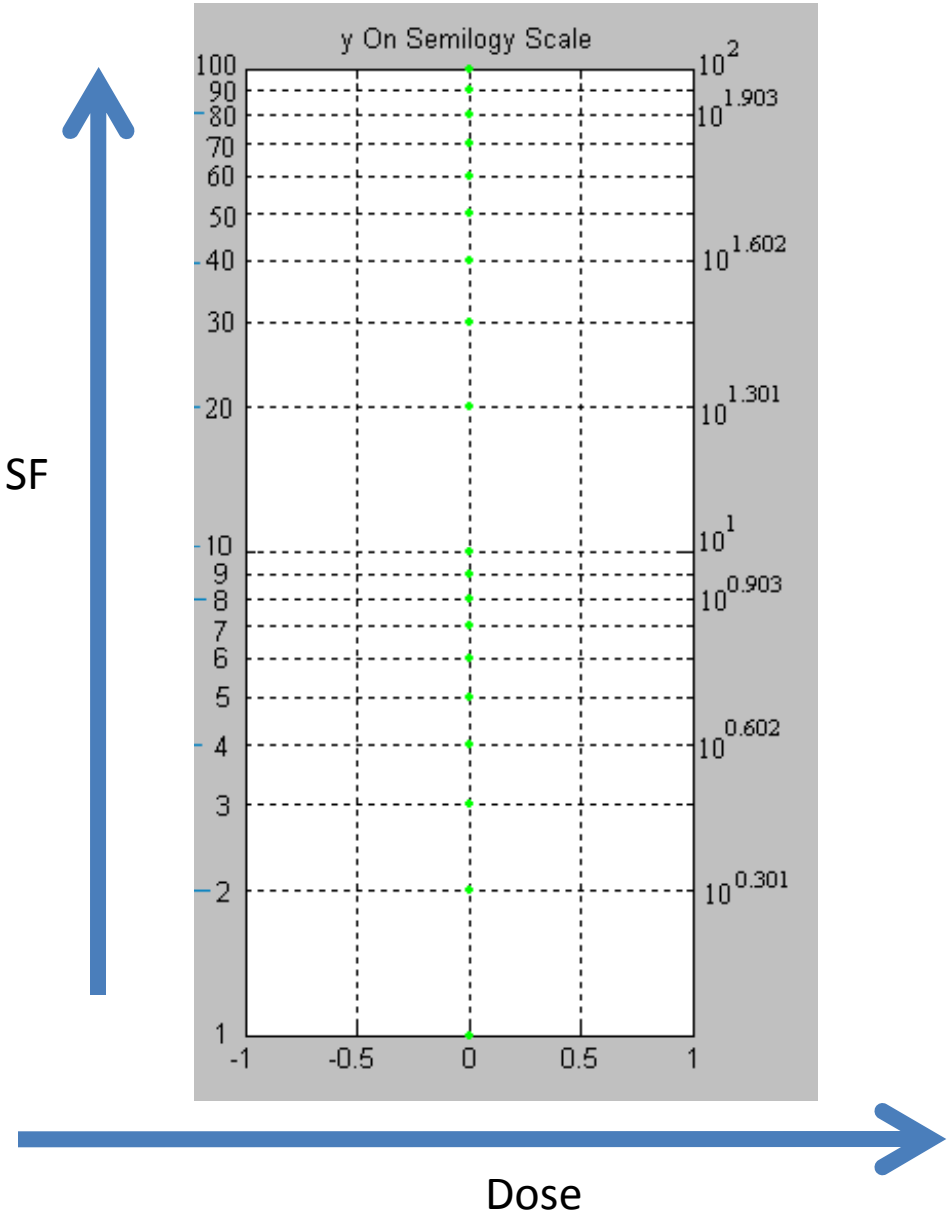
Indira Gandhi Medical College

Shimla

ICRO Teaching Course at Bathinda

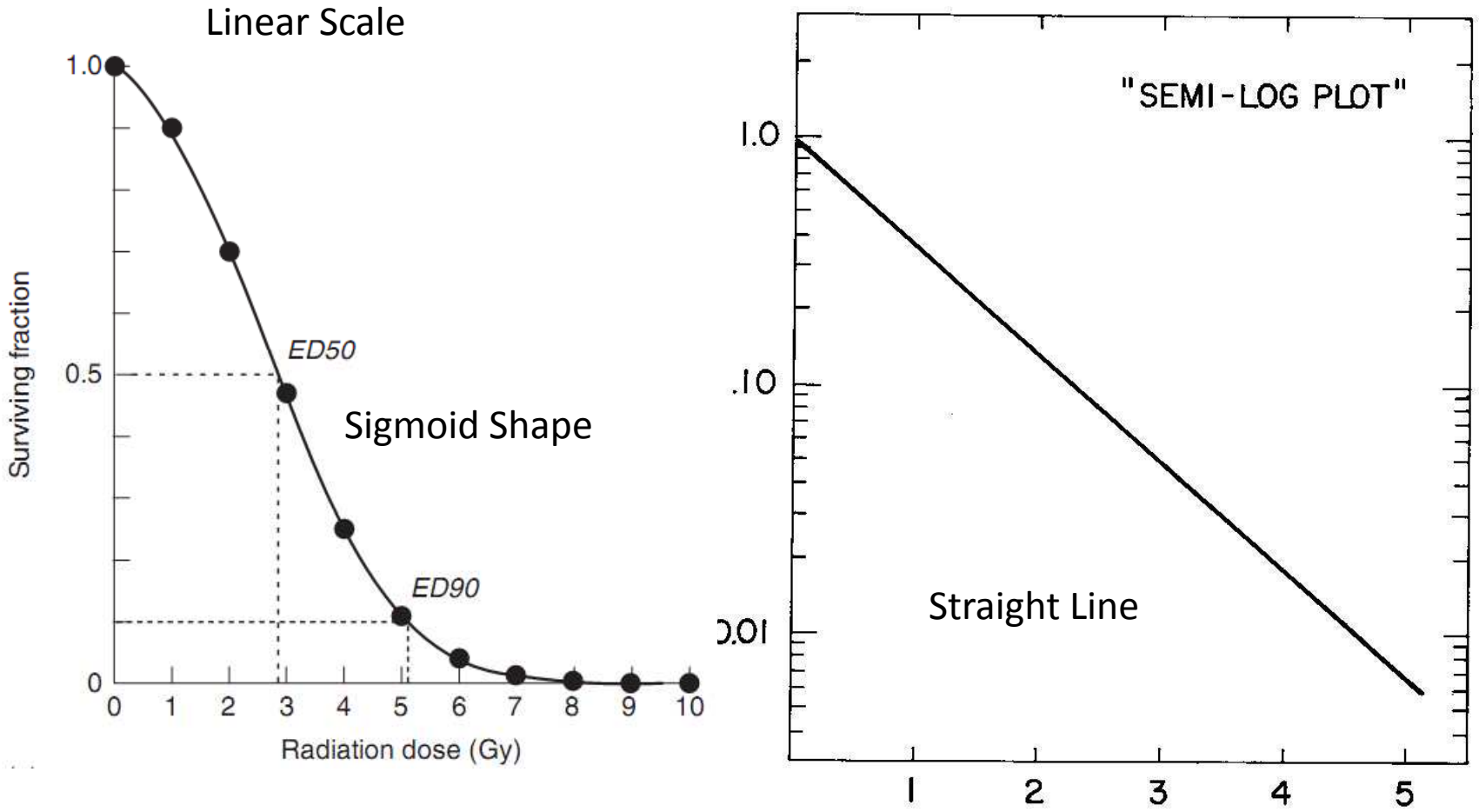
5th Nov. 2012

What is a cell survival curve?



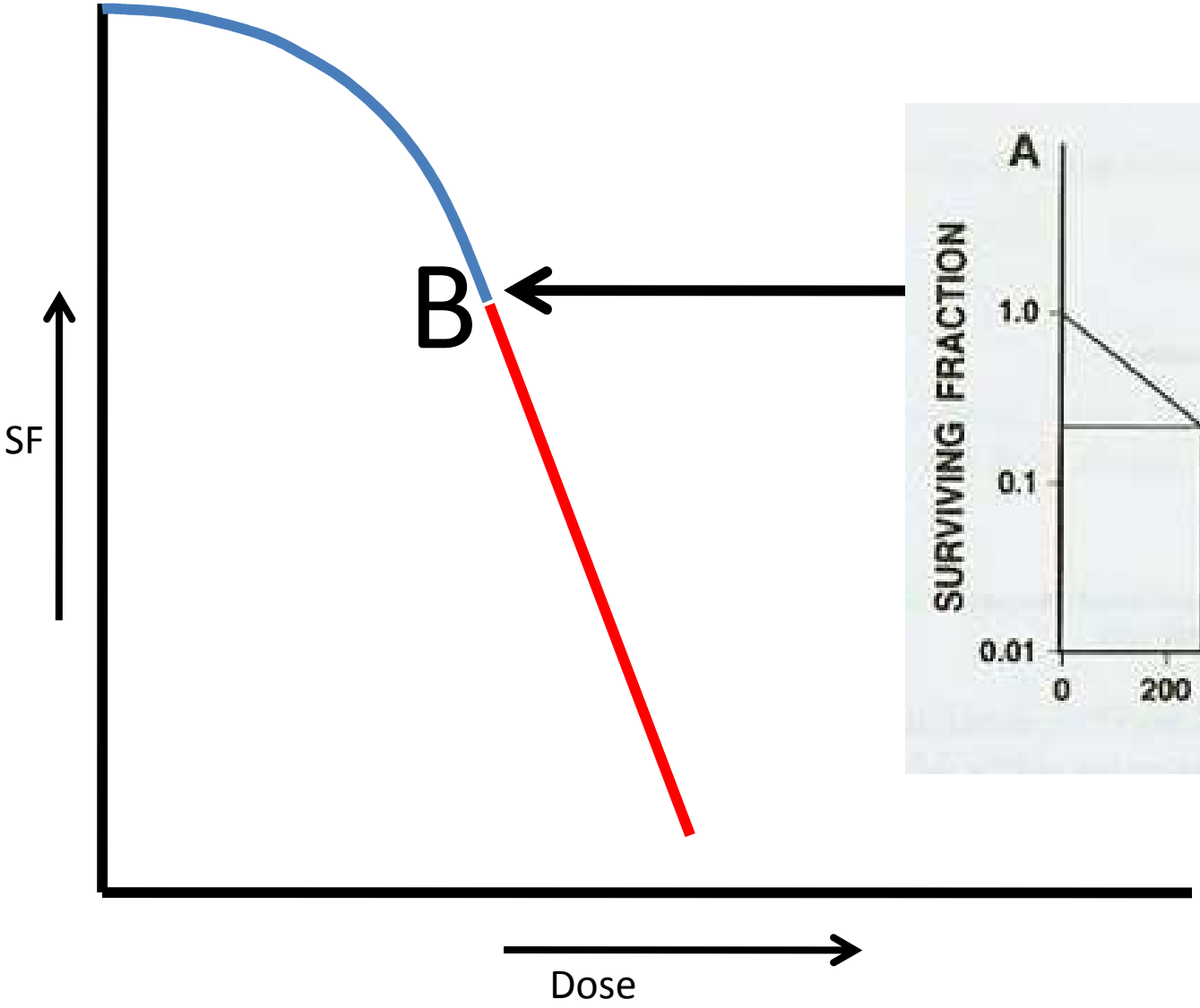
- A cell survival curve is a graphical representation of the fraction of cells surviving a given dose of radiation
- This graph is obtained by plotting the surviving fraction along the logarithmic y-axis and the dose along the linear x-axis

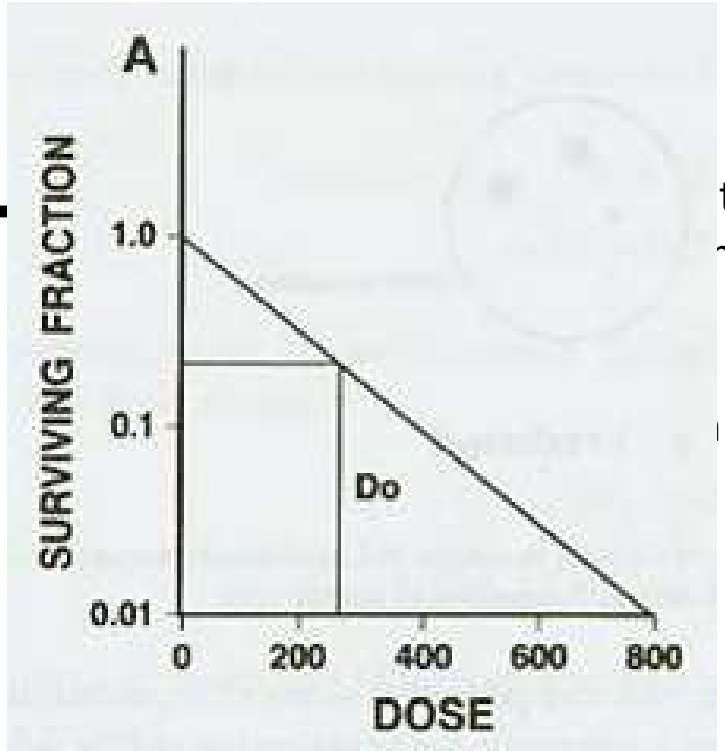
Reminder: All curves are plotted on semi-log plots



Cell Survival Curve of Micro-organism

Mammalian Cell Survival Curve



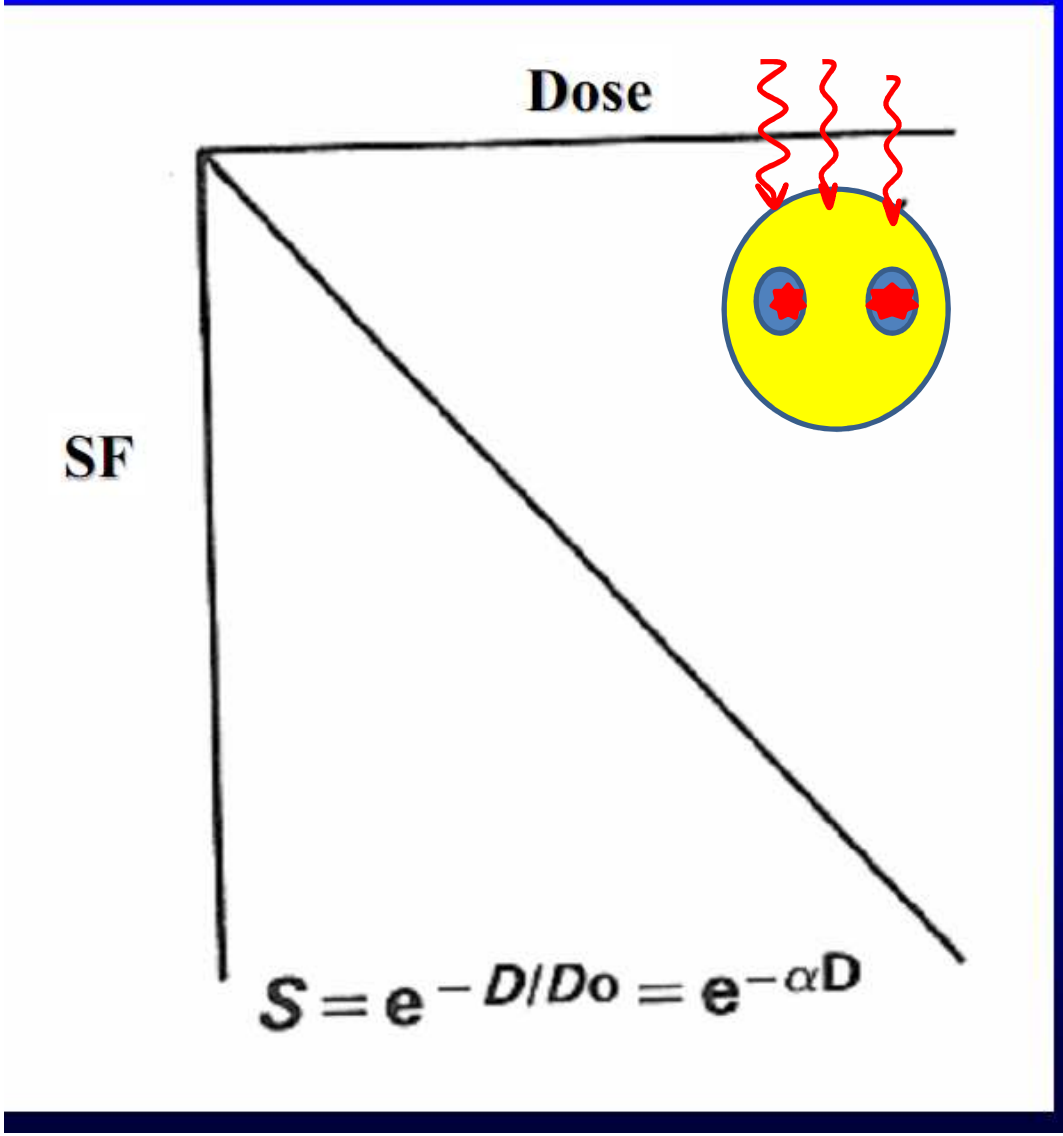


Two Models to describe mammalian cell survival curve

- Multi Target Model
- Linear Quadratic (LQ) Model

Linear Quadratic model (LQ Model)

Single target, single hit (linear model)



- Only one target has to be inactivated.
- This target is considered to be two strands of DNA
- Effect α D

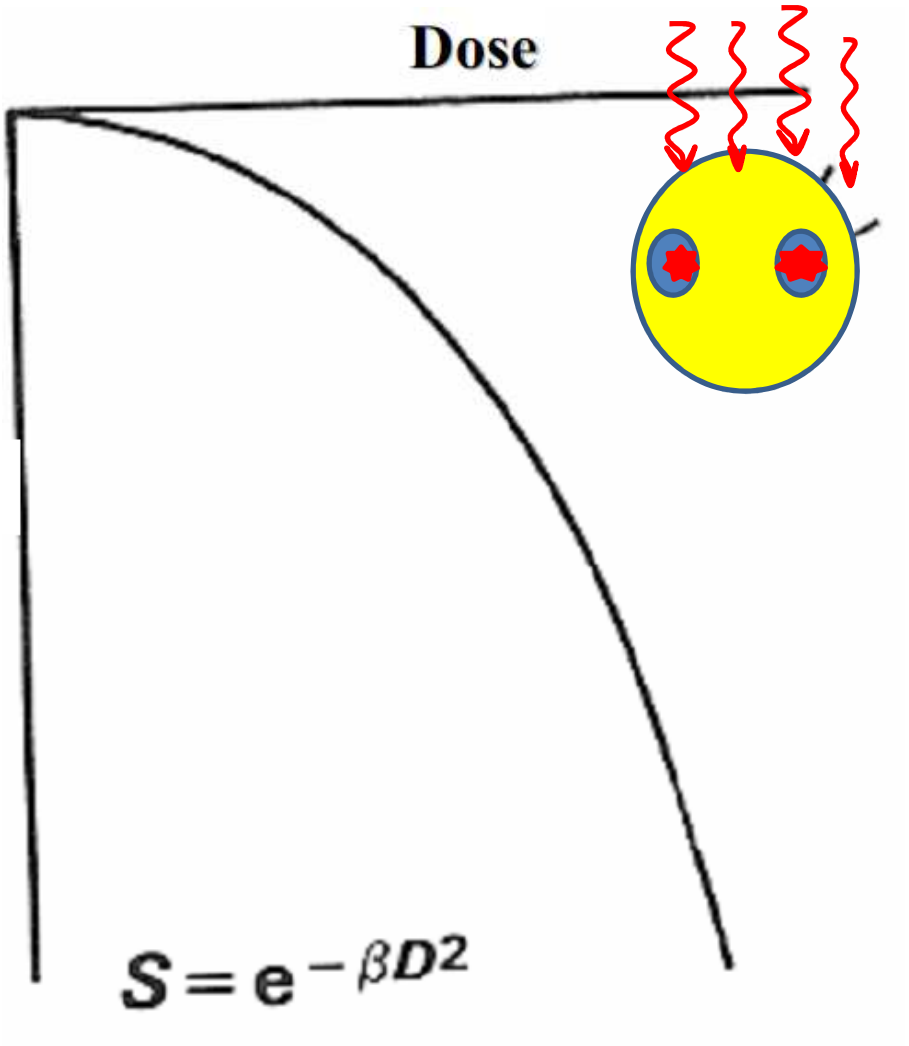
$$\text{Effect} = \alpha D$$

$$SF = e^{-\alpha D}$$

- The α term represent the probability of inactivating a target directly by single hit, meaning two strands of DNA are hit by single exposure.

Linear Quadratic model (LQ Model)

Single target, two hits (quadratic model)



The term represent the inactivation of two strands of DNA by two different radiation events, each strand inactivation represent sub lethal damage, interaction of which result into cell death. The sub lethal damage may be repaired called Elkind's Recovery

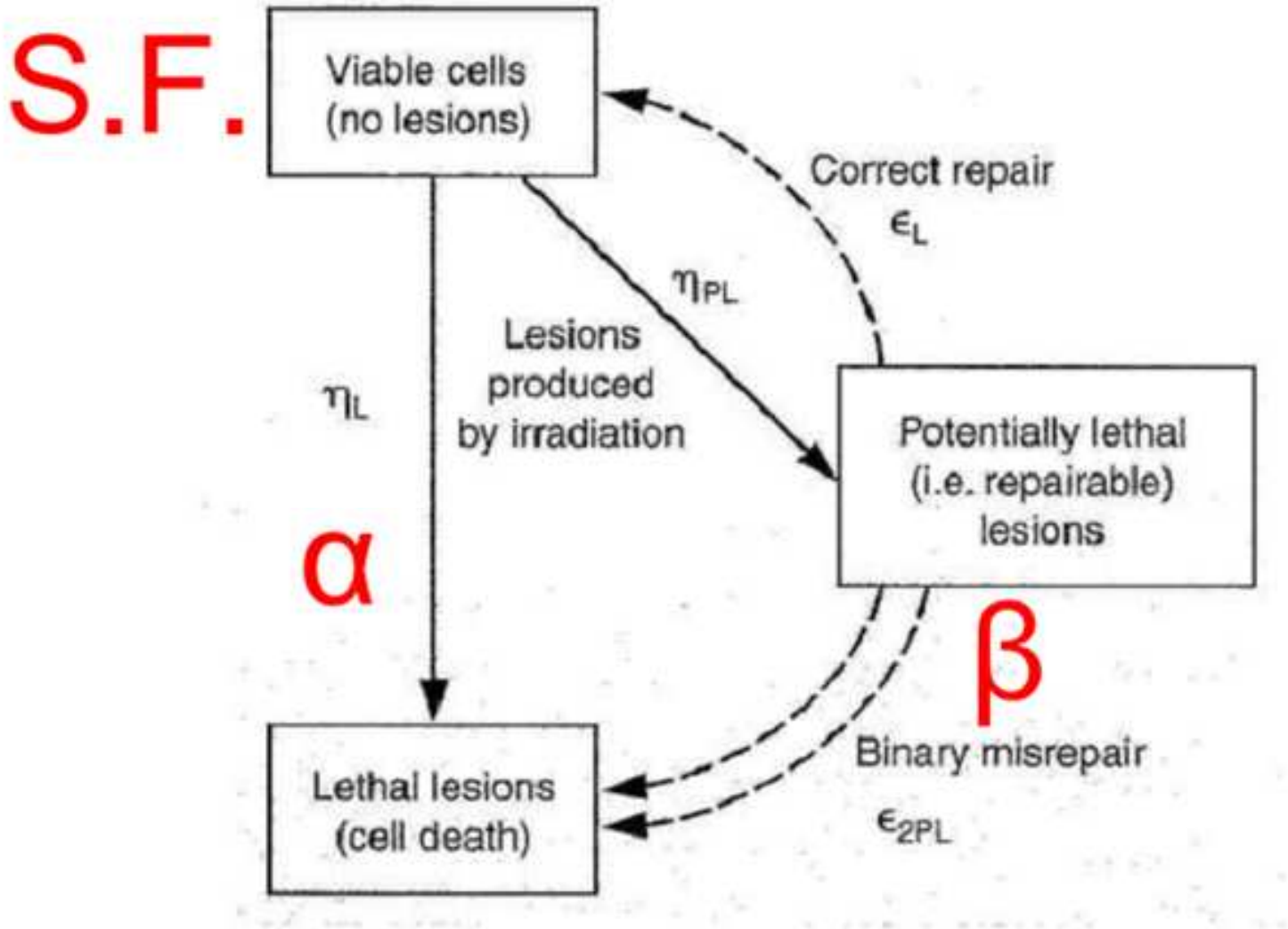
Effect α D^2

$$\text{Effect} = \beta D^2$$

$$SF = e^{-\beta D^2}$$

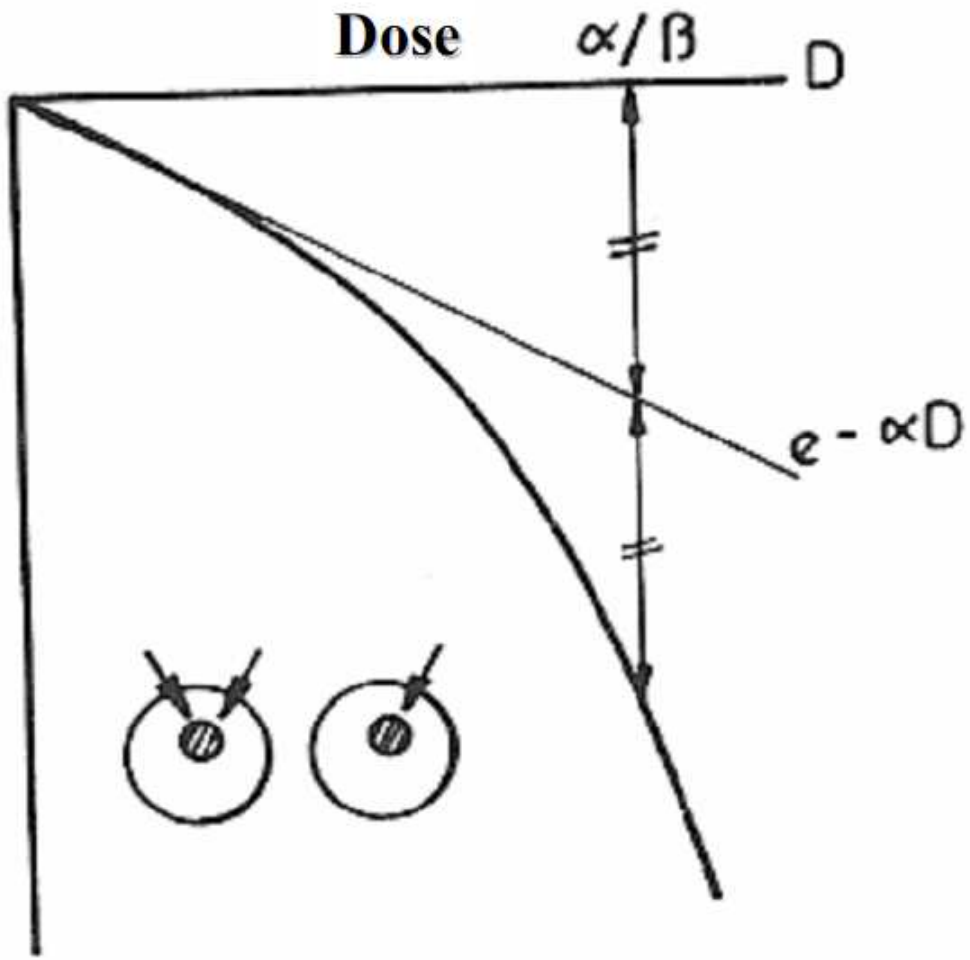
Double hit kill is similar to the MHE

Linear Quadratic model (LQ Model)



The sum of the two process of cell killing (linear and quadratic) will decide the final survival fraction.

Linear-quadratic model

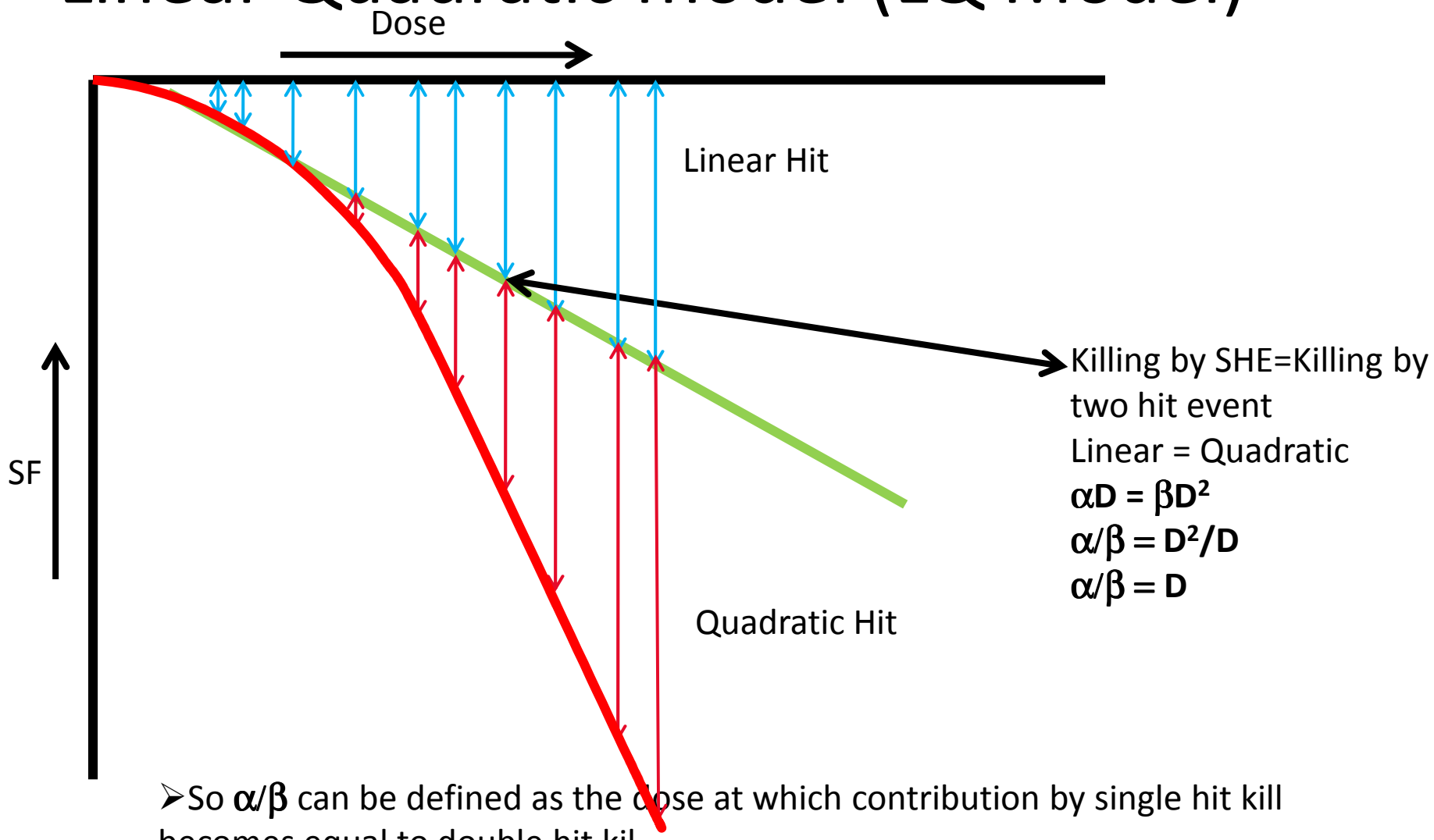


$$S = e^{-(\alpha D + \beta D^2)}$$

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

$$SF = e^{-(aD+\beta D^2)}$$

Linear Quadratic model (LQ Model)

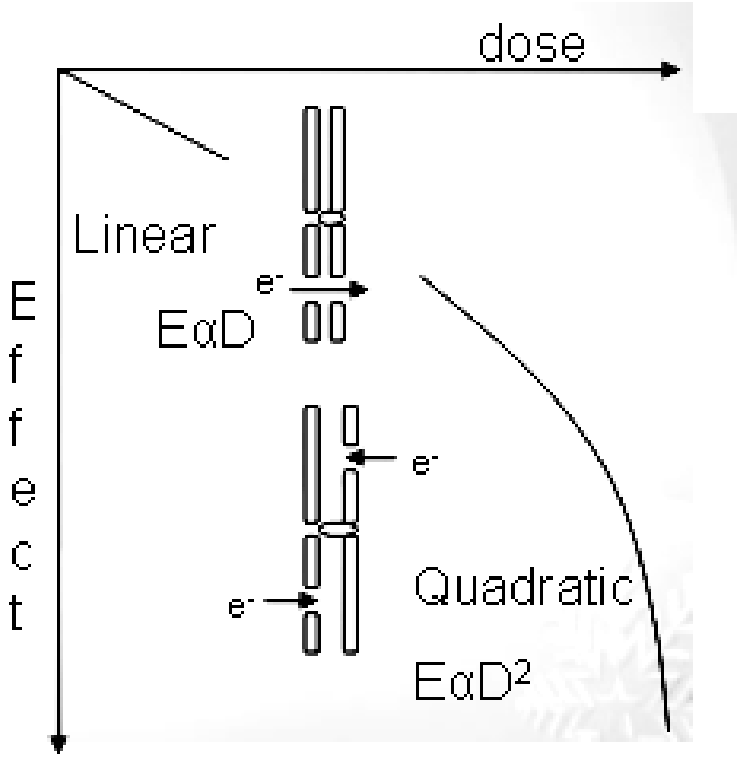


- So α/β can be defined as the dose at which contribution by single hit kill becomes equal to double hit kil.

- It represent the dose beyond which the double hit kill becomes main mode of cell kill and before that the cell kill is mainly by single hit.

WHAT IS α/β?

- α/β = D, dose at which the contribution in cell kill by both processes becomes equal.
- α/β also represents the point beyond which the curve becomes a straight line and predominantly double hit events take place.

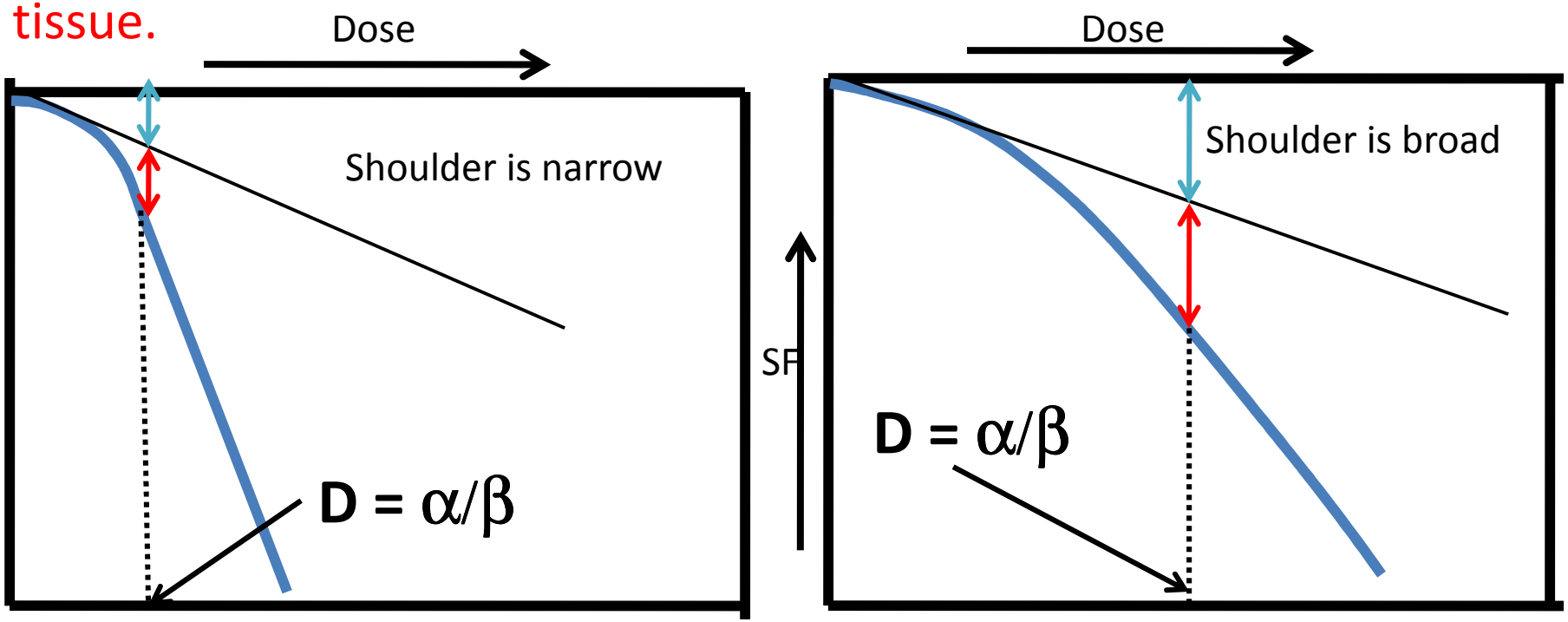


α/β Ratio defines "curviness" of survival curve

Small α/β ratio indicate more curvy nature of the shoulder As seen in late responding tissue

large α/β ratio indicate less curvy nature as seen in early responding tissue

In late reacting tissue, the killing by MHE will surpass the killing by SHE quicker and at lower dose as compare to the early reacting tissue.



Late responding tissue α/β = 1Gy to 7 Gy (3Gy)
Responsible for late effect of radiation
Eg. Spinal cord, urinary bladder, kidney, liver etc.

Early responding tissue α/β = 6Gy to 15 Gy (10)
Responsible for acute effect of radiation
Eg, skin, mucosa, lining of intestine, bone marrow etc.

Calculated α/β ratios for some tissues

TABLE 22.1. *Ratio of Linear to Quadratic Terms From Multifraction Experiments*

Reactions	α/β, Gy
Early	
Skin	9–12
Jejunum	6–10
Colon	10–11
Testis	12–13
Callus	9–10
Late	
Spinal cord	1.7–4.9
Kidney	1.0–2.4
Lung	2.0–6.3
Bladder	3.1–7

Calculated α/β ratios for some tumors

Tumors	
Head and neck: nasopharynx	16 (–11; 43) Gy
Vocal cord	~13 Gy
Buccal mucosa	~6.6 (2.9; ∞) Gy
Tonsil	7.2 (3.6; ∞) Gy
Larynx	14.5 (4.9; 24) Gy
Lung: squamous cell carcinoma	~50-90 Gy
Cervix: squamous cell carcinoma	>13.9 Gy
Skin	
Squamous cell carcinoma	8.5 (4.5; 11.3) Gy
Melanoma	0.6 (–1.1; 2.5) Gy
Prostate	1.1 (–3.3; 5.6) Gy
Breast (early-stage invasive ductal, lobular, and mixed)	4.6 (1.1; 8.1) Gy
Esophagus	4.9 (1.5; 17) Gy
Liposarcoma	0.4 (–1.4; 5.4) Gy

.ondon, 2009, Hodder Arnold.

Difference Between Late and Early Reacting Tisue

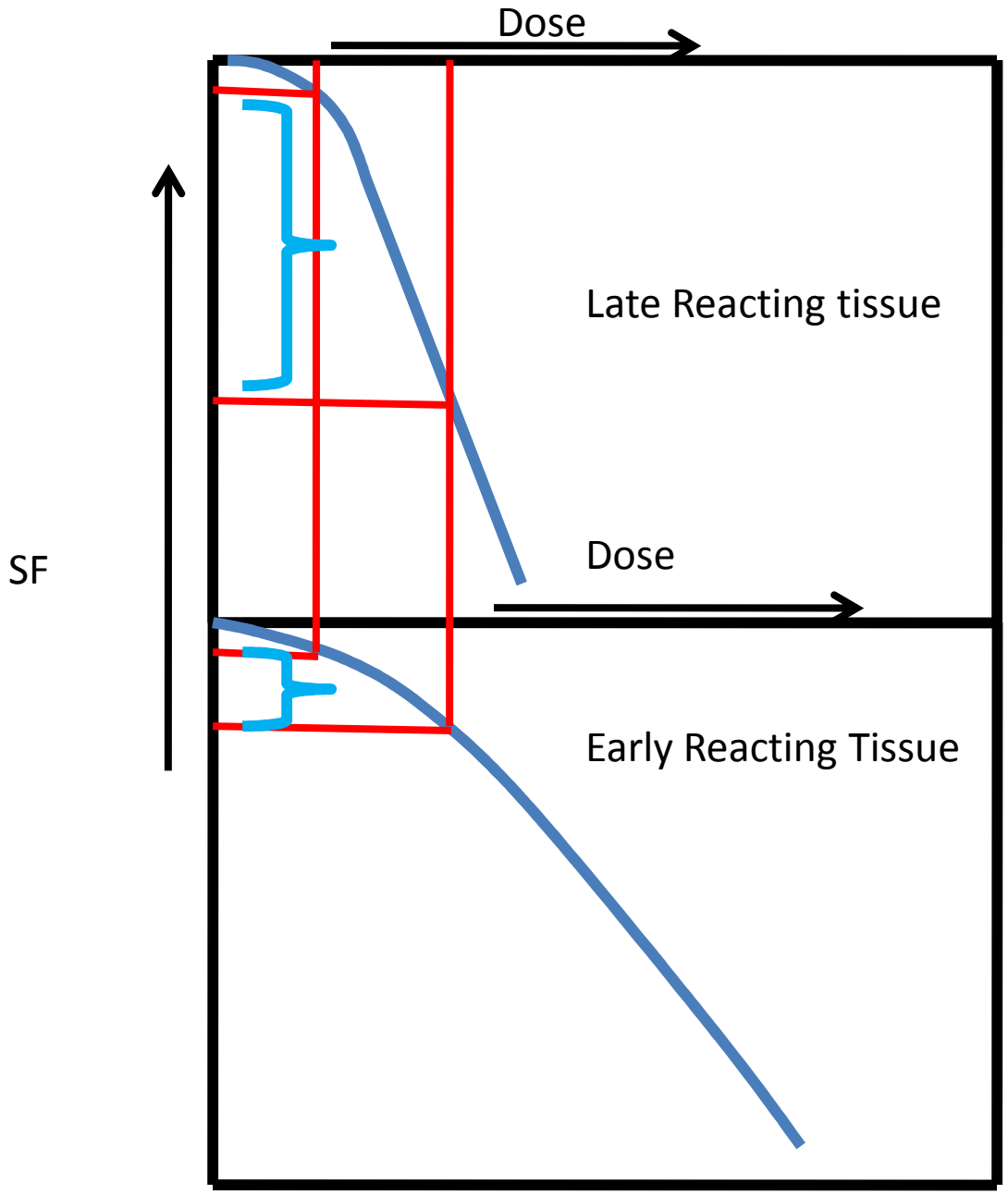
- Late reacting tissue: spinal cord, bladder, kidney.
- Shoulder is narrow.
- Exponential relationship reaches early in late reacting tissue.

- Early reacting tissue: skin mucosa, bone marrow.
- Shoulder is broader.
- Exponential relationship reaches late in early reacting tissue.

Factors affecting Normal Tissue Injury

- Fraction size (Dose per fraction)
- Turnover (proliferative status)
- Overall treatment time.
- Organization of functional subunit in the organ.

Fraction size (Dose per fraction)



- Effect of change in dose per fraction on normal tissue injury depends upon the shape of survival curve.

- Change in dose per fraction damages late reacting tissue more than early reacting tissues

Turnover(Proliferative status)

- Proliferative status mainly determine the timing of expression of injury as radiation injury manifests when cell attempts to multiply.
- Epithelial and hematopoietic have rapid turnover so injury will manifest early as acute effects and usually take days to weeks.
- Late effects occur in tissue with slow turn over like endothelial, neurological tissues and parenchymal tissue of lung, liver and kidney and manifest late, usually takes months to years.

Overall treatment time

- Overall treatment time affects normal tissue injury because of repopulation which occur only in early reacting tissues.
- Increasing overall treatment time will spare early reacting tissues only.
- Late responding tissue do not experience repopulation so increasing overall time during the course of radiotherapy will not spare them.

Organization of functional subunit in the organ.

- If functional subunits are arranged in serial like in spinal cord, damage to some subunit will lead to change in the whole organ.
- In organs where subunits are arranged in parallel like kidneys, each subunit acts independently, and if some subunits are damaged, organ continue to function normally.

CLINICAL SIGNIFICANCE OF α/β RATIO

Early tissues

- Are rapidly proliferating tissues
- Early reactions are reduced by:
  - Lengthening over all time,
  - Keeping intervals between fractions to more than 5-6 hours to allow for repair

CLINICAL SIGNIFICANCE OF α/β RATIO

Late responding tissues

- Slowly proliferating tissues
- Changes in overall time do not have much affect on late responding tissues
- Late reactions are reduced by:
  - Reducing the dose per fraction

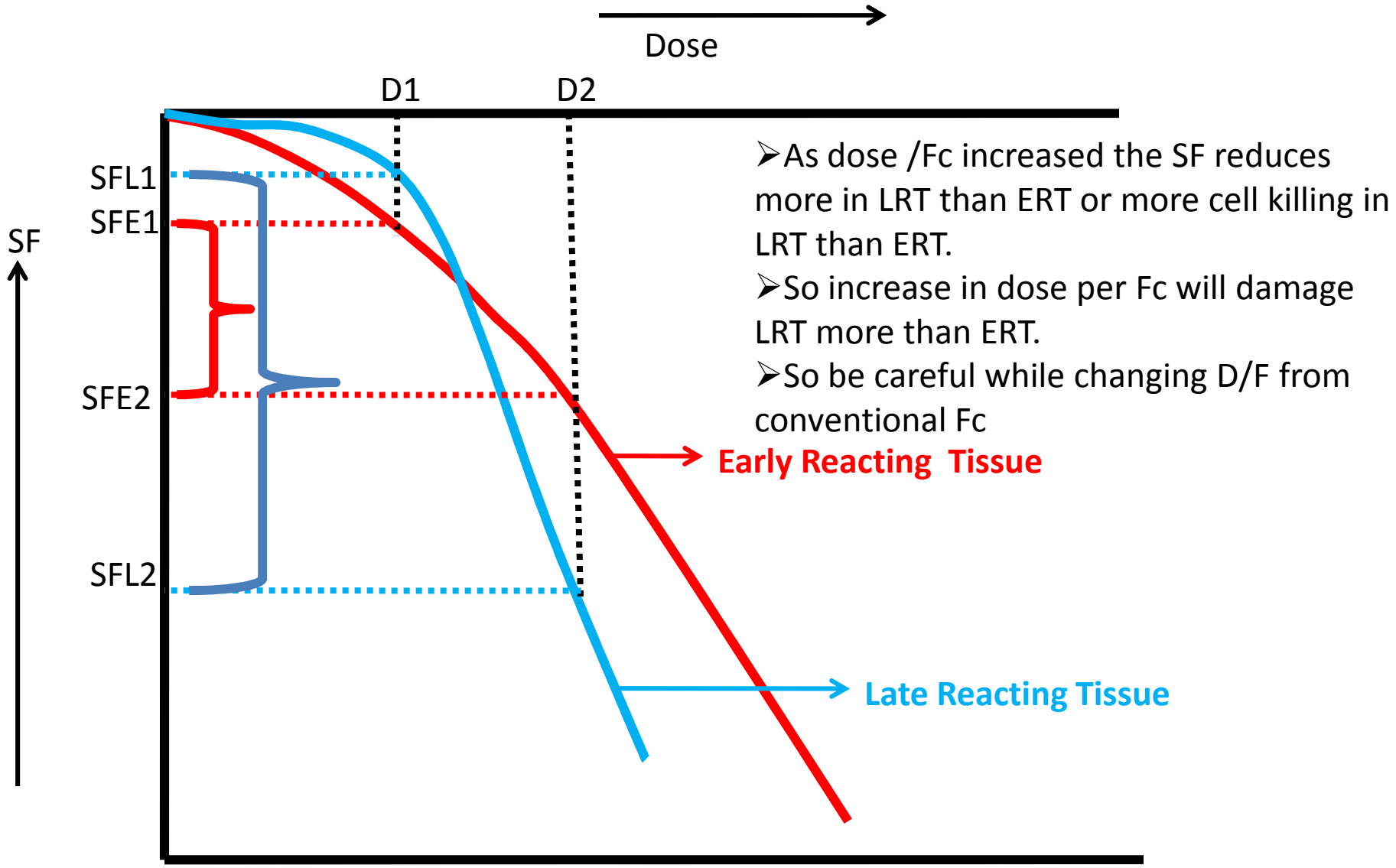
CLINICAL SIGNIFICANCE OF α/β RATIO

Tumour tissues

- Behave like early responding tissues
- May be spared if dose is too low
- May be spared if overall time is too long

CLINICAL SIGNIFICANCE OF α/β RATIO

- When changing one dose schedule to other, one has to be careful.
- When we change fraction size (dose/fraction) we need to take into account the **α/β ratio** of normal tissues for calculating the equivalent dose.
- Usually **α/β ratio** of late reacting tissue is used for calculating the equivalent doses.
- If calculated by α/β value of Early reacting tissues, then it leads to more damage to late reacting tissues



- As dose /Fc increased the SF reduces more in LRT than ERT or more cell killing in LRT than ERT.
- So increase in dose per Fc will damage LRT more than ERT.
- So be careful while changing D/F from conventional Fc

CLINICAL SIGNIFICANCE OF α/β RATIO

Biological Effective Dose(BED)

For a single acute dose D, the biologic effect is given by

$$E = \alpha D + \beta D^2 \qquad (1)$$

For n well separated fractions of dose d, the biologic effect is given by

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

As suggested by Barendsen, this equation may be rewritten as

E = (nd)(α + ßd)

$$E = (nd)(\alpha + \beta d)$$
$$= (\alpha)(nd)\left(1 + \frac{d}{\alpha/\beta}\right) \qquad (3)$$

in which the quantity 1 + [d/(α/ß)] is called relative effectiveness. If this equation is divided through by α, we have

$$\frac{E}{\alpha} = (\text{total dose}) \times (\text{relative effectiveness})$$
$$= (nd) \times \left(1 + \frac{d}{\alpha/\beta}\right) \qquad (4)$$

Biologically Effective Dose (BED)

Biological Effective Dose(BED)

(BED) = $\frac{E}{\alpha} = (\text{total dose}) \times (\text{relative effectiveness})$

$(\text{relative effectiveness}) = \left(1 + \frac{d}{\alpha/\beta}\right)$

- If dose per fraction remain same then RE will depend inversely to α/β value.
- Which means, that same dose per fraction will affect late reacting tissue more than early reacting tissue as average α/β value for late reacting tissue is 3 as compare to 10 for early reacting tissue.
- So increasing the dose per fraction will have more effect on late reacting tissues
- Similarly the BED for a fixed fractionation schedule will be more for late reacting tissue as compare to early reacting tissue.

Clinical Applications

Iso-effective total dose

$$\frac{E}{\alpha} = (\text{total dose}) \times (\text{relative effectiveness})$$

(BED) $$= (nd) \times \left(1 + \frac{d}{\alpha/\beta}\right) \quad (4)$$

(D)

Conventionally we give 60 Gy in 30f with 2 Gy per f.
If dose per F in increased from 2 to 4 Gy the isoeffective total dose will be

$$D_2 \times \left(1 + \frac{d2}{\alpha/\beta}\right) = D_1 \times \left(1 + \frac{d1}{\alpha/\beta}\right)$$

FOR LATE REACTING TISSUES

D_2 X (1 + 4/3) = 60 x (1+ 2/3)

D_2 = 60 x 5/3 x 3/7 = 43 Gy

FOR EARLY REACTING TISSUES

D_2 X (1 + 4/10) = 60 x (1 + 2/10)

D_2 = 60 x 12/10 x 10/14 = 52 Gy

So when dose per fraction is changed and if you calculate isoeffective dose based on early reacting tissue, you are likely to damage late reacting tissue more.

So always calculate the iso effective doses keeping in mind the late reacting tissues.

Altered Fractionation

Fractionation Schedule	Schedule
Conventional	IIIII IIIII IIIII IIIII IIIII IIIII 200 cGy per day; 5 days a week
Hyperfractionation	II II II II II II II II II II II II II II II II II II II II II II II II II II II II II II II II II II II 115 cGy X 2 per day; 5 days a week.
Accelerated Fractionation	II II II II II II II II II II II II II II II II II II II II II II II II II 150-200 cGy X 2 per day; 5 days a week
CHART	II II II II II II II II II II II II II II II II II II II II II II II II II 150-200 cGy X 2 per day; 7 days a week
Hypofractionation	I I I I I I I I I I 400 -500 cGy per day; twice a week
Split Course	IIIII IIIII Rest → IIIII IIIII > 250 cGy per day

Clinical Examples of BED

Conventional	IIIII IIIII IIIII IIIII IIIII IIIII 200 cGy per day; 5 days a week X 6 W

- Conventional treatment: 30 fractions of 2 Gy given one fraction per day, 5 days per week, for an overall treatment time of 6 weeks (this is written as 30F × 2 Gy/6 w

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

OR

Tumor

$= 60\left(1 + \frac{2}{10}\right)$

$= 72\ Gy_{10}$

Late effects: $\frac{E}{\alpha} = 60\left(1 + \frac{2}{3}\right)$

$= 100\ Gy_3$

Biological Effective Dose(BED)

Conventional	IIIII IIIII IIIII IIIII IIIII IIIII IIIII 200 cGy per day; 5 days a week X 7 W

- A one-fraction-a-day control schedule frequently used to compare with hyperfractionation: 35 fractions of 2 Gy given once a day for 5 days a week, for an overall
  Gy/7 weeks

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

OR

Tumor

$$= 70\left(1 + \frac{2}{10}\right)$$

$$= 84\ Gy_{10}$$

Late effects: $\frac{E}{\alpha} = 70\left(1 + \frac{2}{3}\right)$

$$= 116.7\ Gy_3$$

Hyperfractionation	115 cGy X 2 per day; 5 days a week. **X 7 W**	

- Hyperfractionation: 70 fractions of 1.15 Gy given twice daily, 6 hours apart, 5 days per week, for an overall treatment time of 7 weeks; that is, 70F × 1.15 Gy twice

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

OR Tumor

$= 80.5\left(1 + \frac{1.15}{10}\right)$

$= 89.8\ Gy_{10}$

Conventional Fractionation = 84Gy

Late effects: $\frac{E}{\alpha} = 80.5\left(1 + \frac{1.15}{3}\right)$

$= 111.4\ Gy_3$

Conventional Fractionation = 116.7Gy

Comment: This treatment is much "hotter," that is, more effective, than the conventional 60 Gy for both early and late effects.

Hyperfractionated RT when dose per fraction is reduced, is hotter as compare to conventional fractionation for the acute effects and tumor both as both have similar α/β ratio (increases from 84 to 89.8 Gy) while late effects decreases (from 116.7 to 111.4 Gy) as dose per fraction is reduced from 2Gy to 1.15Gy.

EORTC 22791 Trial in Head & Neck Cancer

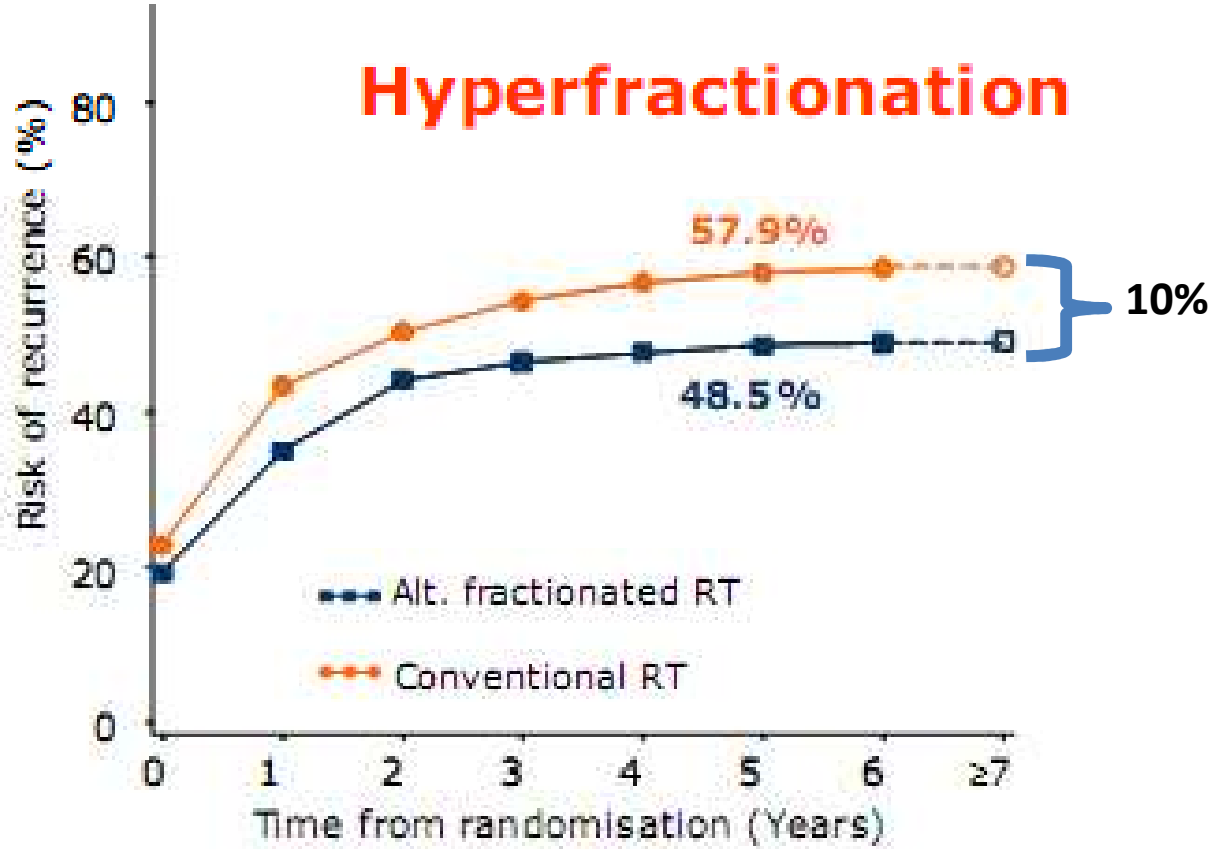
As an example, the EORTC 22791 trial[54] gave 80.5 Gy delivered as 70 F of 1.15 Gy per fraction, 2 F per day, over 7 weeks as definitive therapy in patients with T_2-T_3 oropharyngeal carcinomas. For a tumor with α/β = 10 Gy, the equivalent dose in 3Gy fractions would be:

- With hyper fractionation, dose to the tumor will be 5.8 Gy (6.9%) higher than in control arm (89.8 Gy-84 Gy).
- Late responding tissues will receive 5.3 Gy(5%) less than in control arm (116.7Gy-111.4Gy)
- These changes in doses should be translated into 12% increase in tumor control and around 20% reduction into subcutaneous fibrosis.
- In this trial, 19% difference was observed in local tumor control, which is reasonable in agreement with calculate difference of 12%.
- However there was no difference in subcutaneous fibrosis in two arms, probable reflecting 6 hours gap between two fraction being insufficient for complete recovery.

Approaches to locally advanced Head and Neck Cancer

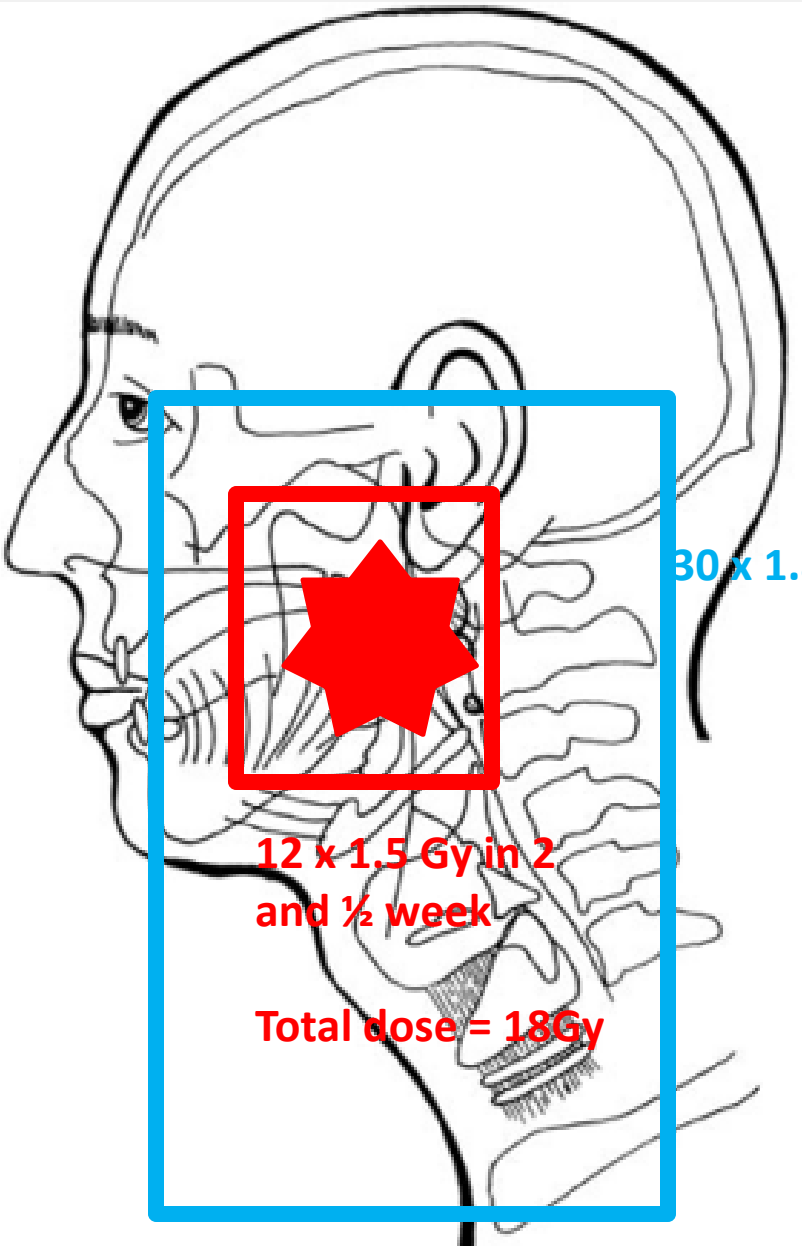
- MARCH: Meta-Analysis of Radiotherapy in Carcinomas of Head & Neck (n= 6,515 patients)

Bourhis et al Lancet 2006



Improvement in local control should be 12% as calculated from L-Q model, which is in close agreement with clinically observed improvement of 10%

Concomitant boost:



Total Dose to the tumor will be 72 Gy in 6 weeks.

- Concomitant boost: 30 fractions of 1.8 Gy given once a day, 5 days a week, and at the same time (concomitant) a boost to a smaller field of 12 fractions of 1.5 Gy once a day; overall treatment time 6 weeks; that is, ([30F × 1.8 Gy] + [12F × 1.5 Gy])/6 weeks (this protocol is much favored at the University of Texas M. D. Anderson Hospital and Tumor Institute; by giving the boost concomitantly, a prolongation of overall time is avoided)

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

OR

Tumor

$$= 54\left(1 + \frac{1.8}{10}\right) + 18\left(1 + \frac{1.5}{10}\right)$$

$$= 84.4\ Gy_{10}$$

Conventional Fractionation = 84Gy

Late effects: $\frac{E}{\alpha} = 54\left(1 + \frac{1.8}{3}\right) + 18\left(1 + \frac{1.5}{3}\right)$

$$= 113.4\ Gy_3$$

Conventional Fractionation = 116.7Gy

Concomitant boost as compare to conventional fractionation is equally effective for tumor and acute reaction (84 vs 84.4 Gy) but less damaging for late reacting tissues (116 vs 113 Gy).

However compare with hyper fractionation, the effect is same for late reacting tissue(111.4 vs 113.4) but less effective for early reacting tissues including tumor (89.8 vs 84.4 Gy).

CHART	II II II II II II II II II II II II II II II II II II II II II II II II II 150-200 cGy X 2 per day; 7 days a week

- CHART: 36 fractions of 1.5 Gy given three fractions a day, 6 hours apart, for 12 consecutive days, with an overall treatment time of 12 days; that is, 36F × 1.5 Gy (3F/day)/12 days.

Early effects including tumor:

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

$$= 54\left(1 + \frac{1.5}{10}\right)$$

$$= 62.1\ \mathrm{Gy}_{10}$$

Conventional Fractionation = 84Gy

$$\text{Late effects: } \frac{E}{\alpha} = 54\left(1 + \frac{1.5}{3}\right)$$

$$= 81.0\ \mathrm{Gy}_{3}$$

Conventional Fractionation = 116.7Gy

Direct comparison of CHART with other fractionation should not be done as we know that some cancer specially Head & Neck cancers show accelerated repopulation and overall treatment time is important.

The accelerated repopulation will have a negative effect on biologically effective dose as it represent new cells production.

So time factor has to be added to the BED equation.

Time Factor in L-Q Model

- The effect of accelerated repopulation will depends upon
  - Timing of repopulation during radiation treatment.
  - Potential tumor doubling time.
  - Total duration of repopulation.

Time Factor in L-Q Model

- This will have negative effect on BED and this is given by following expression..

$$0.693\frac{t}{T_{pot}}$$

Where t is the total time in days for accelerated repopulation & T(pot) is potential tumor doubling time

The biologically effective dose E/α becomes

$$\frac{E}{\alpha} = (nd)\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693}{\alpha}\frac{t}{T_{pot}} \qquad (9)$$

or, in words,

Biologically effective dose

= (total dose) × (relative effectiveness) — - Accelerated repopulation

So Accelerated repopulation = $\frac{0.693}{\alpha}\frac{t}{T_{pot}}$

- The accelerated repopulation start 21 to 28 days after beginning of radiotherapy in Head & Neck cancer.
- So t=T-21 or 28 days for head and neck cancers where T is over all treatment time
- It can also be expressed as t=T-Tk where Tk is time when repopulation start

$\frac{0.693}{\alpha}\frac{T\text{-}Tk}{T_{pot}}$

α ~ 0.3 (initial slope of survival curve), T = 39 days

T_{pot} ~ 5 days (median), Tk = 21 days

For typical 6-week (39-day) schedules referred to earlier, proliferation may reduce the biologically effective dose by

Dose equivalent to accelerated repopulation $= \frac{0.693}{0.3} \times \frac{(39-21)}{5} = 8.3\ Gy_{10}$

Note that because we are concerned with tumor proliferation, the reduction in biologically effective dose is in Gy_{10}; that is, an early-effect α/β value is used. By the same token, proliferation during a 7-week protocol (i.e., 46 days) would decrease the biologically effective dose by

$$\frac{E}{\alpha} = \frac{0.693}{0.3} \times \frac{(46-21)}{5} = 11.6\ Gy_{10}$$

Dose of radiation which goes waste

So this much of dose is to be reduced from BED on account of repopulation.
This also shows as overall treatment time increases the BED decreases.

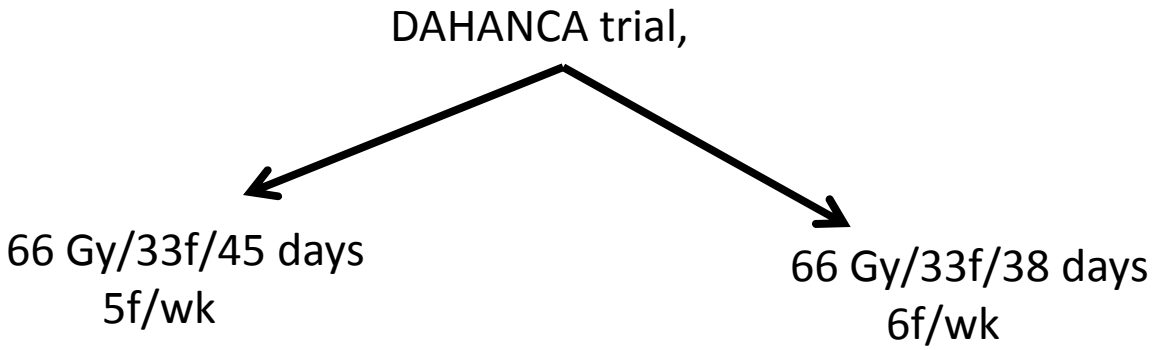
For CHART, the Tk (21 days) is greater than T as treatment finishes in 12 days so repopulation does not affect the BED.

TALBE 22.3 Effect of Tumor Proliferation on Biologically Effective Doses Characteristic of Various Treatment Regimens

Protocol	E/α Early, i.e., Tumor, Gy_{10}	Proliferation Correction, Gy_{10}	Corrected for Time, Gy_{10}
Conventional protocol: 30F × 2 Gy/6 wk (39 d)	72	-8.3	63.7
Hyperfractionation: 70F × 1.15 Gy/7 wk (46 d)	89.8	-11.6	78.2
Concomitant boost: (30F × 1.8 Gy) + (12F × 1.5 Gy)/6 wk (39 d)	84.4	-8.3	76.1
Chart: 36F × 1.5 Gy/12 d	62.1	0	62.1
This correction for time assumes T_p = 5 days; T_k = 21 days; and α = 0.3 in per Gy.			

- Hyperfractionated Radiotherapy results into the largest BED and therefore may be expected to result in the best tumor control followed closely by the concomittnat boost schedule.
- CHART is less effective based on T(pot) of 5 days.
- CHART may be effective in a very fast growing tumor with T(pot) of less than 3 days.

Clinical application of overall treatment time

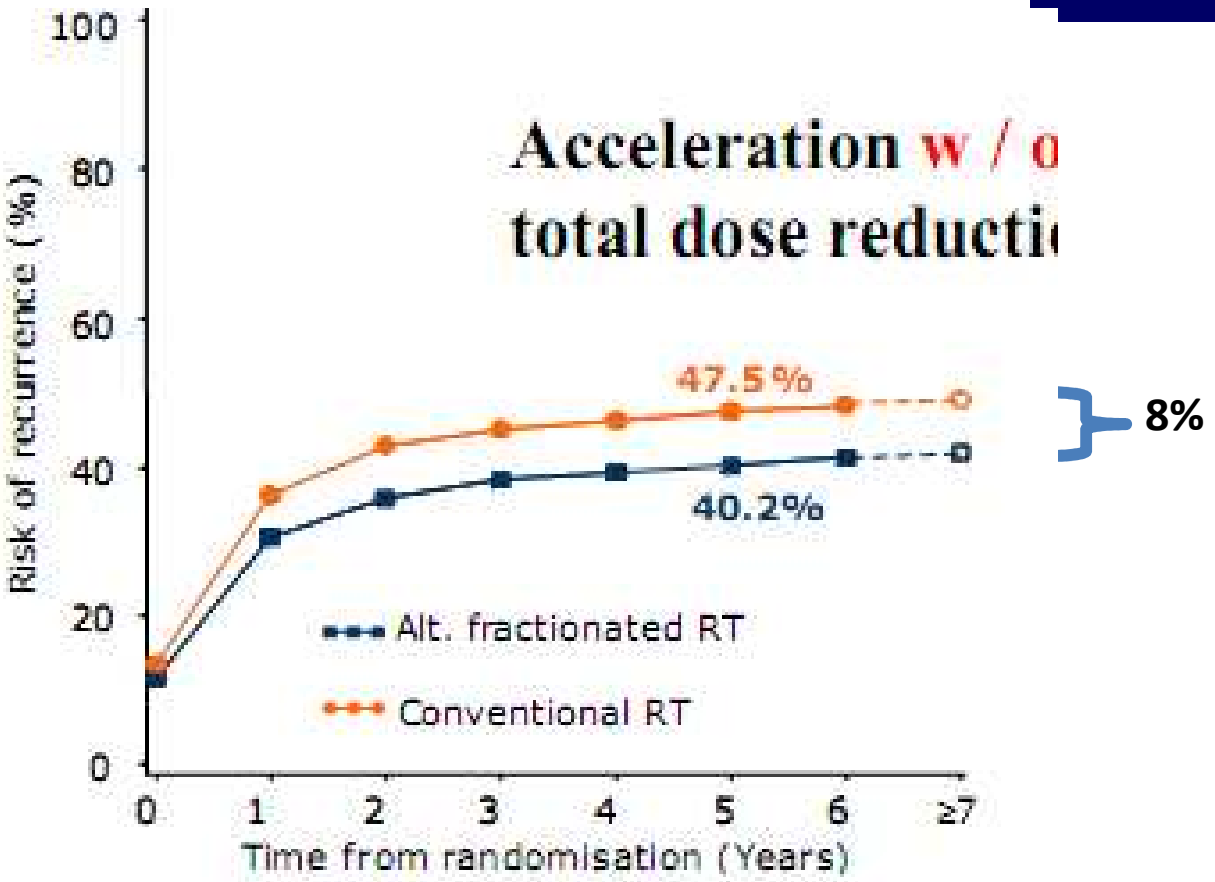


- Dose compensated for repopulation is .6 Gy/day
- Total gain in the dose is .6x7=4.2 Gy, roughly 6.5%
- This should translate into an improvement of 12% in tumor control.
- The results of this trial showed an improvement of local tumor control from 64% to 76% (i.e. 12% gain), which is in agreement of the calculated gain of 12%.
- This clinical trial provide direct evidence of the importance of over all treatment time.

Approaches to locally advanced Head and Neck Cancer

- MARCH: Meta-Analysis of Radiotherapy in Carcinomas of Head & Neck (n= 6,515 patients)

Bourhis et al Lancet 2006



Improvement in local control should be 12% as calculated from L-Q model, which is in close agreement with clinically observed improvement of 8%

Radiotherapy Treatment Potentiation

- So with altered fractions like hyper-fractions RT, treatment is potentiated by giving more total dose than conventional RT (80.5 vs 70 Gy) as in EORTC trial or by reducing over all treatment time from six and half week to five and half week to reduce the effect of repopulation as in DHANCA
- The other method to potentiate the treatment is by adding concurrent chemotherapy with radiotherapy, as done for H&N and cervical cancers.

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 4, pp. 1030–1036, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.03.048

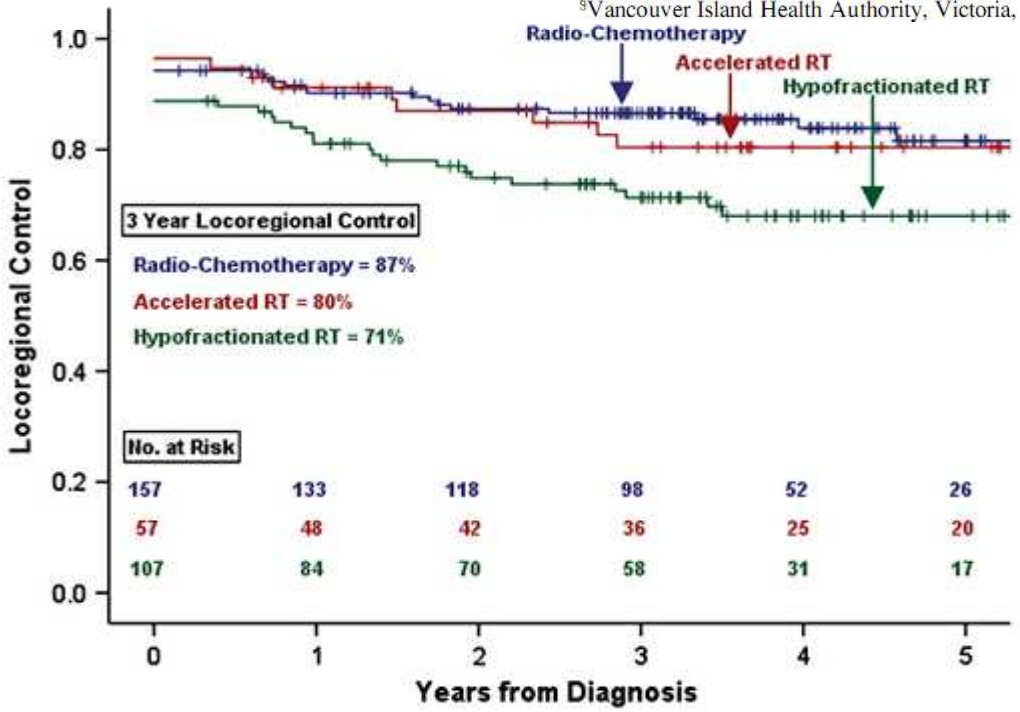
British Columbia Study

CLINICAL INVESTIGATION **Head and Neck**

TREATMENT OUTCOMES OF LOCALLY ADVANCED OROPHARYNGEAL CANCER: A COMPARISON BETWEEN COMBINED MODALITY RADIO-CHEMOTHERAPY AND TWO VARIANTS OF SINGLE MODALITY ALTERED FRACTIONATION RADIOTHERAPY

HOSAM A. KADER, M.D.,*† AMINUDIN R. MYDIN, M.D.,* MATTHEW WILSON, B.SC.,‡ CHERYL ALEXANDER, C.C.H.R.A.,* JEEVIN SHAHI, B.SC.,* IRVIN PATHAK, M.D.,§ JONN S. WU, M.D.,*† AND PAULINE T. TRUONG, M.D., C.M.*†

*Radiation Therapy Program, British Columbia Cancer Agency, †University of British Columbia, ‡University of Victoria; and §Vancouver Island Health Authority, Victoria, BC, Canada



British Columbia Study

- In one of the study from British Columbia, the concurrent conventional CRT was compared Accelerated RT alone in which overall treatment time was reduced from six and half week to five and half week.
- There was no difference in local control between two arms at 3 years.
- While from DAHANCA trial the gain in dose was 4.2 Gy or 6.5% by reducing the overall treatment time by one week, which translated into 12% improvement in local control.
- Since there is no difference in local control, it can be presumed that same potentiation of radiotherapy was done by concurrent chemotherapy.
- Applying the findings DAHANCA trial here we can say that there was chemotherapy potentiation of the magnitude of 4.2Gy which could have translated into a 12% gain in local control if compared with conventional fraction.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

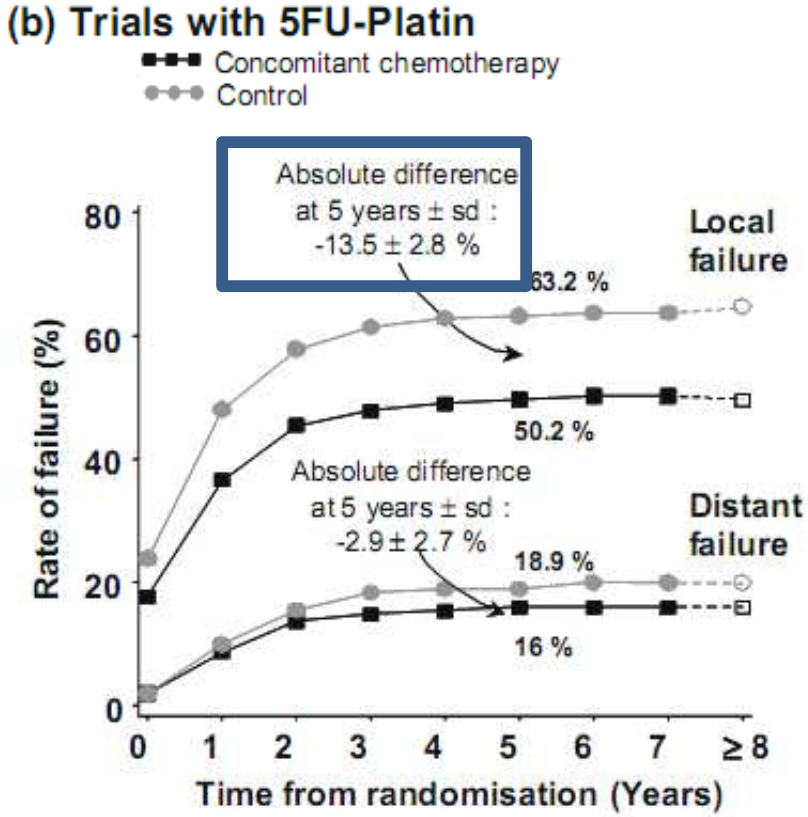
journal homepage: www.thegreenjournal.com

Meta analysis

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon [a,*], Aurélie le Maître [a], Emilie Maillard [a], Jean Bourhis [b], on behalf of the MACH-NC Collaborative Group [1]

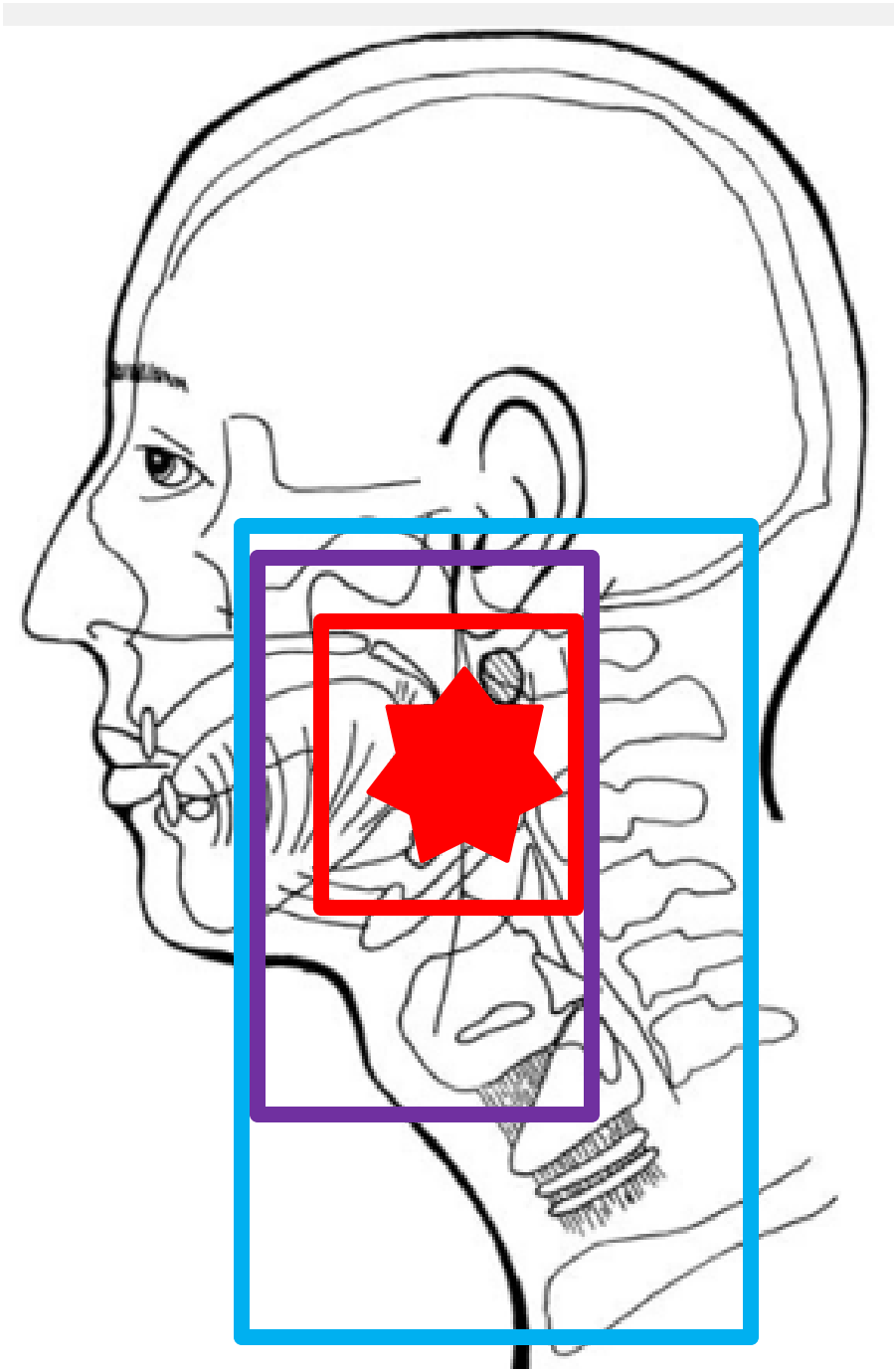
[a] Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France
[b] Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France



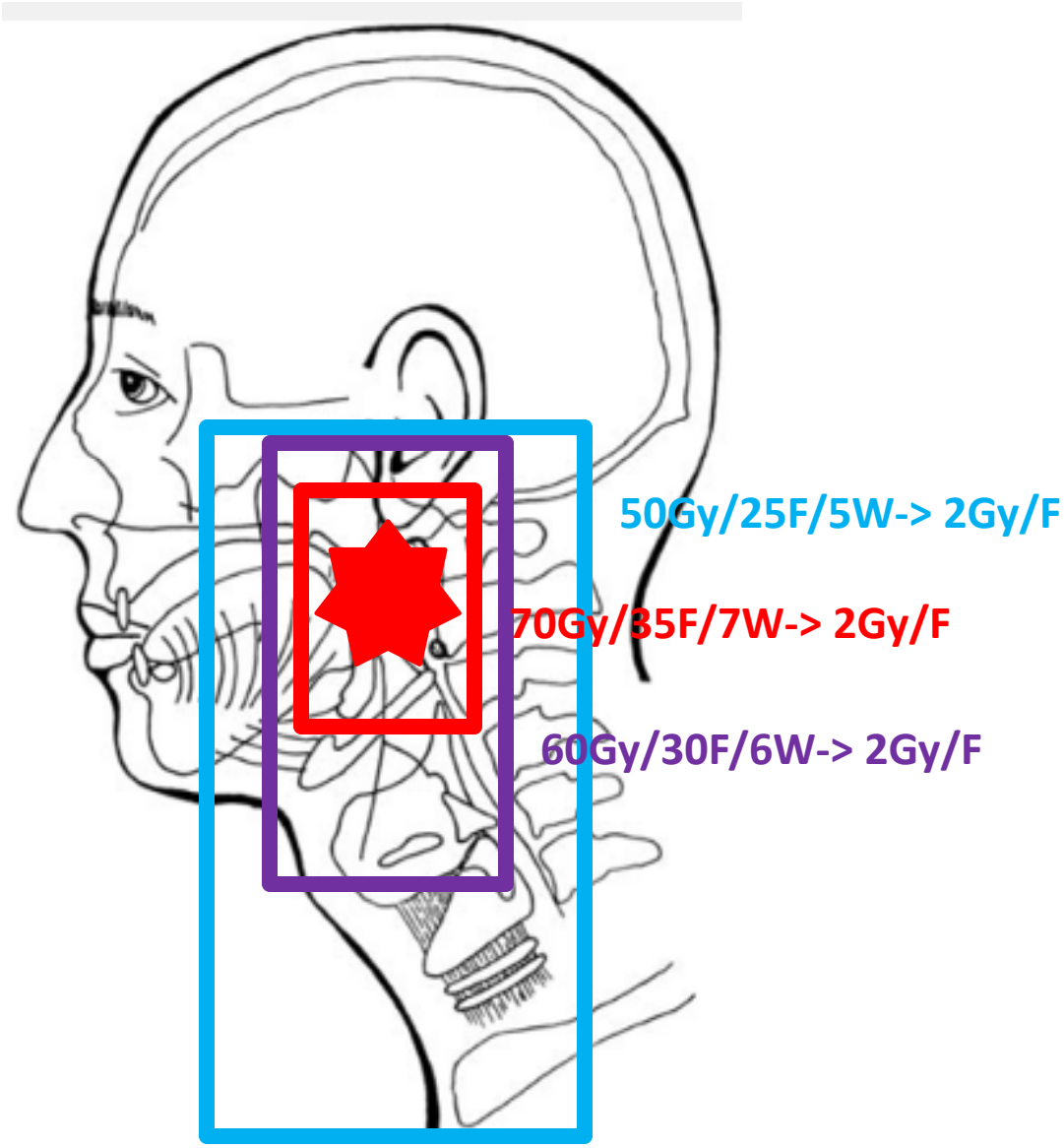
- Comparing CRT with RT alone.
- Chemotherapy potentiation as seen in previous study should result into difference of 12% in local control.
- This meta analysis also showed a differnece of 13.5 +/- 2.8% at 5 years which is in close agreement of calculated 12%.

Clinical application of overall treatment time

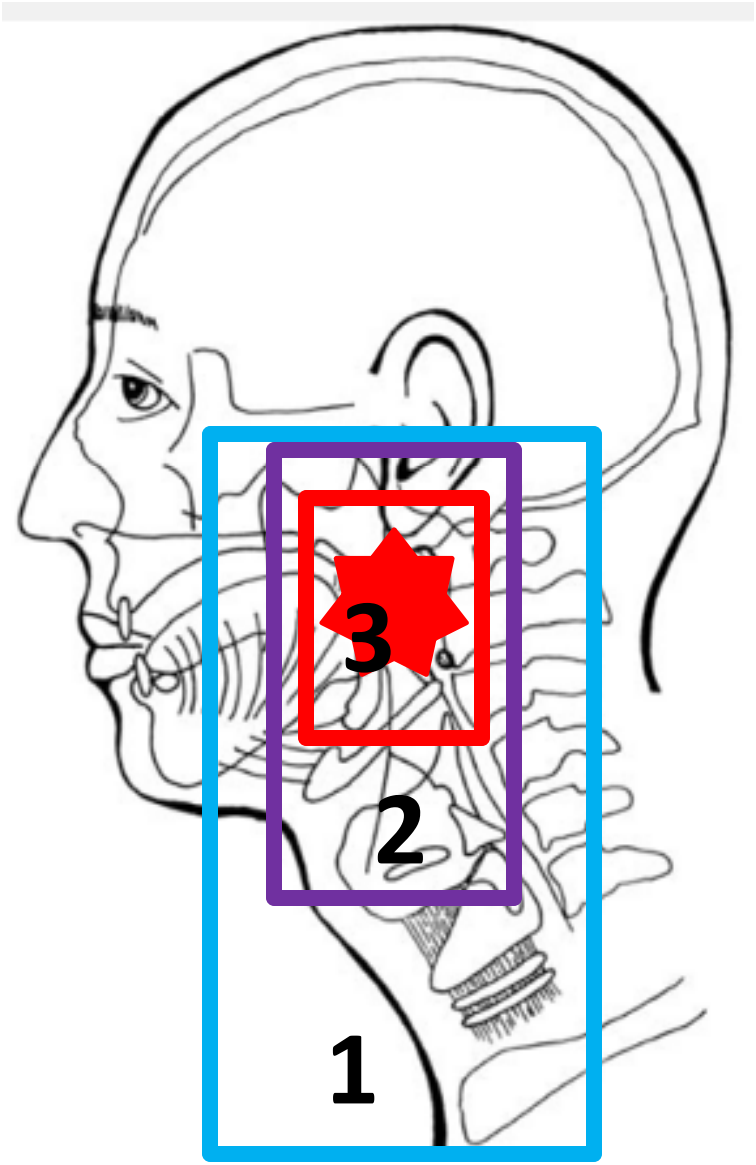
- In head and neck cancers, usually there are three regions to be treated with different doses of radiation.
  - Region 1:-Microsocopic region to be given 50 Gy.
  - Region 2:-High tumor burdened microscopic disease to be treated with 60 Gy.
  - Region 3:- Gross tumor to be treated with 70 Gy.



Clinical application of overall treatment time

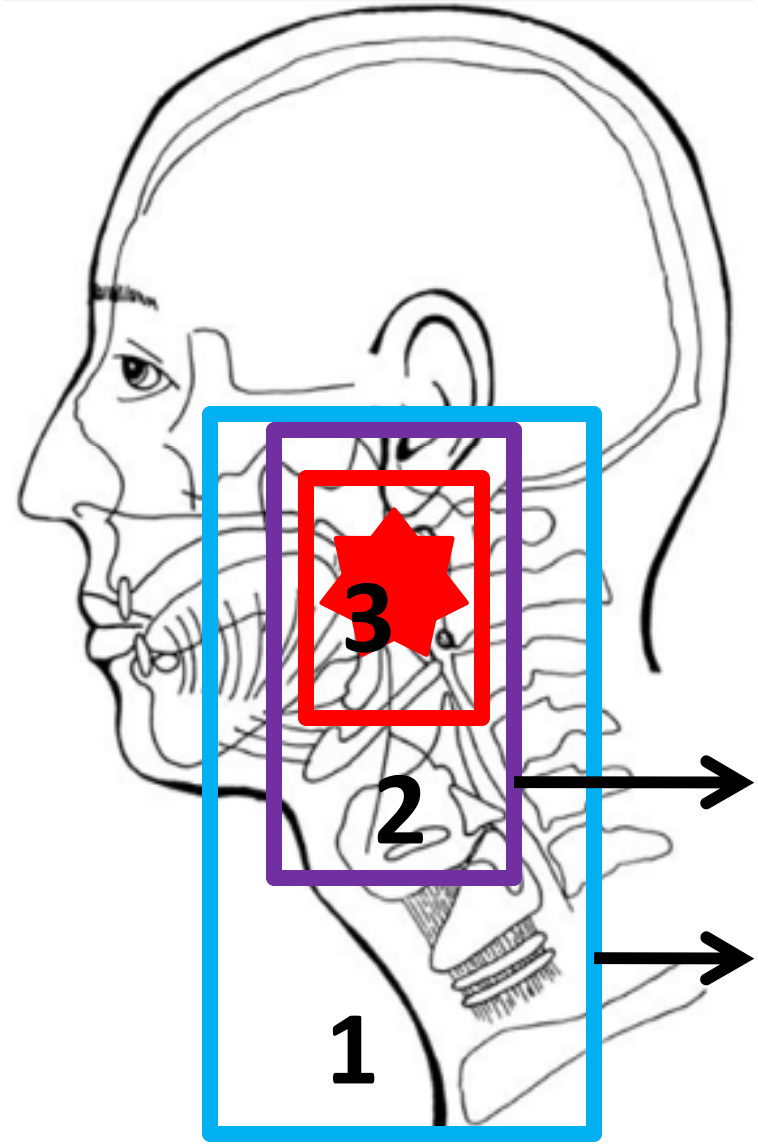


- In conventional fractionation, this goal is achieved with a technique called shrinking field technique and delivering 2 Gy per fraction to all the three regions, treating region 1 for 5 weeks, region 2 for 6 weeks and region 3 for 7 weeks.



- But in IMRT, usually one plan is prepared to deliver different doses to different regions over a period of 7 weeks. Thus all the regions are treated for 7 weeks.
- So for region 1 and 2 we need to find out the equivalent doses for 50 Gy in 5 weeks and 60 Gy in 6 weeks, which can be delivered in 7 weeks.
- The equivalent dose need to be higher for countering the effect of repopulation.

Per week increase of dose for repopulation is .6x5 = 3 Gy



Increasing overall treatment time from 6 to 7 Wks will require 3Gy additional making it 63 Gy in 7 weeks with 1.8 Gy per fx

Increasing overall treatment time from 5 to 7 Wks will require 6Gy additional making it 56 Gy in 7 weeks with 1.6Gy per fx

Hypofractionation

- Total number of fraction is less as compare to conventional fraction, resulting into higher dose per fraction.
- Mainly used for palliative treatment eg bone metastasis (30 Gy in 10 F).
- Recently being used as curative treatment in breast and prostate.
- The principle is that α/β value for subclinical disease in ca breast is 4.6 Gy and for late changes in the breast it is 3.6 Gy.
- So higher dose per F will result into more damages in sub clinical disease.
- Many trials from UK and Canada have shown same results with hypofraction (40Gy/3wk/15f) as with conventional fractions (50 Gy/25f/5wk) with similar late effects.

Hypofractionation

- For prostate cancer, α/β value is 1.5 while for rectum and for rectal toxicity it is 3.
- So increasing the dose per fraction will damage cancer cell more than rectal tissue.
- Many phase III trials are ongoing comparing hypofraction with conventional fraction in ca prostate.
- RTOG 0415 comparing 70 Gy in 28 F vs 73.8 Gy in 41 F
- CHHiP from UK comparing 74 Gy in 37 F vs 60 Gy in 20 vs 57 Gy in 19 F.

Altered Fractionation

Hyper fractions
Multiple daily fractionation (MDF)

- Could be more effective in rapidly growing tumors with a high growth fraction,

Hypofractionation: (1, 2 or 3 fractions a week with higher doses)

- May be more efficacious for slow growing tumors (large D_o cell populations) or for tumor with a large D_q (e.g., melanoma).

Effect of inhomogeneity inside the target.

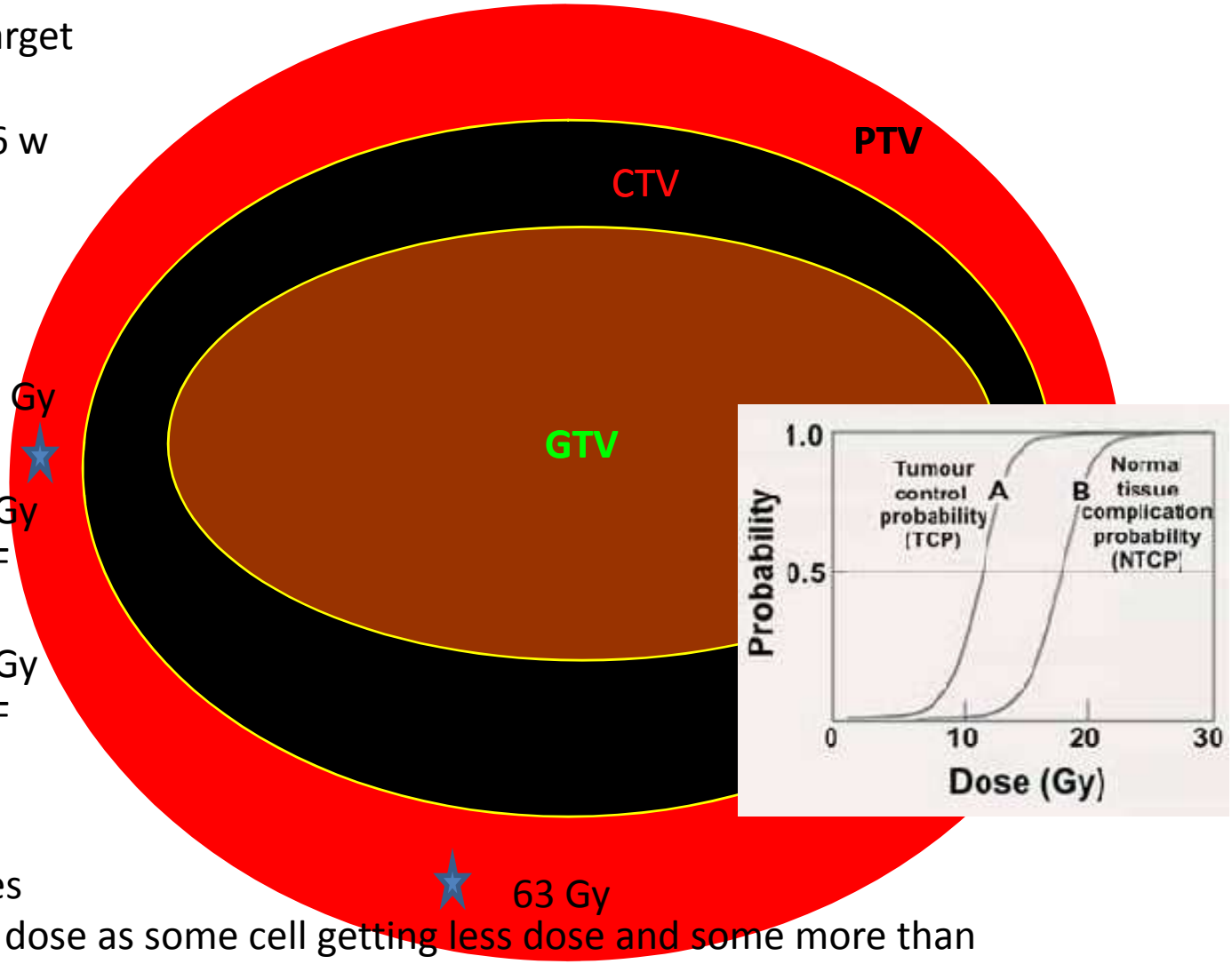
Dose homogeneity is considered when there is 10% variation of dose distribution across the target

Consider 60 Gy/ 30 F/ 6 w

All points across the target should receive between 57 to 63 Gy.

All points receiving 57 Gy in 30F with 1.9 Gy per F

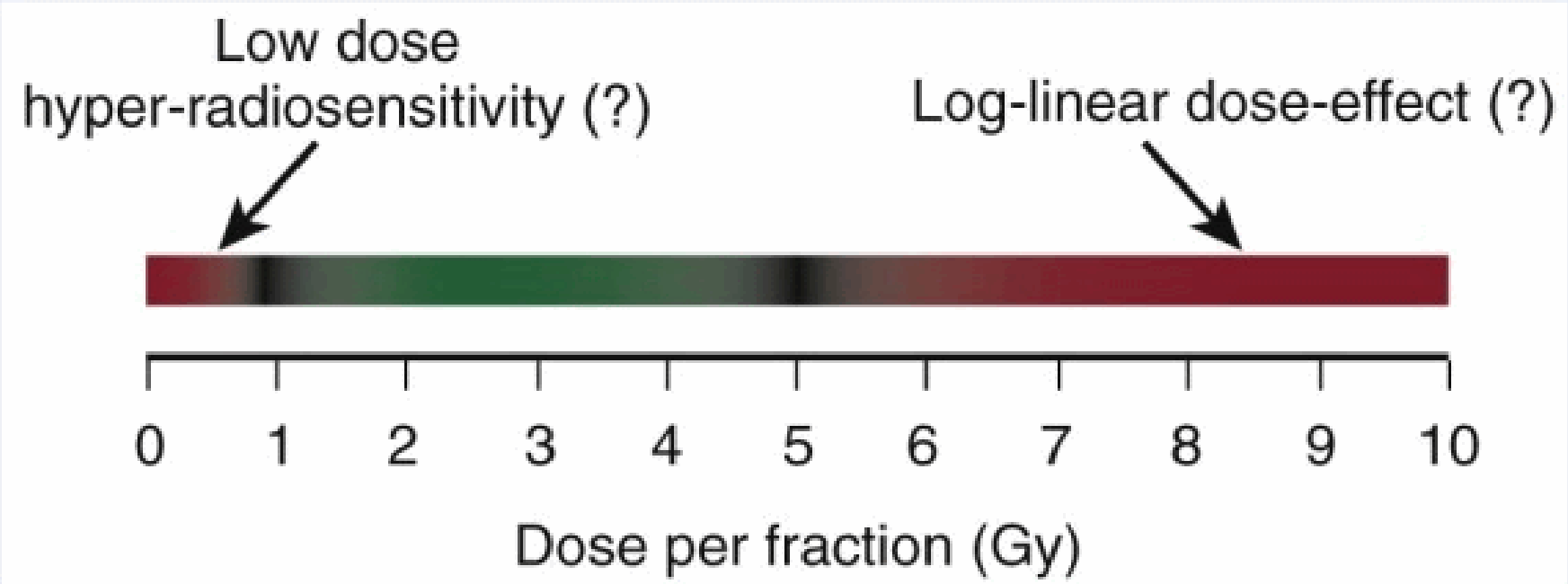
All points receiving 63 Gy in 30F with 2.1 Gy per F



There are two variables

- Variation in physical dose as some cell getting less dose and some more than the prescribed dose
- Variation in Radiobiological dose as some cells receive 1.9 Gy per F which is less damaging and some 2.1 Gy which is more damaging.
- if less doses fall on cancer cells, all cells may not be sterilized and if high dose fall on normal tissue will result higher late toxicity as fibrosis.

Limitation of LQ model



- At dose lower than 1 Gy per fraction, LQ model underestimate biological effect.

- At higher dose per fraction, it overestimate the biological effects. Since we are using higher dose per fraction commonly in SBRT and HDR brachytherapy, we have to be careful in applying LQ model to these clinical situations.

Clinical Significance of Low dose Irradiation

- With modern radiotherapy techniques like IMRT, IGRT, etc, large volume of normal tissue is irradiated with lower doses of radiation.
- In vitro tumor cell survival estimation display excess cell killing at low dose per fraction than predicted by LQ model.
- This phenomenon is called low dose hyper-radiosensitivity (HRS).
- HRS is due to apoptotic death of the cells in G2 phase of cell cycle at doses less than .3 Gy.
- At doses more than .3 Gy, G2 check point is activated which resulted into repair of the DNA damage leading to increased cell survival.
- HRS may result into more damage to dose limiting late reacting tissues in IMRT.
- But in late reacting tissues, very small no of cells are present in G2 phase, thus HRS may not be the important issue.