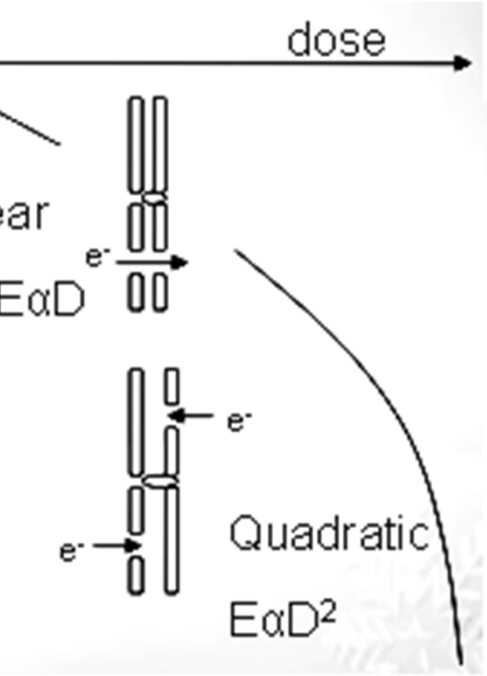
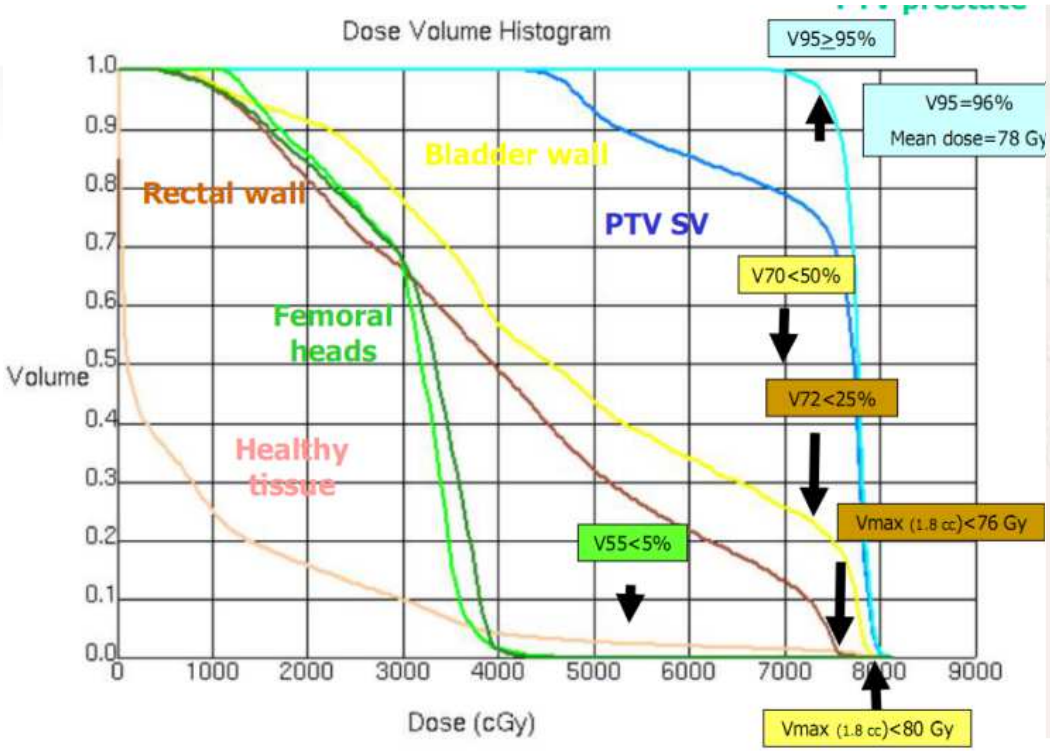
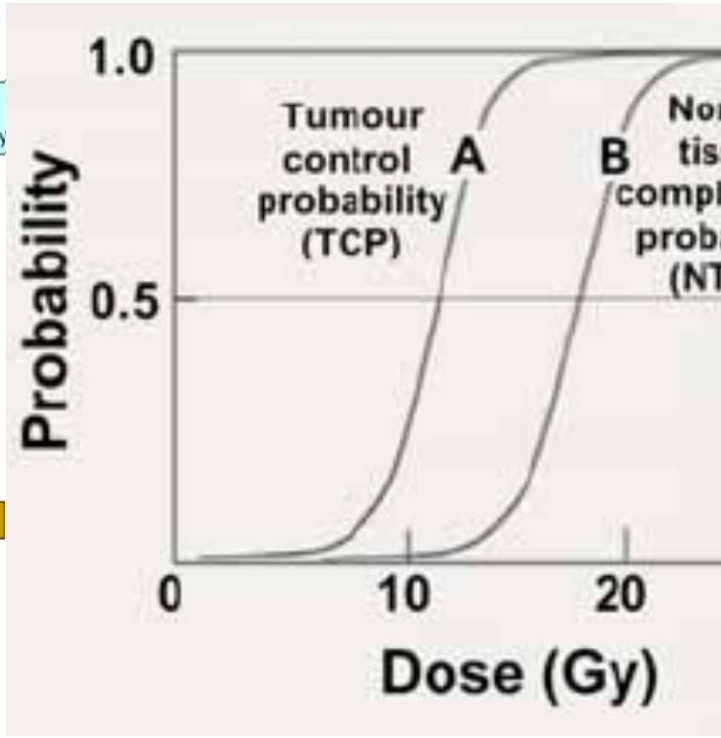
Mathematical Models in Radiotherapy







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Road Map

- **Cell Survival Curve**
  - **Multi Target Model**
  - **Linear Quadratic Model**
  - **Biological Effective Dose (BED)**
  - **Time Factor**
- **Biological Model**
  - **Tumor Control Probability (TCP)**
  - **Normal Tissue Complication Probability (NTCP)**

- **Clonogenic Cell:-**

- A cell that is able to proliferate indefinitely and form a large colony from a single cell is said to be clonogenic.

- **Cell Death**

- For proliferating cells: loss of capacity for sustained proliferation- that is loss of reproductive integrity. (2 Gy)

- For differentiated cells: loss of a specific function. (100 Gy)

  Example: for trigeminal neuralgia the dose required is

Cell Death

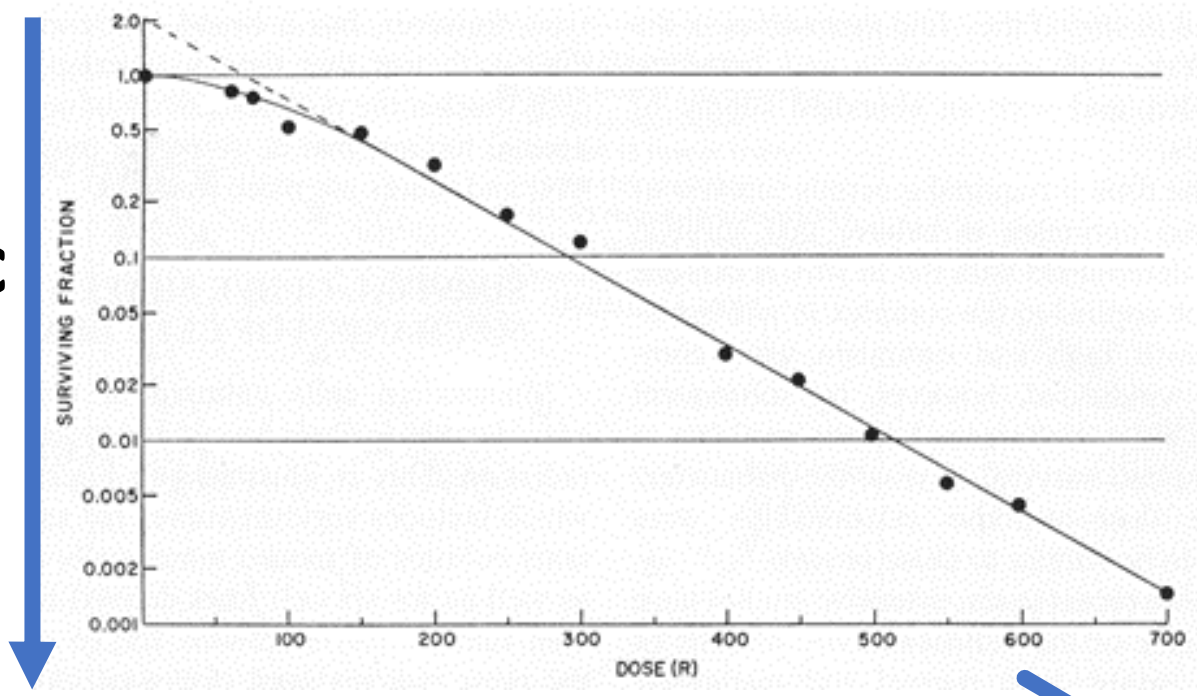
- **Following irradiation, cells may still be intact and able to produce proteins, synthesize new DNA and even go through few cell divisions**

- **However, if it has lost the capability to reproduce indefinitely, it is considered dead.**

What is a cell survival curve?

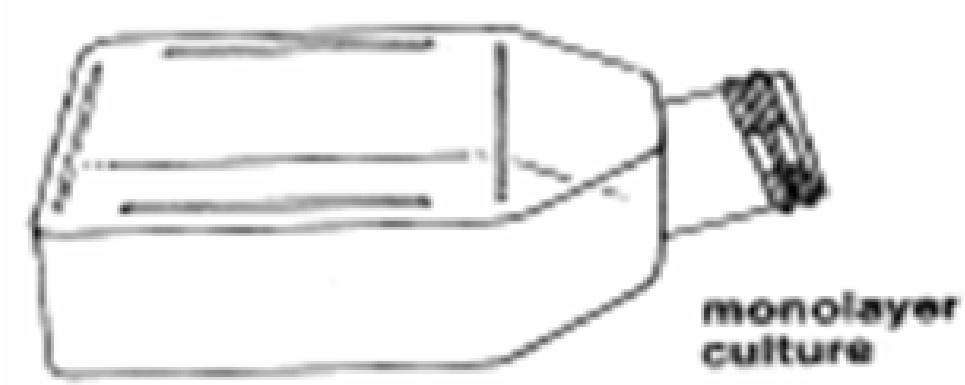
- **A cell survival curve is a graphical representation of the fraction of cells surviving a given dose of radiation**
- **This graph is obtained by plotting the dose along the *linear x-axis* and the surviving fraction along the *logarithmic y-axis***

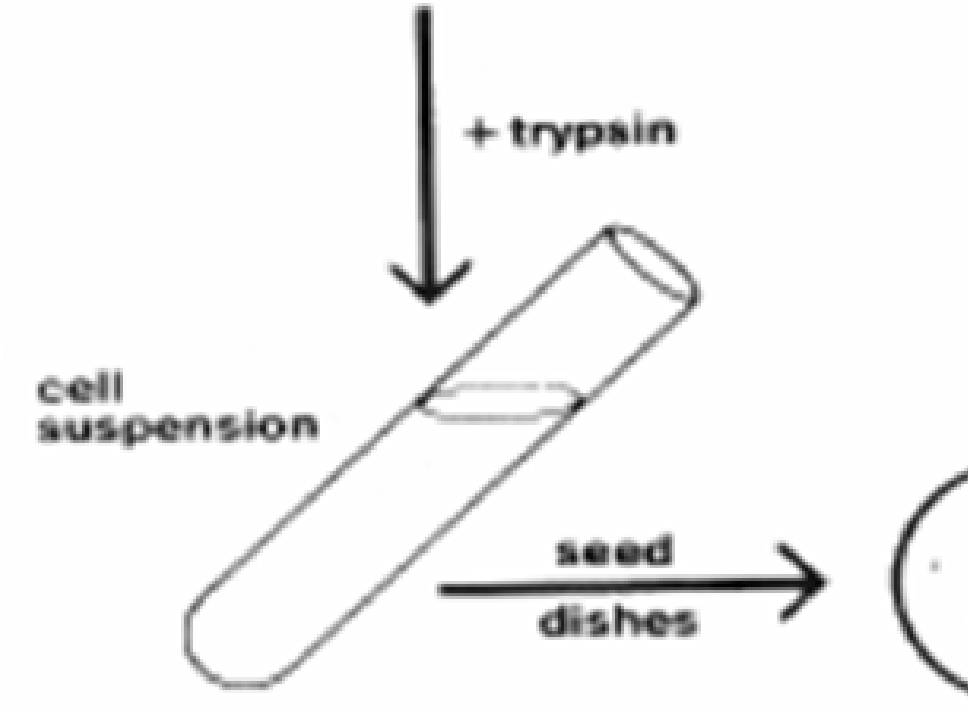
Logarithmic Y-Axis



Linear X-Axis

In vitro cell culture





Take a specimen from a tumour → Chop it into small pieces → Prepare a single cell suspension by enzyme trypsin

OBSERVATION

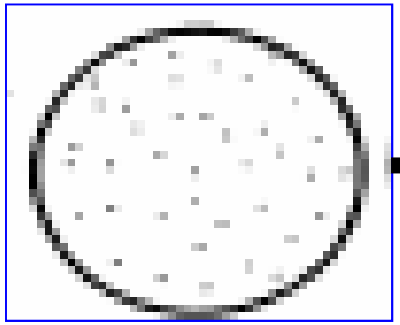
- **Some of the seeded single cells are still single and have not divided.**
- **Some cells die an apoptotic death.**
- **Some cells have managed to complete one or two divisions to form a tiny abortive colony.**
- **Many of the cells have grown into large colonies that differ little . These cells are said to have survived, because they have retained their reproductive integrity.**

Plating efficiency= What is the efficiency of the Petri dish to form colonies from known number of seeded cells

Plating Efficiency

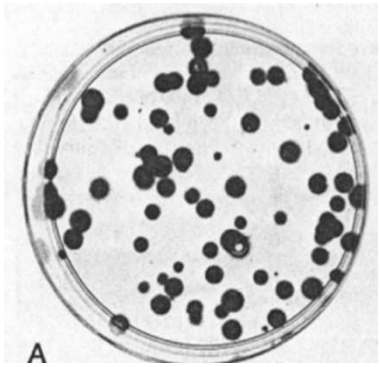
Definition **:- Percentage of cells seeded that grow into colonies is known as plating efficiency.**

Plating efficiency= no of colonies counted X 100
cells seeded



100 cells

Incubate for 1-2 week



90 Colonies

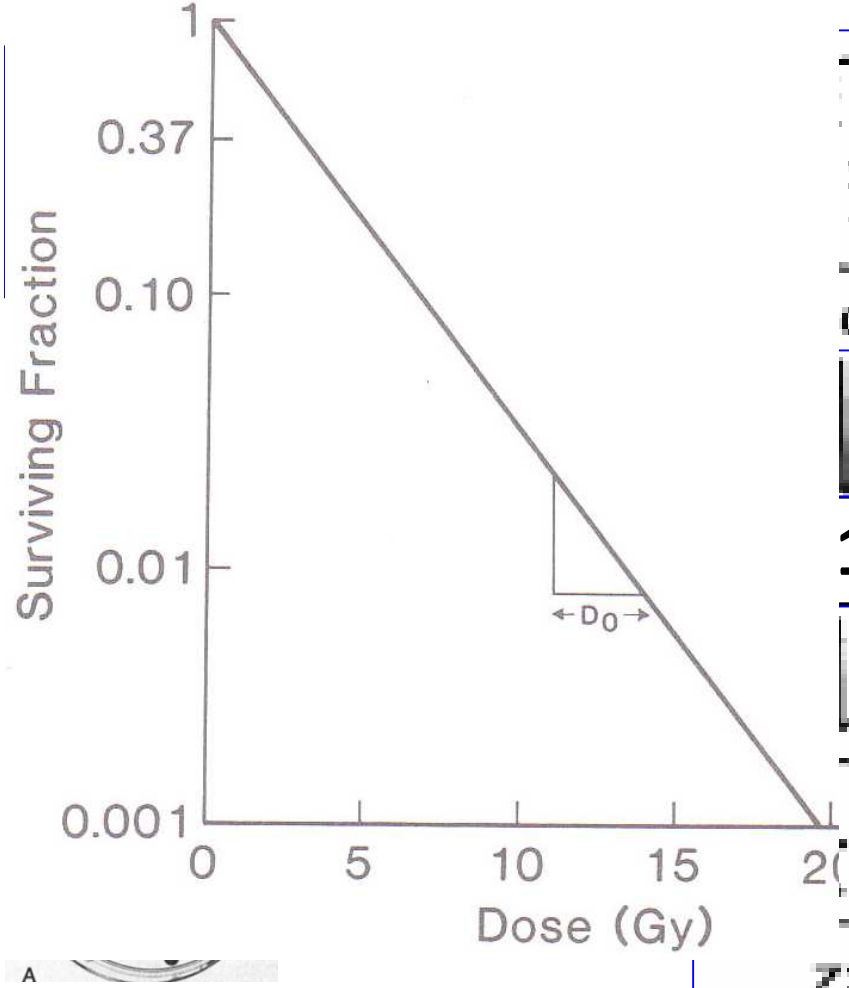
$$PE = \frac{90 \times 100}{100} = 90\%$$

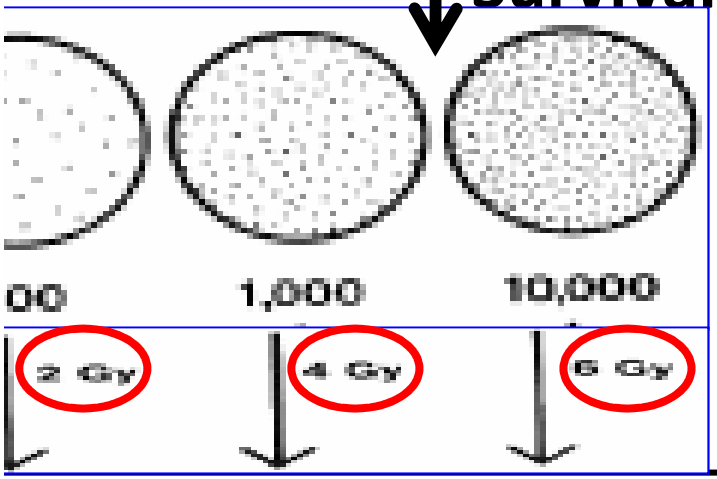
$$\text{Surviving fraction} = \frac{\text{Colonies counted}}{\text{Cells seeded x (PE/100)}}$$

Cell Survival Curve

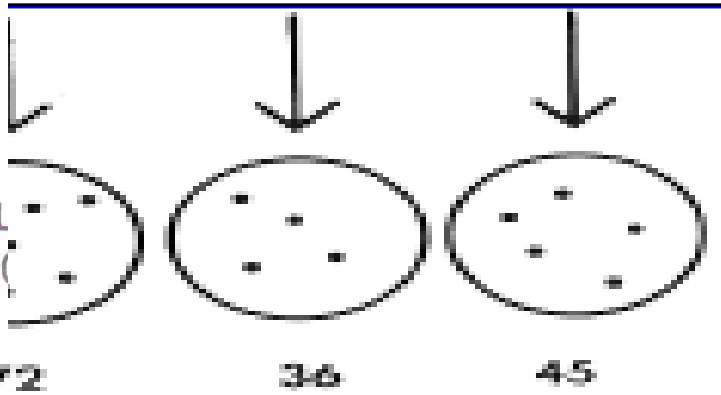
Dose of Radiation

Survival Fraction





1-2 weeks



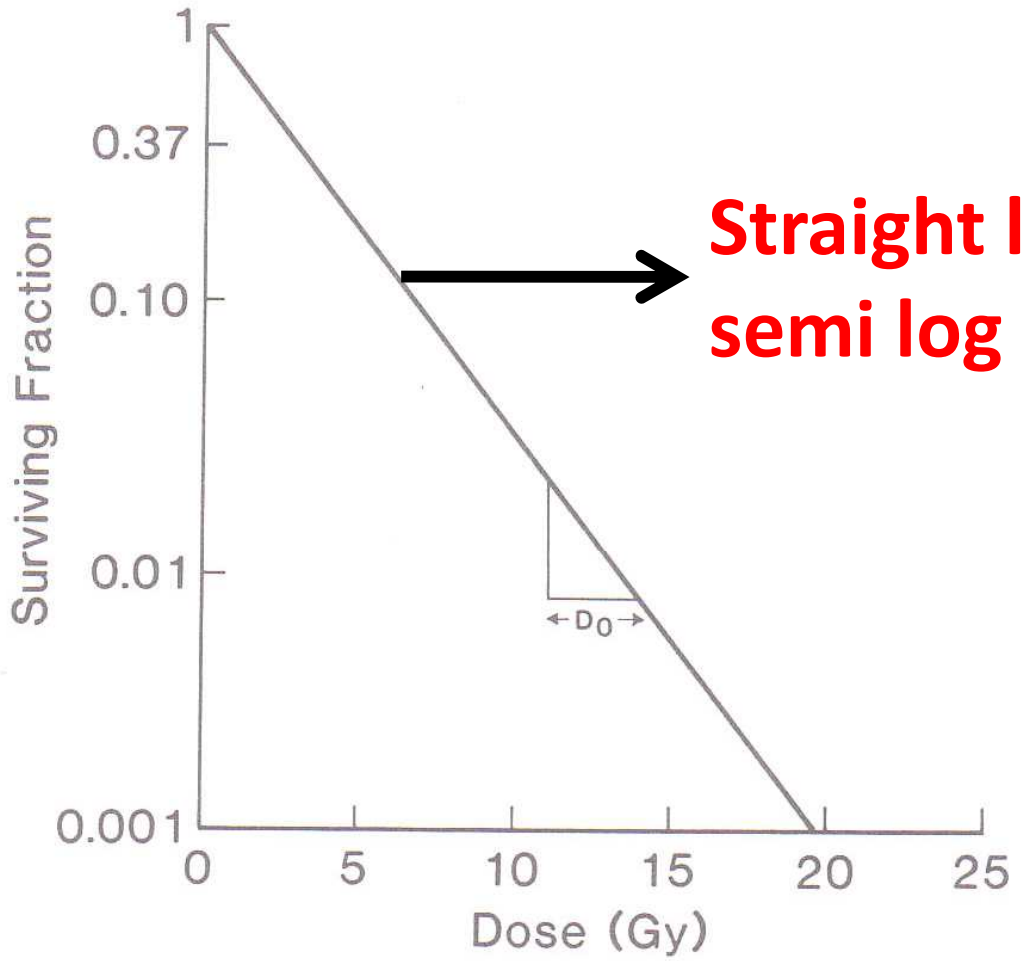
90 Colonies

Plating Efficiency = 90%

Surviving fraction =

$$\frac{72}{400 \times 0.9} = 0.2 \qquad \frac{36}{1000 \times 0.9} = 0.04 \qquad \frac{45}{10{,}000 \times 0.9} = 0.005$$

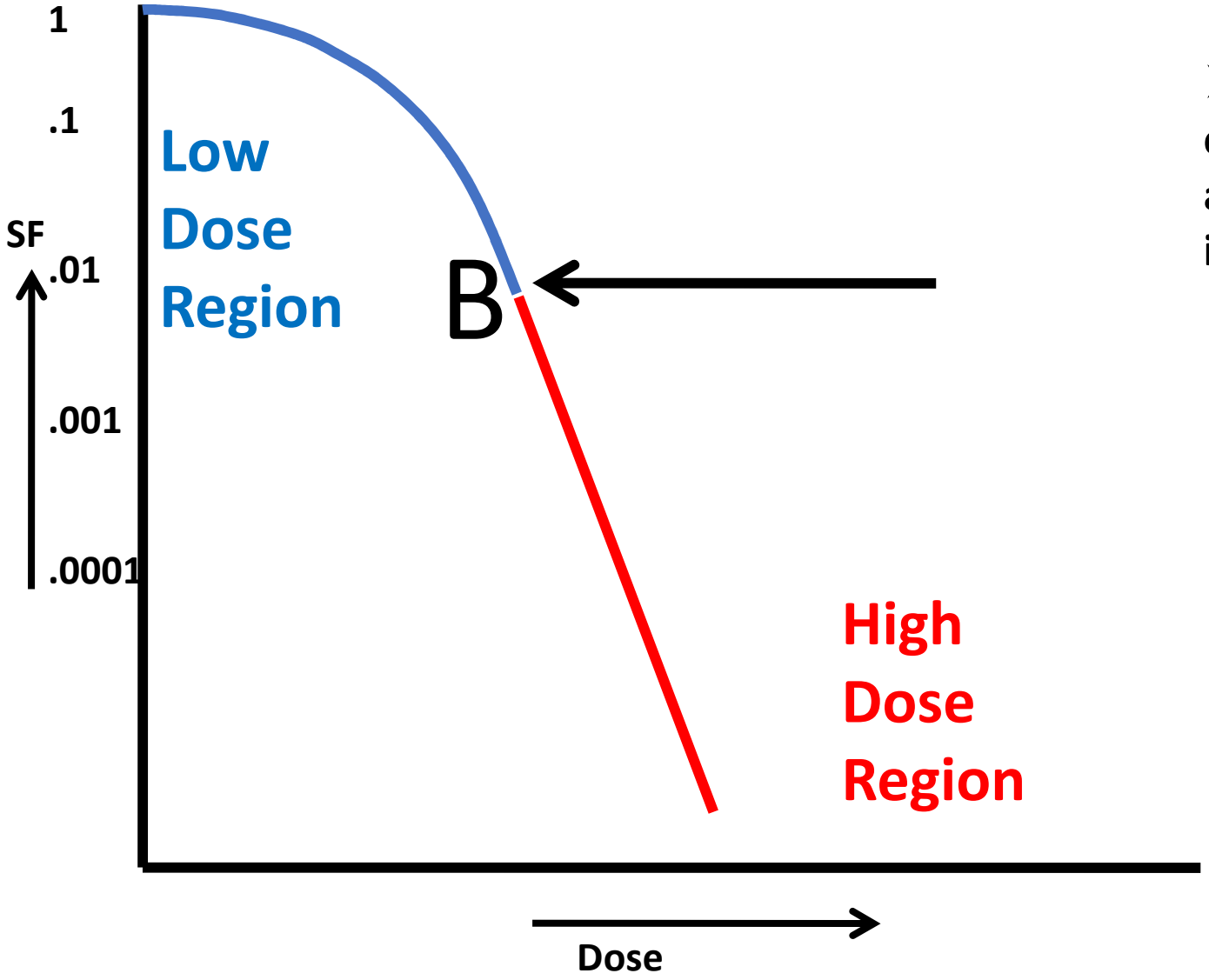
Cell Survival Curve of Micro-organism



Straight line on a semi log plot

FIG 3–4.
Survival curve for bacteria *(Escherichia coli)*, showing that in this system survival is a simple exponential function of dose.

Mammalian Cell Survival Curve



- Initial portion is continuously bending at low dose region till it reaches at point B.
- At higher dose region the curve becomes a straight line.

Two Models to describe mammalian cell survival curve

- **Multi Target Model**
- **Linear Quadratic (LQ) Model**

Multi Target Model

- **Each cell contain more than one target (may be assumed n number of target and n may be any number more than one)**
- **In order to bring cell death by radiation, all the target should be deactivated.**
- **If n-1 targets are hit then cell survives.**
- **There are two type of cell killing taking place simultaneously to inactivate n target resulting into cell death.**

Low Dose Region

- ***Cell kill by single hit event (SHE)***

High Dose Region

- ***Cell kill by multiple hit event (MHE)***

Low Dose Region

SHE

↓

Deactivation of n target

↓

Lethal Damage

↓

Cell Death

Contribution in cell kill is by *SHE* and no contribution by *MHE*

MHE

↓

Deactivation of n-1 target

↓

Sub-lethal Damage

↓

Repair

↓

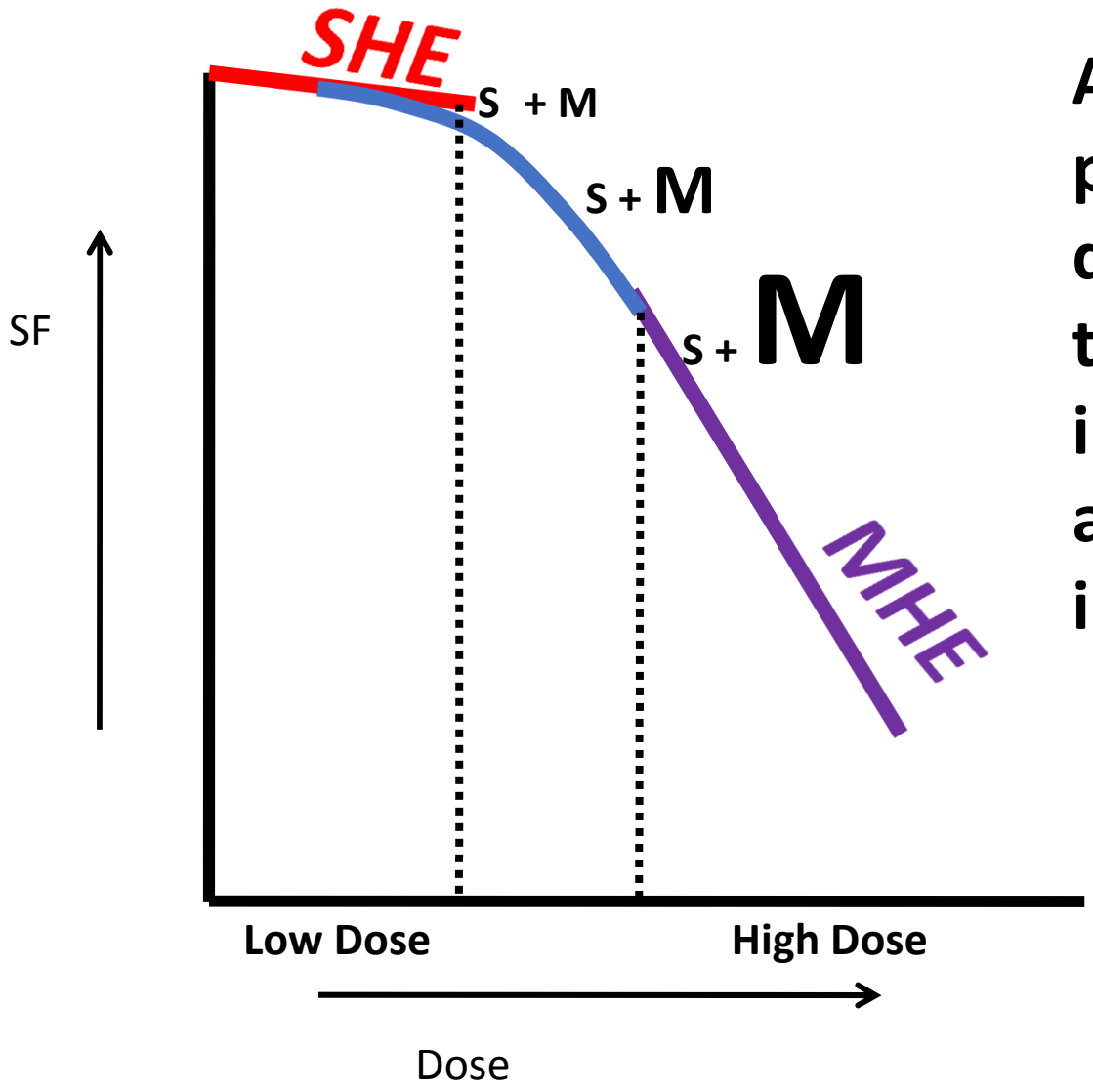
No Cell Death

High Dose Region

Main contribution in cell kill is by *MHE.*

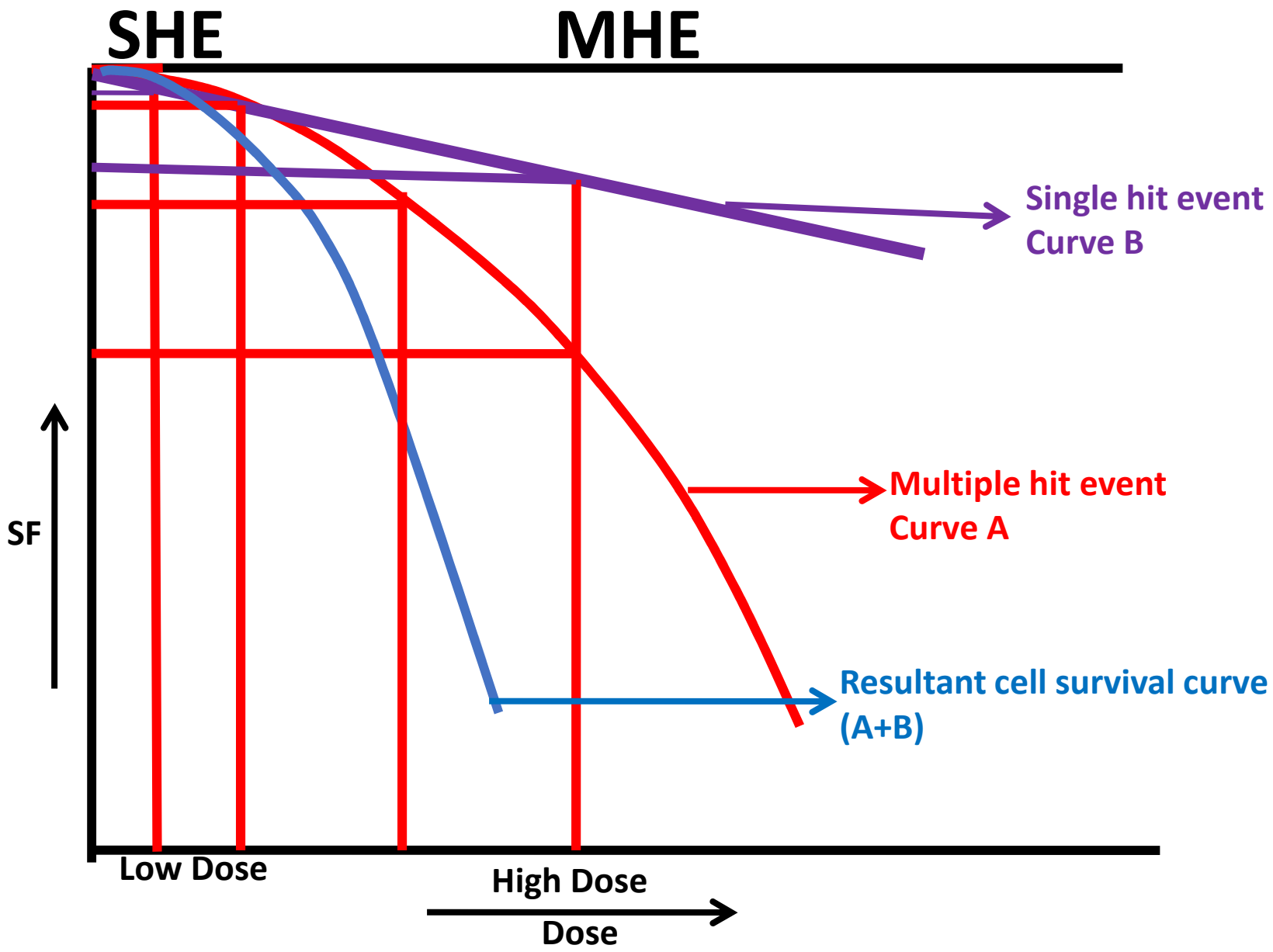
Relative contribution by *SHE* is small.

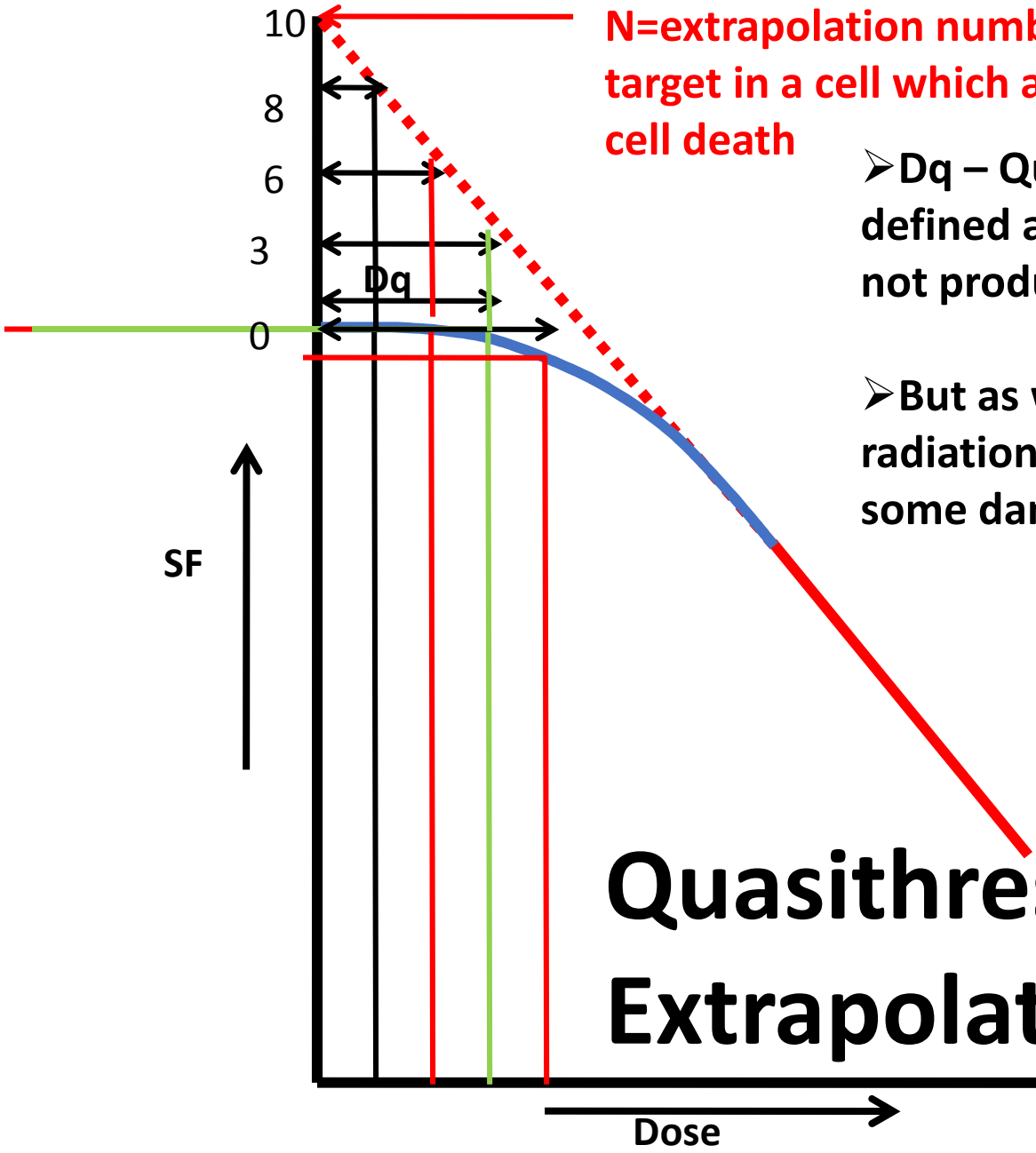
Multi Target Model



As dose increases the probability of deactivation of n target by *MHE* also increases and *MHE* also start contributing in total cell kill.

Multi Target Model





N=extrapolation number = represent number of target in a cell which are required to be hit to bring cell death

- **Dq – Quasithreshold dose ->which is defined as dose of radiation which do not produce any cell killing.**
- **But as we know that no dose of radiation is safe and it always produces some damages so the name is Quasi**

Quasithreshold Dose Extrapolation Number

Parameters used to describe these curves

Multi Target Model

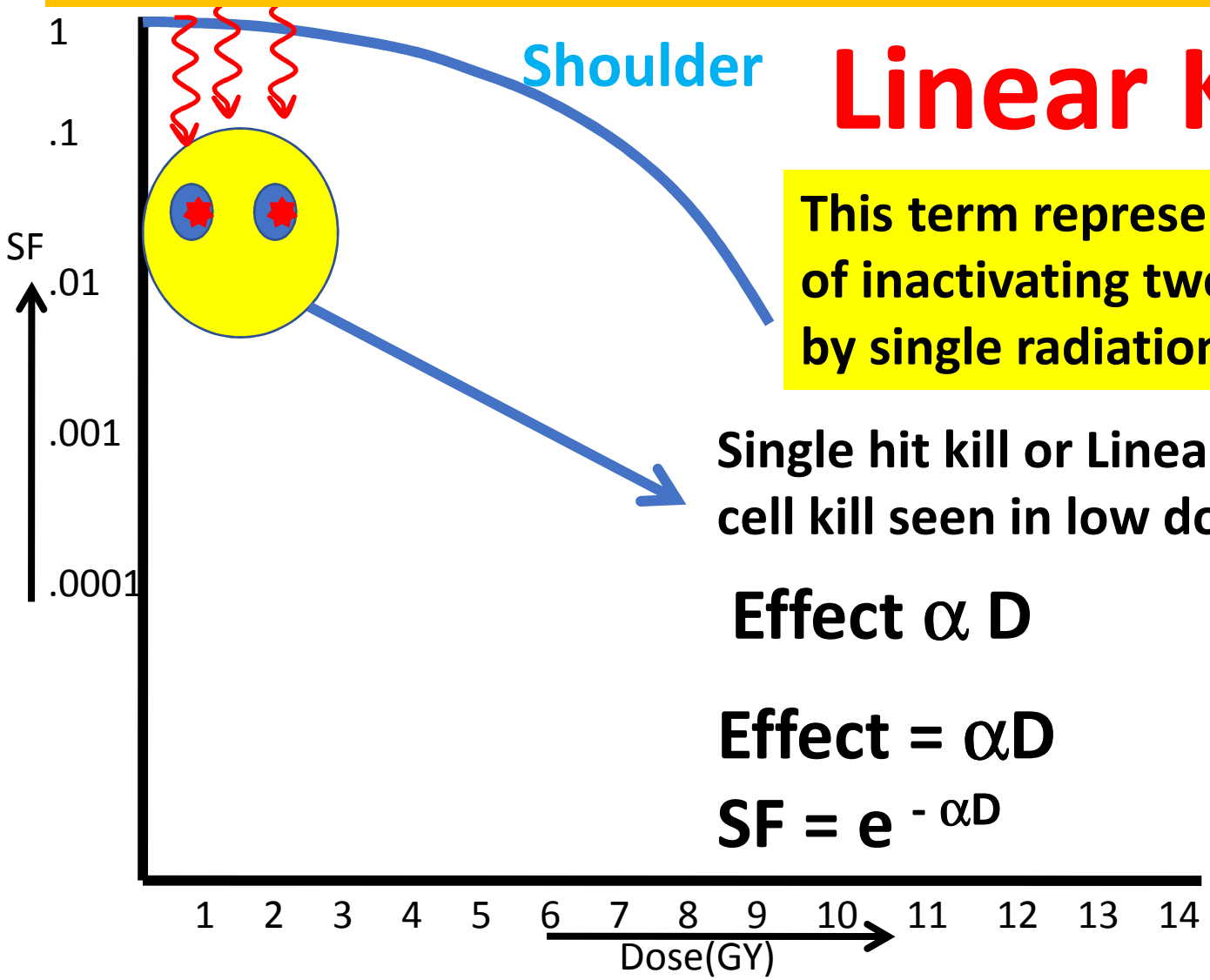
- **This is a theoretical model as we know there is no threshold dose of radiation below which, there is no damage.**
- **While this model based on quasi threshold dose.**
- **This model can not be used in clinical practice.**
- **Fails to identify that acute and late reacting tissue behave differently with radiation.**

Two Models to describe mammalian cell survival curve

- **Multi Target Model**
- **Linear Quadratic (LQ) Model**

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

Linear Quadratic model (LQ Model)



Linear Kill

This term represent the probability of inactivating two strands of DNA by single radiation event.

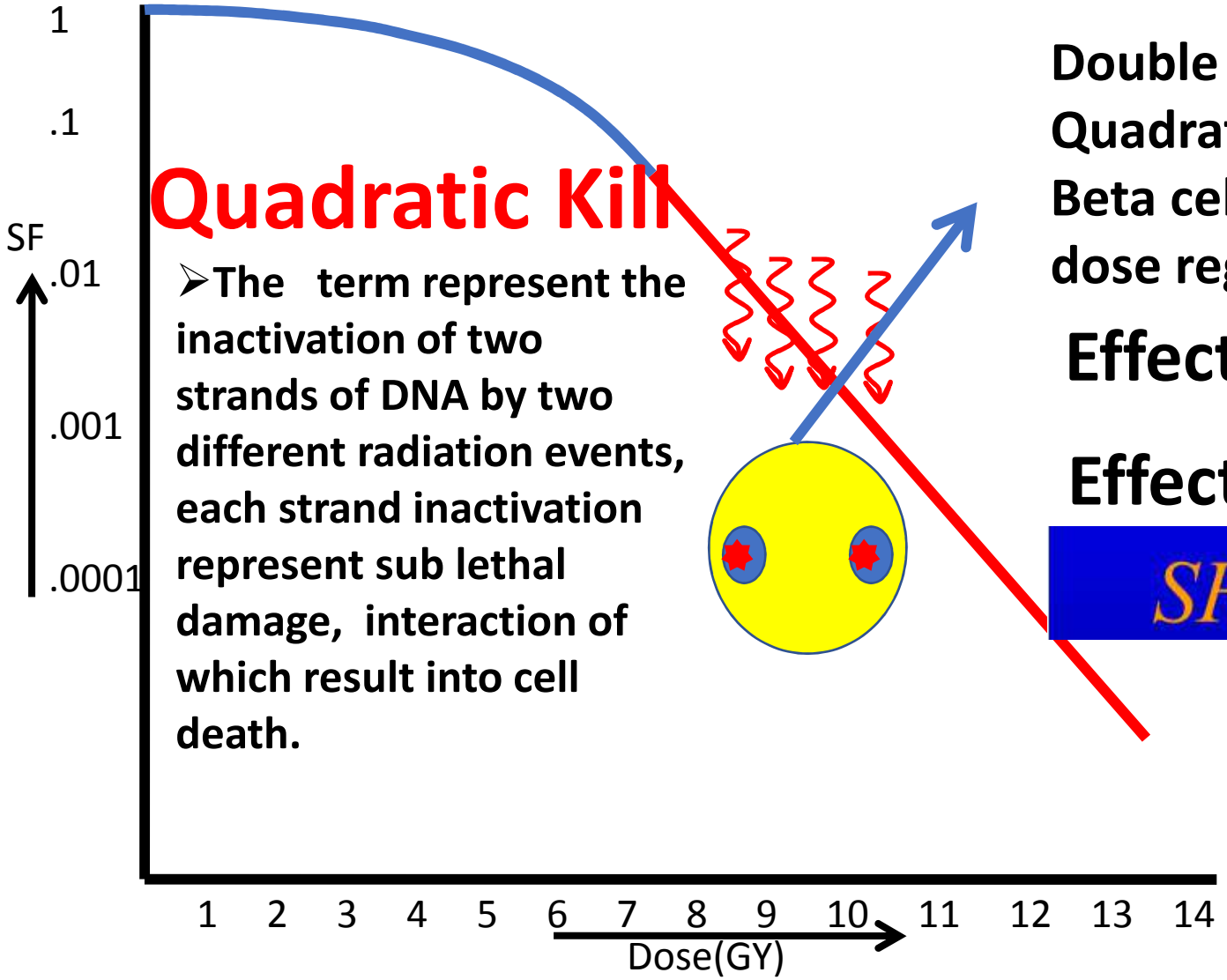
Single hit kill or Linear Cell kill or Alpha cell kill seen in low dose region

$$\text{Effect} \propto D$$

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

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

Linear Quadratic model (LQ Model)



Quadratic Kill

- 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.

Double hit kill or Quadratic Cell kill or Beta cell kill seen in high dose region

Effect α D^2

Effect = βD^2

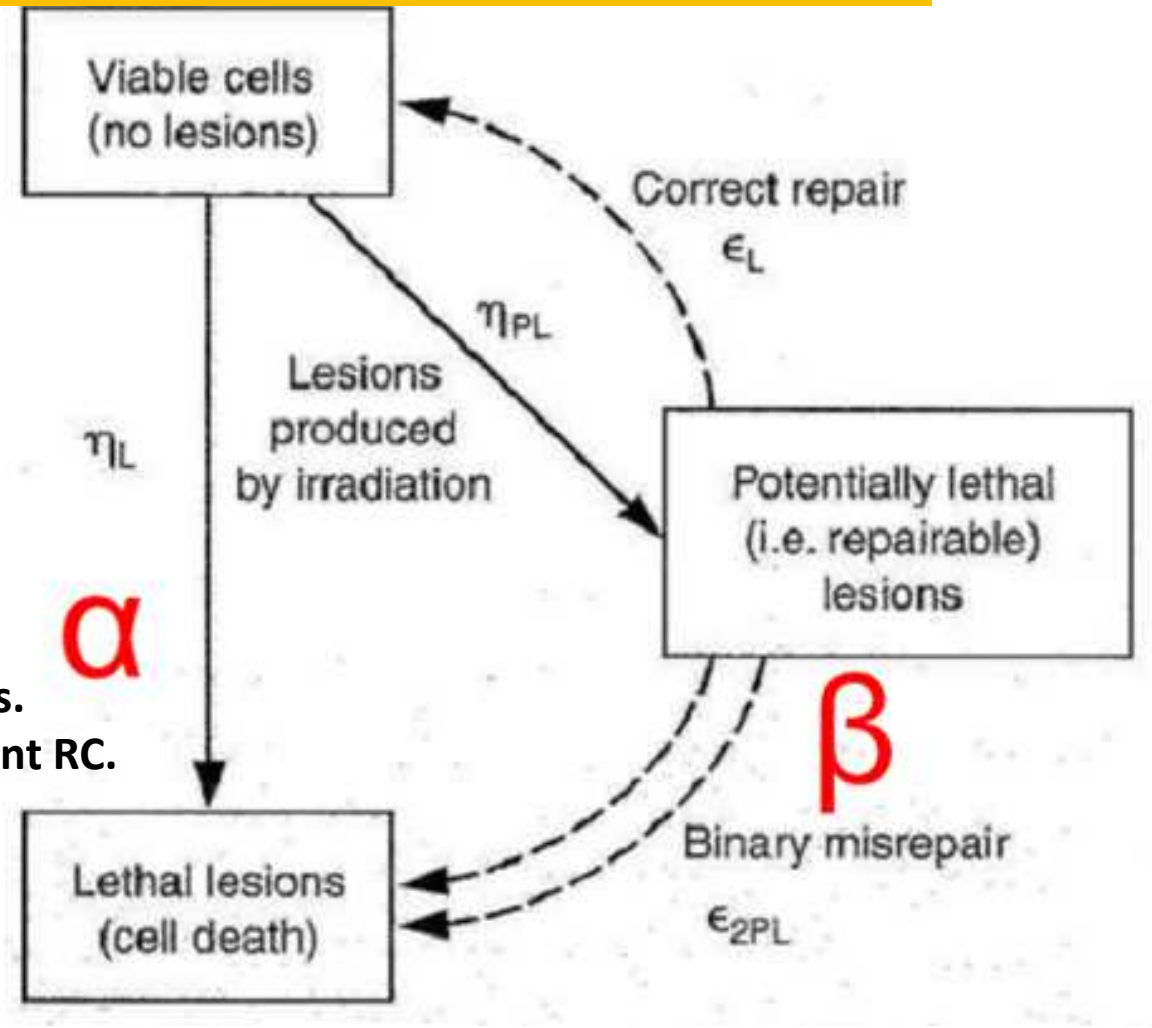
$$SF = e^{-\beta D^2}$$

Double hit kill is similar to the MHE

Linear Quadratic model (LQ Model)

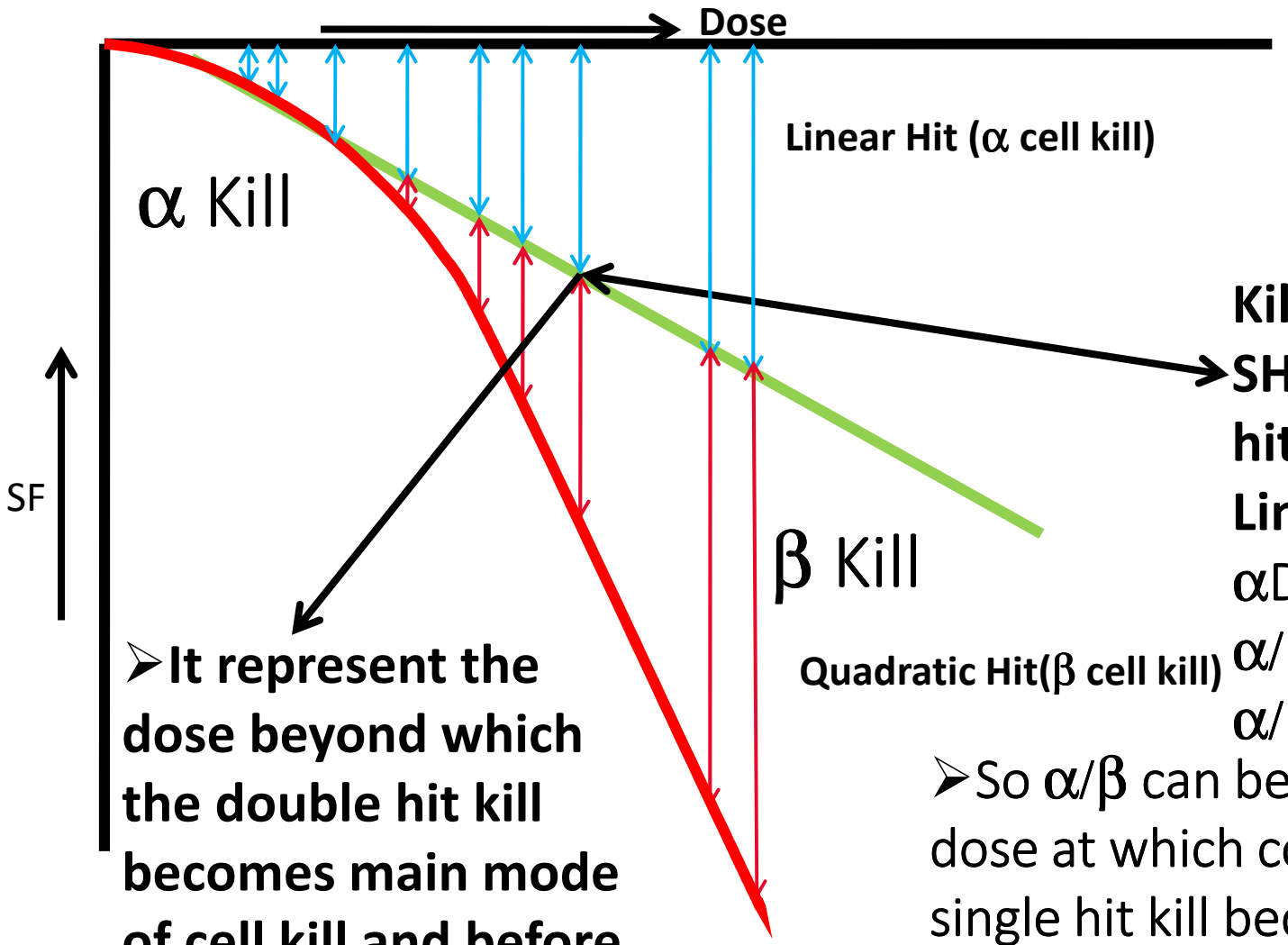
$$S.F. = e^{-\alpha D + \beta D^2}$$

- Repair Capacity of the Tissues.
- Different Tissues have different RC.
- *Late tissue higher RC*
- *Early Reacting Tissue low RC*



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

Linear Quadratic model (LQ Model)



Killing by SHE=Killing by two hit event

Linear = Quadratic

$\alpha D = \beta D^2$

$\alpha/\beta = D^2/D$

$\alpha/\beta = D$

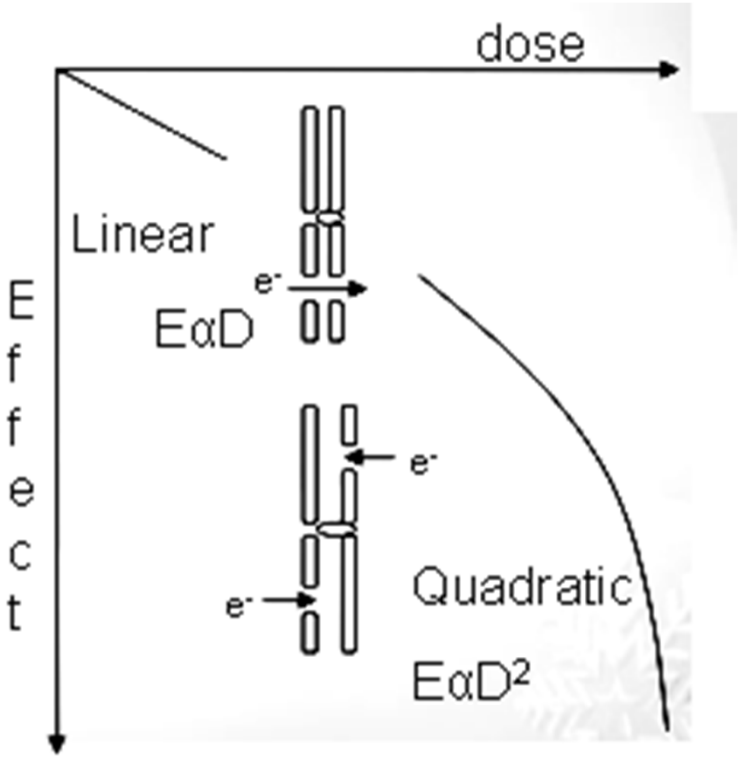
➢ So α/β can be defined as the dose at which contribution by single hit kill becomes equal to double hit kill.

➢ **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.**

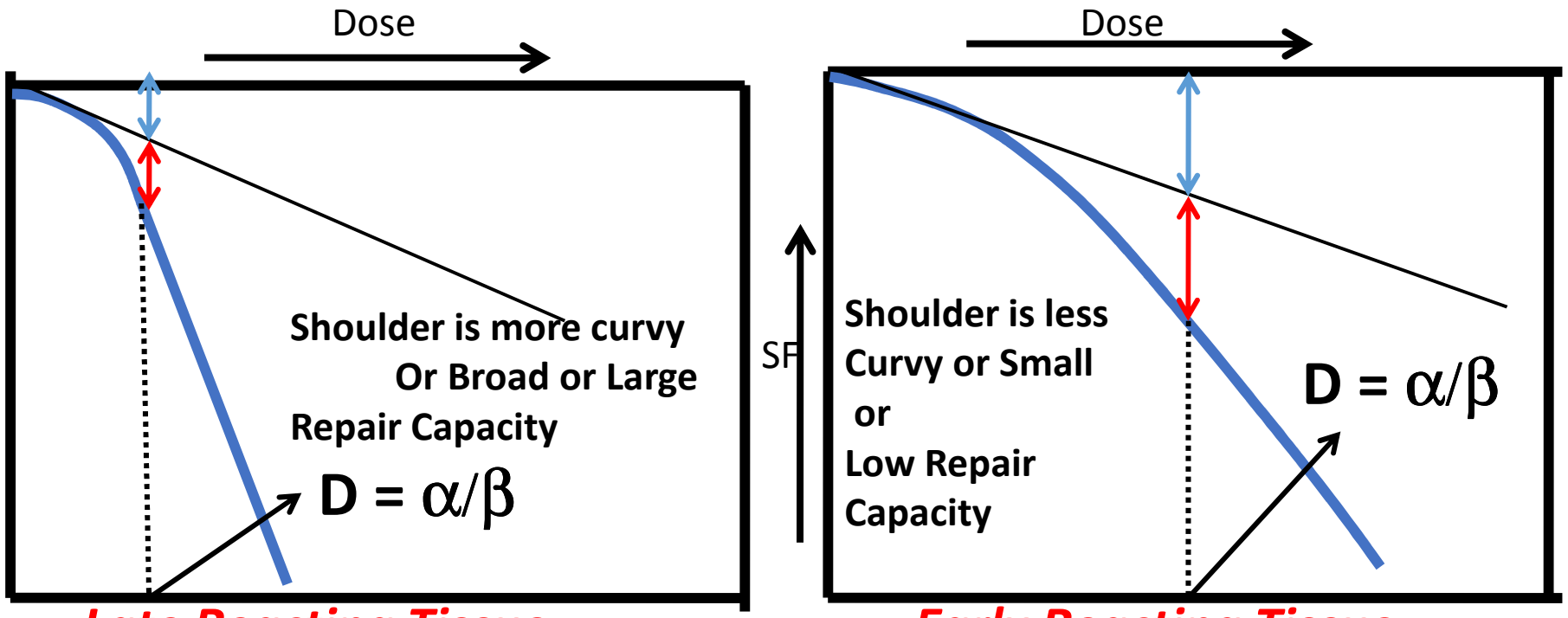
- **α/β also represents the point beyond which the curve becomes a straight line and predominantly double hit events take place.**



α/β Ratio defines "curviness" of survival curve

Based on α/β ratio, the body tissues have been divided into two category.

Malignant Tumor behave like Early Reacting Tissue and have similar shape of cell survival curve and same α/β Ratio i.e. an average of 10



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

α/β = 6Gy to 15 Gy **(10Gy)**
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

Average 10

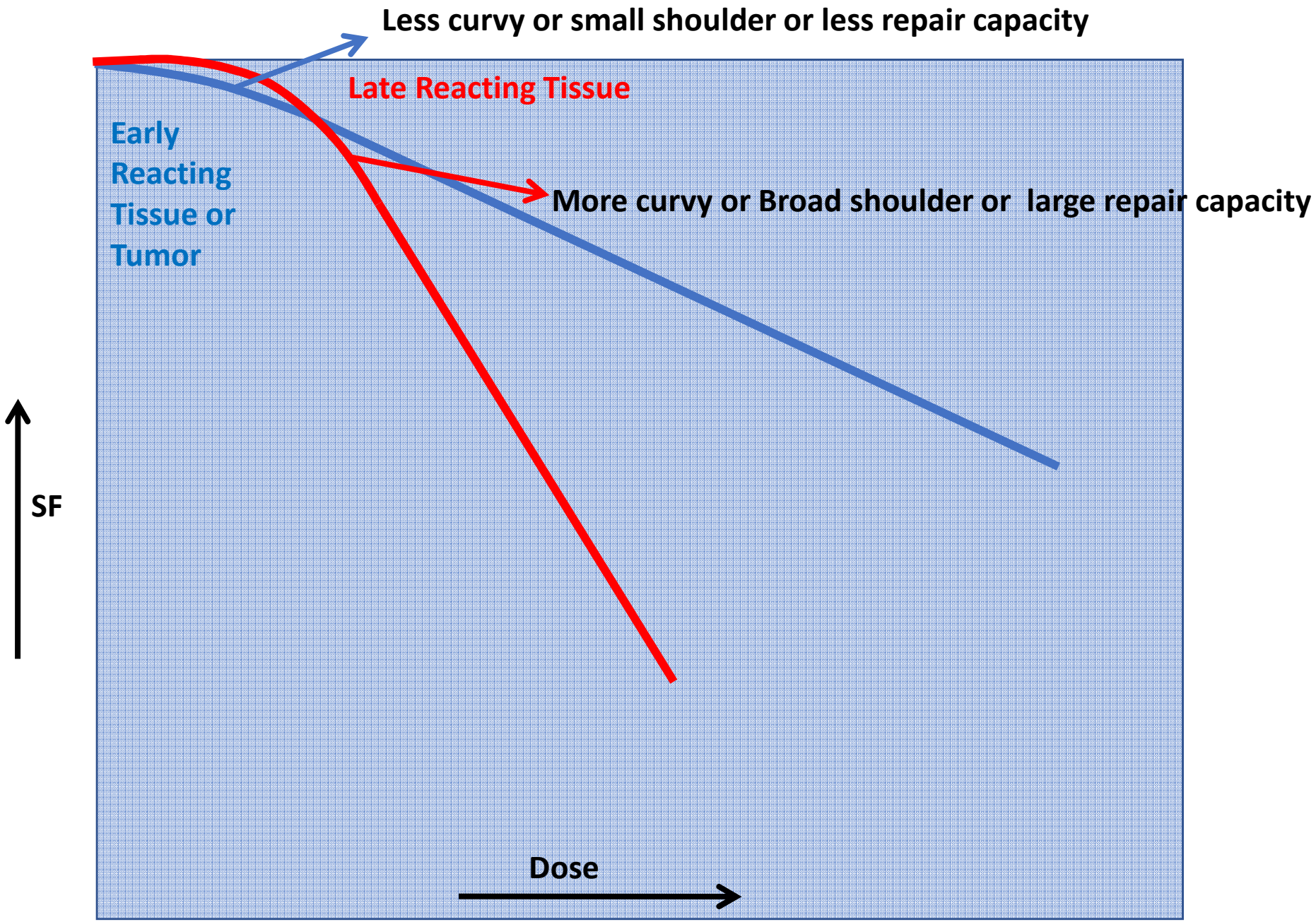
Average 3

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

Average 10

.ondon, 2009, Hodder Arnold.



Cell Survival Curve of Early and Late Reacting Tissues

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

$E = (nd)(\alpha + \beta d)$

$$E = (nd)(\alpha + \beta d)$$

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

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

Biologically Effective Dose (BED) =

Biological Effective Dose(BED)

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

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

Same

$$\text{RE } \alpha \ \frac{1}{\alpha/\beta}$$

- Late Reacting tissue α/β ratio is low so RE is more
- Early Reacting tissue α/β ratio is high so RE is less
- So increasing the dose per fraction will have more effect on late reacting tissues. Eg

If dose/fx = 3 Gy

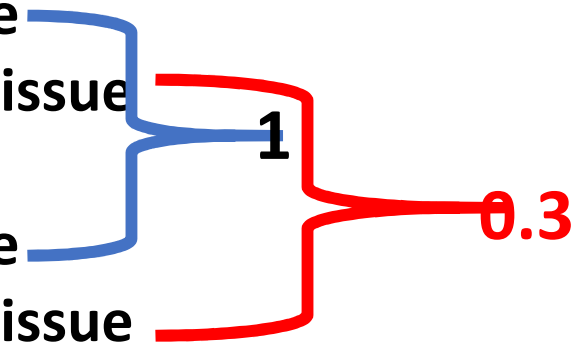
RE(3Gy) = 1+3/3 = 2 for late reacting tissue

RE(3Gy) = 1+3/10 = 1.3 for early reacting tissue

dose/fx is doubled i.e. 6 Gy

RE(6Gy) = 1+6/3 = 3 for late reacting tissue

RE(6Gy) = 1+6/10 = 1.6 for early reacting tissue



Iso-effective total dose

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

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

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

(BED)2 = (BED)1

$$D_2 \times \left(1 + \frac{d_2}{\alpha/\beta}\right) = D_1 \times \left(1 + \frac{d_1}{\alpha/\beta}\right)$$

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

Always calculate Iso-effective dose based on α/β ratio of late reacting tissue

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 when Repopulation Start

Overall Treatment Time

So Accelerated repopulation = $\frac{0.693}{\alpha} \frac{T\text{-}Tk}{T_{pot}}$

21 to 28 days after beginning of radiotherapy in Head & Neck cancer.

α 0.3/ Gy

T_{pot} 2 to 25 days with a median of 5 days

6 weeks (39 days) schedule

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

0.46Gy per day

7 weeks (46 days) schedule

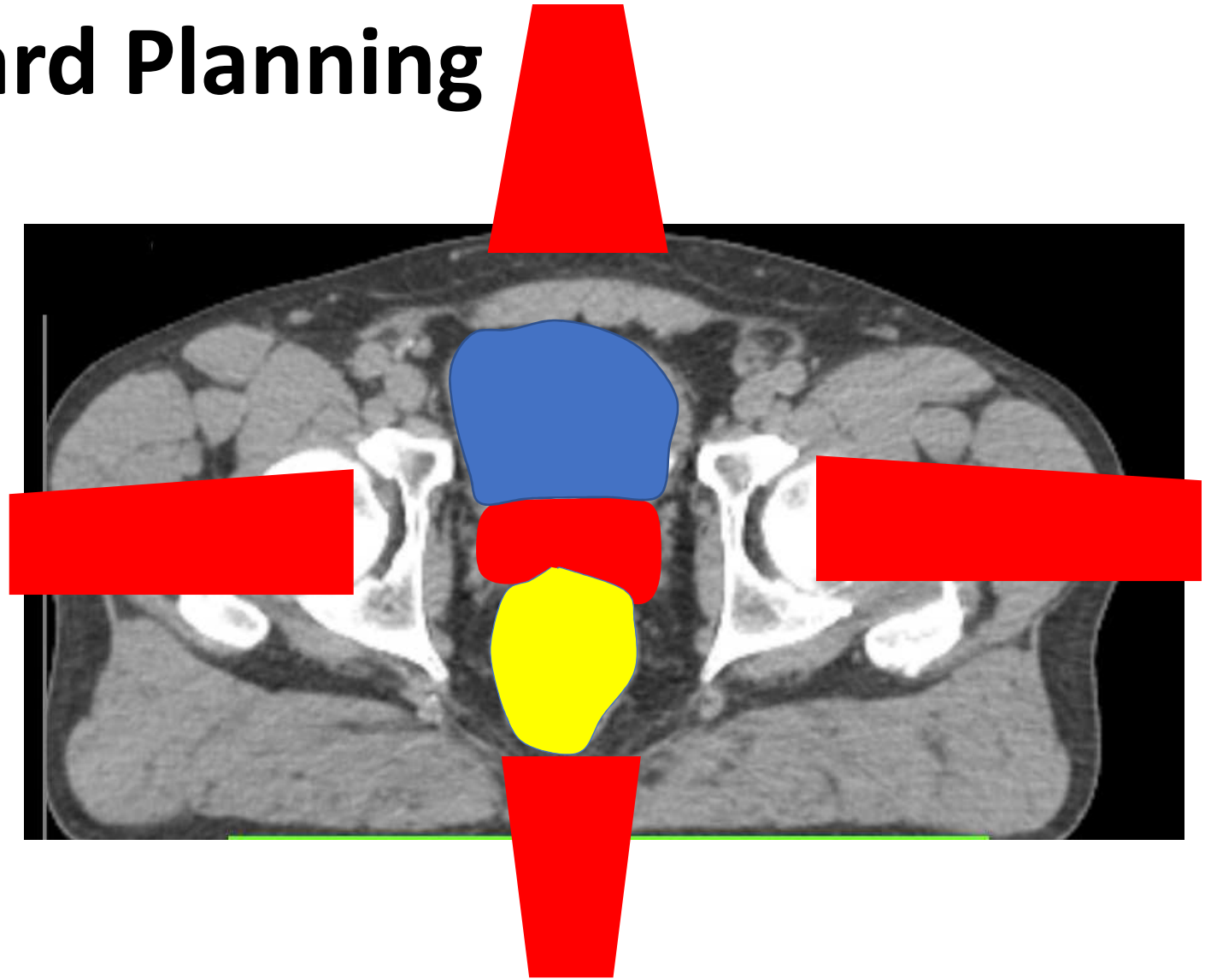
Dose equivalent to accelerated repopulation $= \frac{0.693}{0.3} \times \frac{(46-21)}{5} = 11.6\ Gy_{10}$

Dose of radiation which goes waste

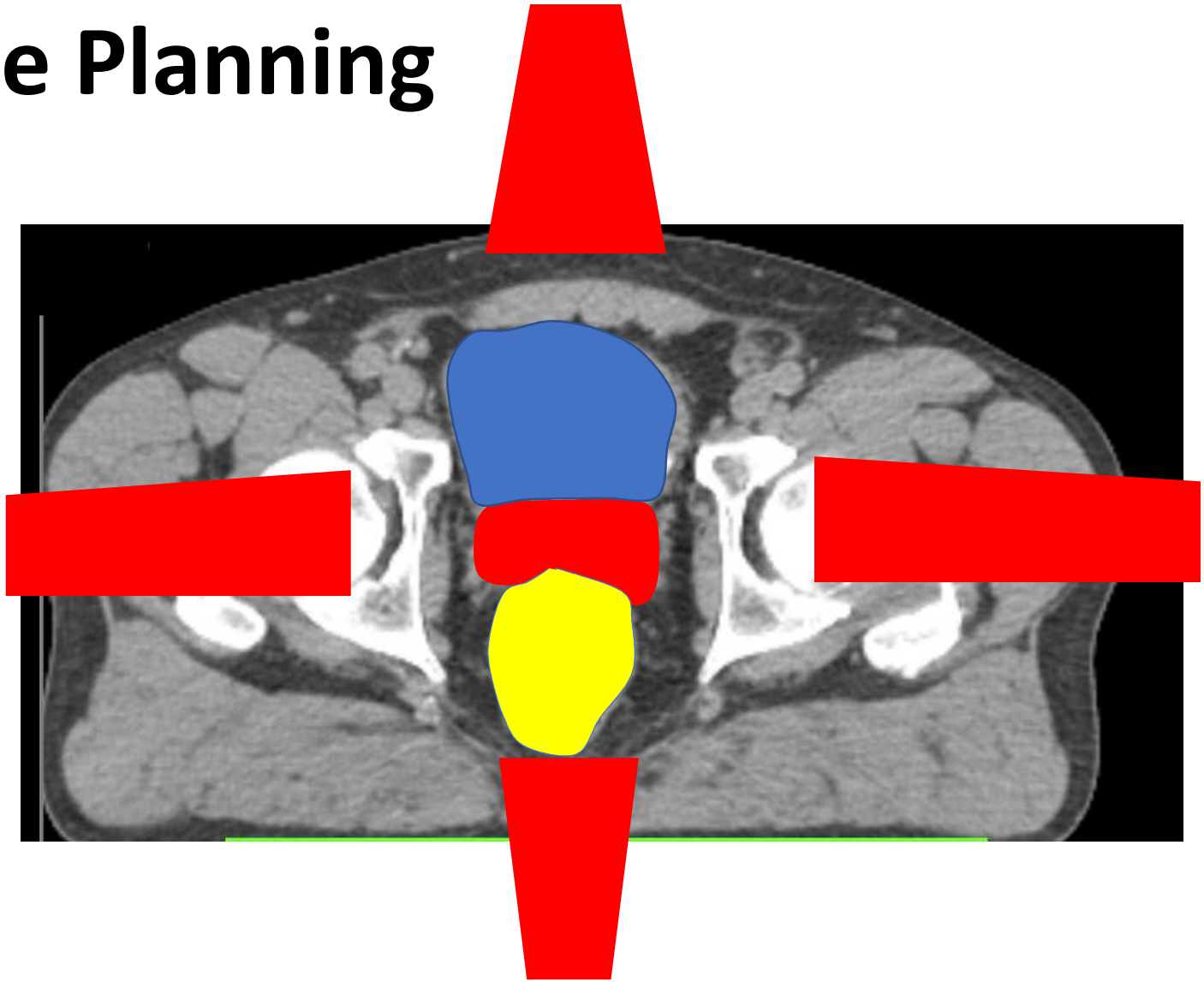
So this much of dose is to be reduced from BED on account of repopulation. This also shows as overall treatment time increases the BED decreases.

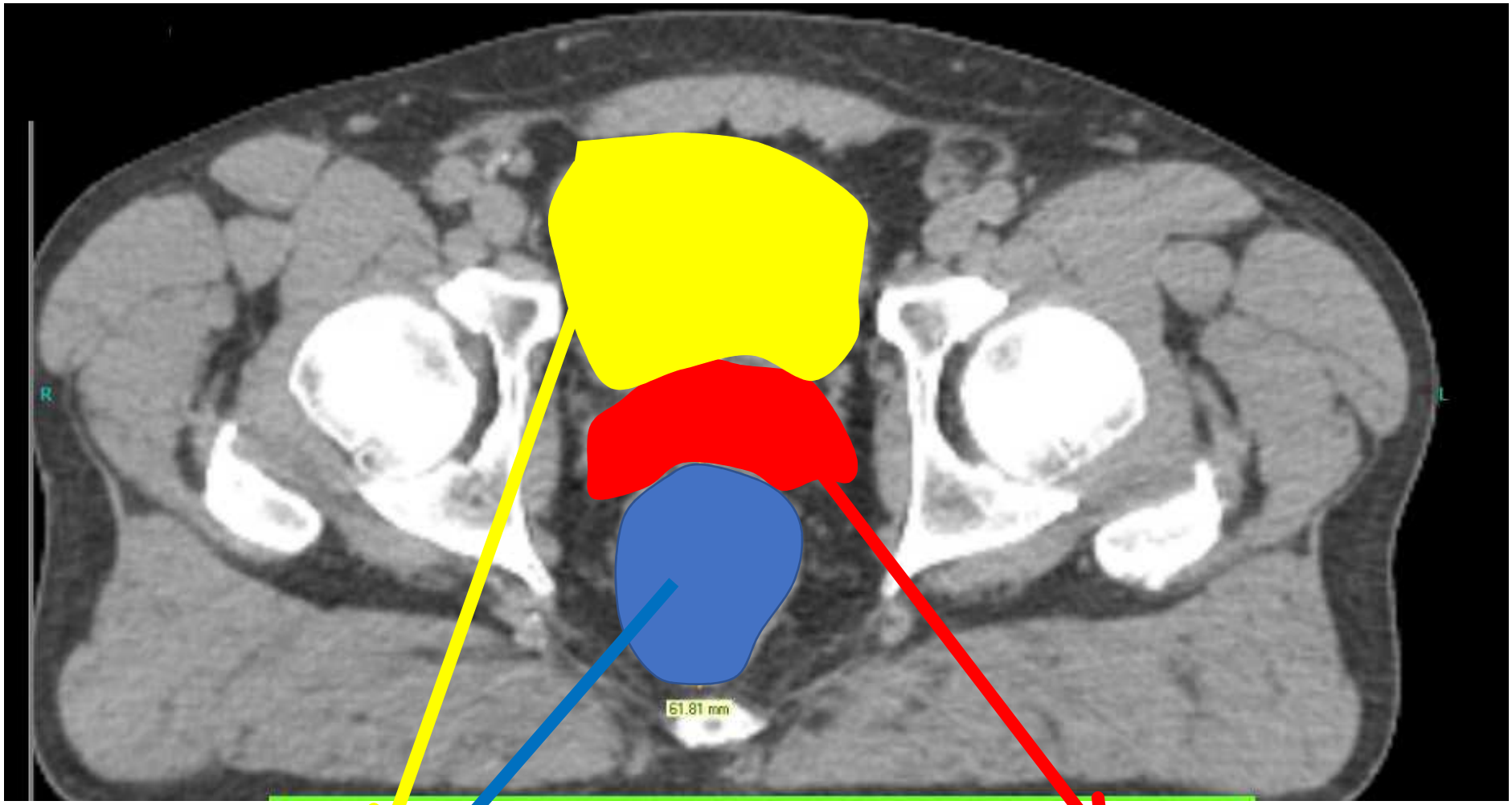
Biological Model

Forward Planning



Inverse Planning





Normal Tissue Complication

↓

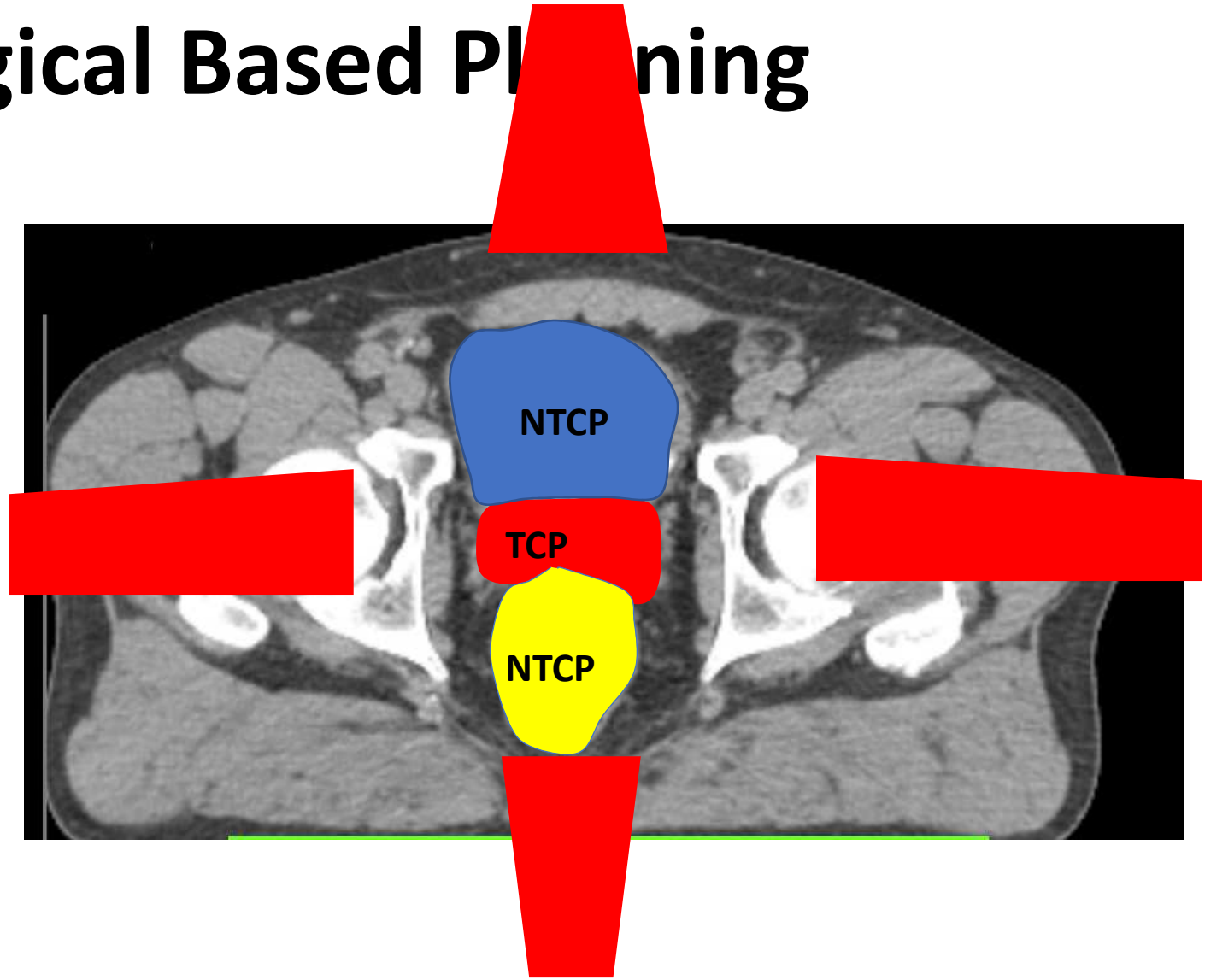
Normal Tissue Complication Probability(NTCP)

Tumor Control

↓

Tumor Control Probability (TCP)

Biological Based Pl ning



Therapeutic Ratio

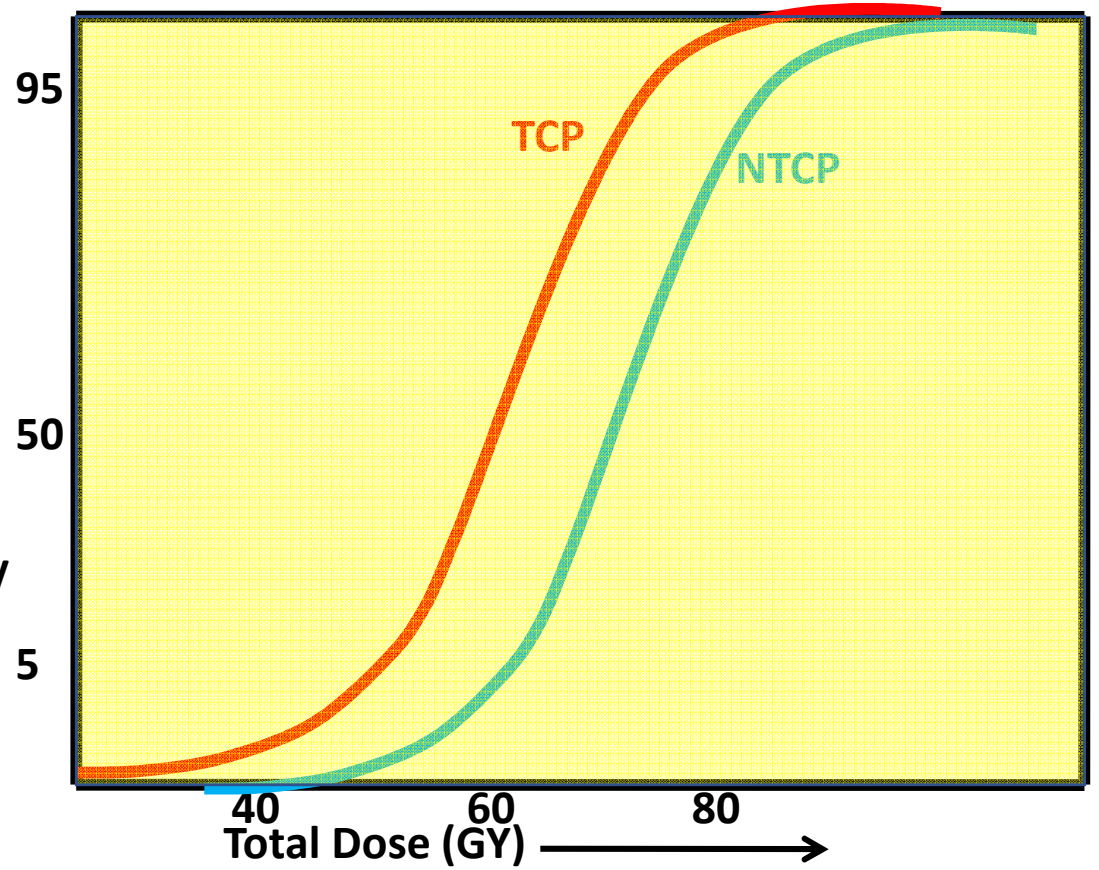
$$TR = \frac{(TCP)}{(NTCP)}$$

Dose Response Curve **is between probability of effect on one axis vs total dose of radiation on other axis**

Dose Response curve is plotted for tumor and normal tissues are usually sigmoid or S shaped.

•Therapeutic Ratio may be

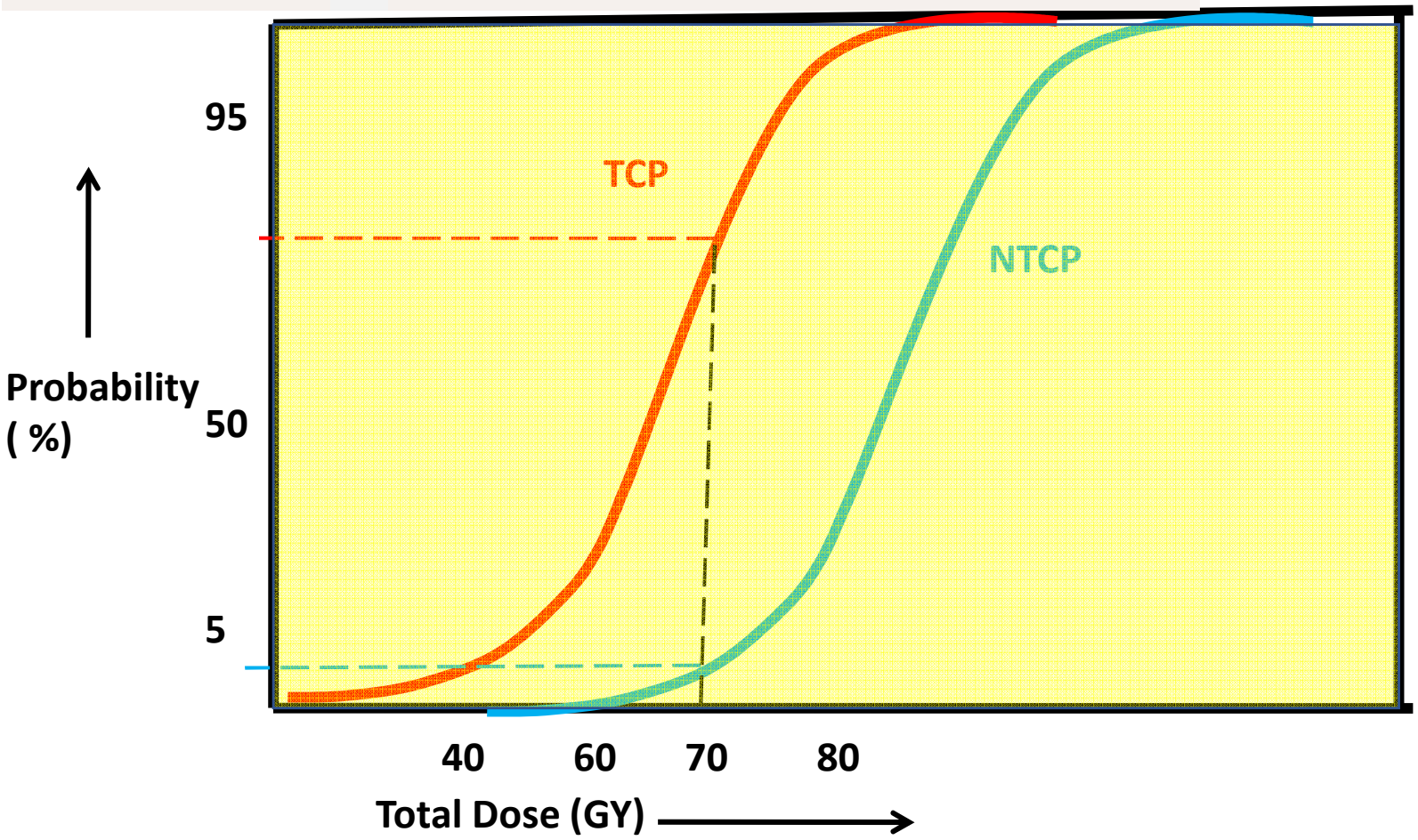
- ***Favorable***
- ***unfavorable***



Favorable Therapeutic Ratio

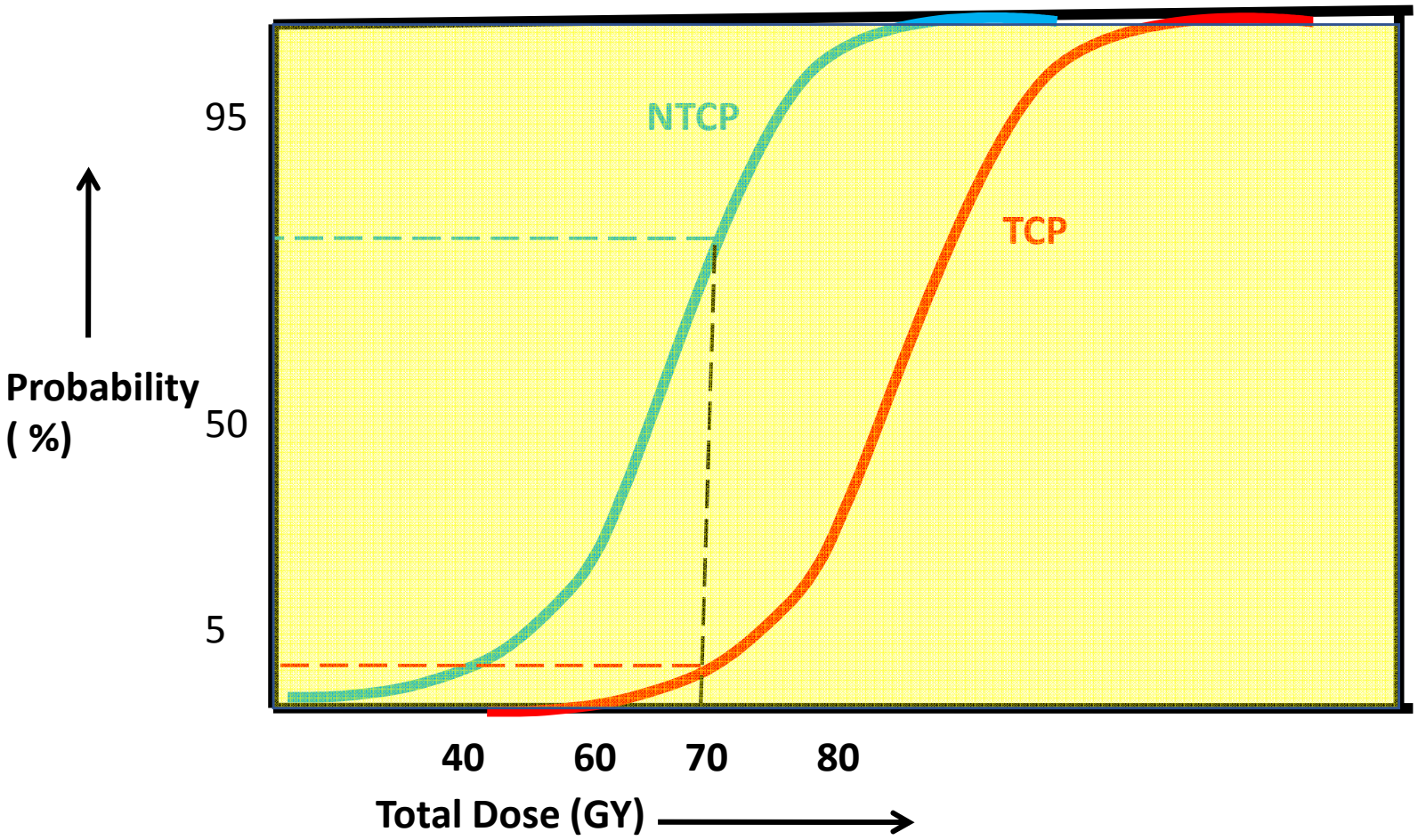
➢ ***TCP curve should be left and NTCP should be right***

- For a typical good radiotherapy treatment:
  - TCP ≥ 0.5 **(50%)**
  - NTCP < 0.05 **(5%)**



Unfavorable Therapeutic Ratio

- ***If for any clinical situation NTCP curve is on left and TCP is on right***

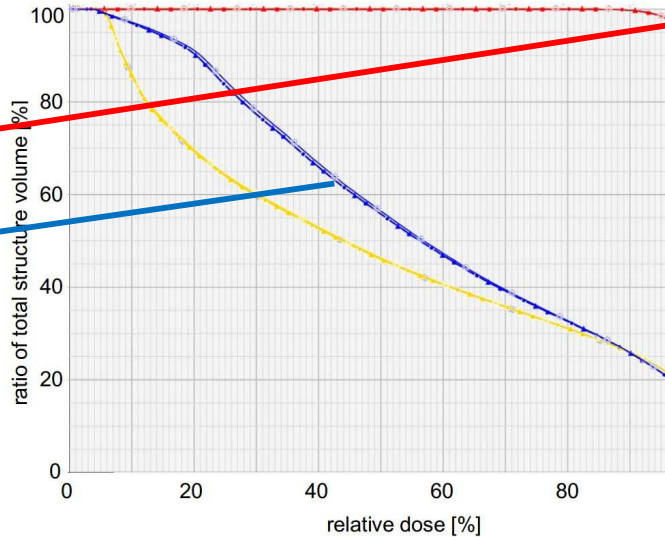


Introduction

Dose Volume Histogram(DVH) reflect dose to volume of organ

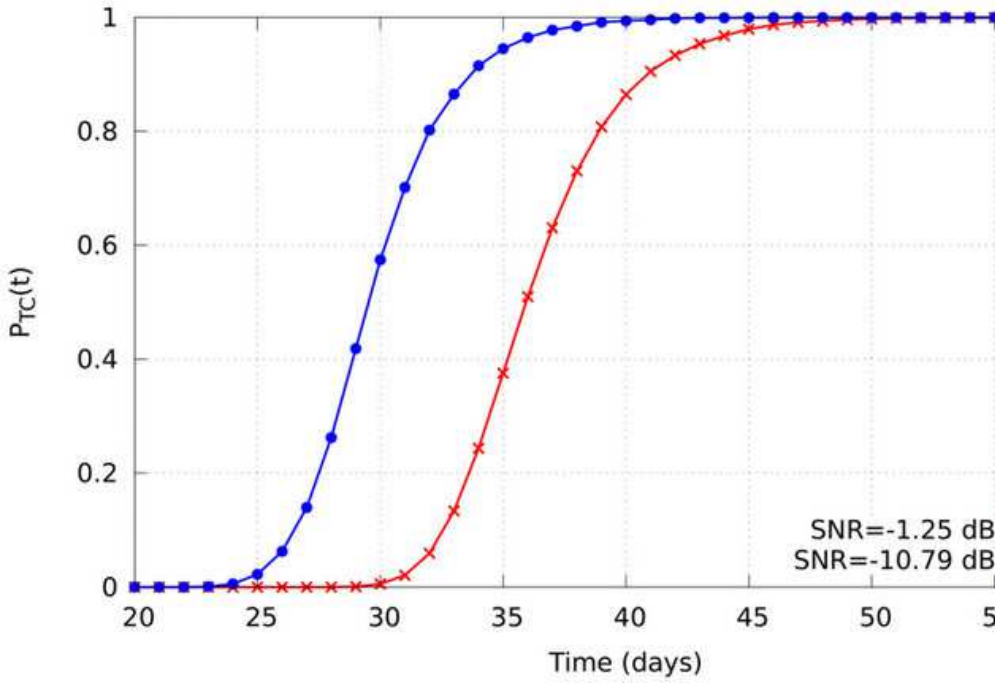
Tumour

Normal Organ



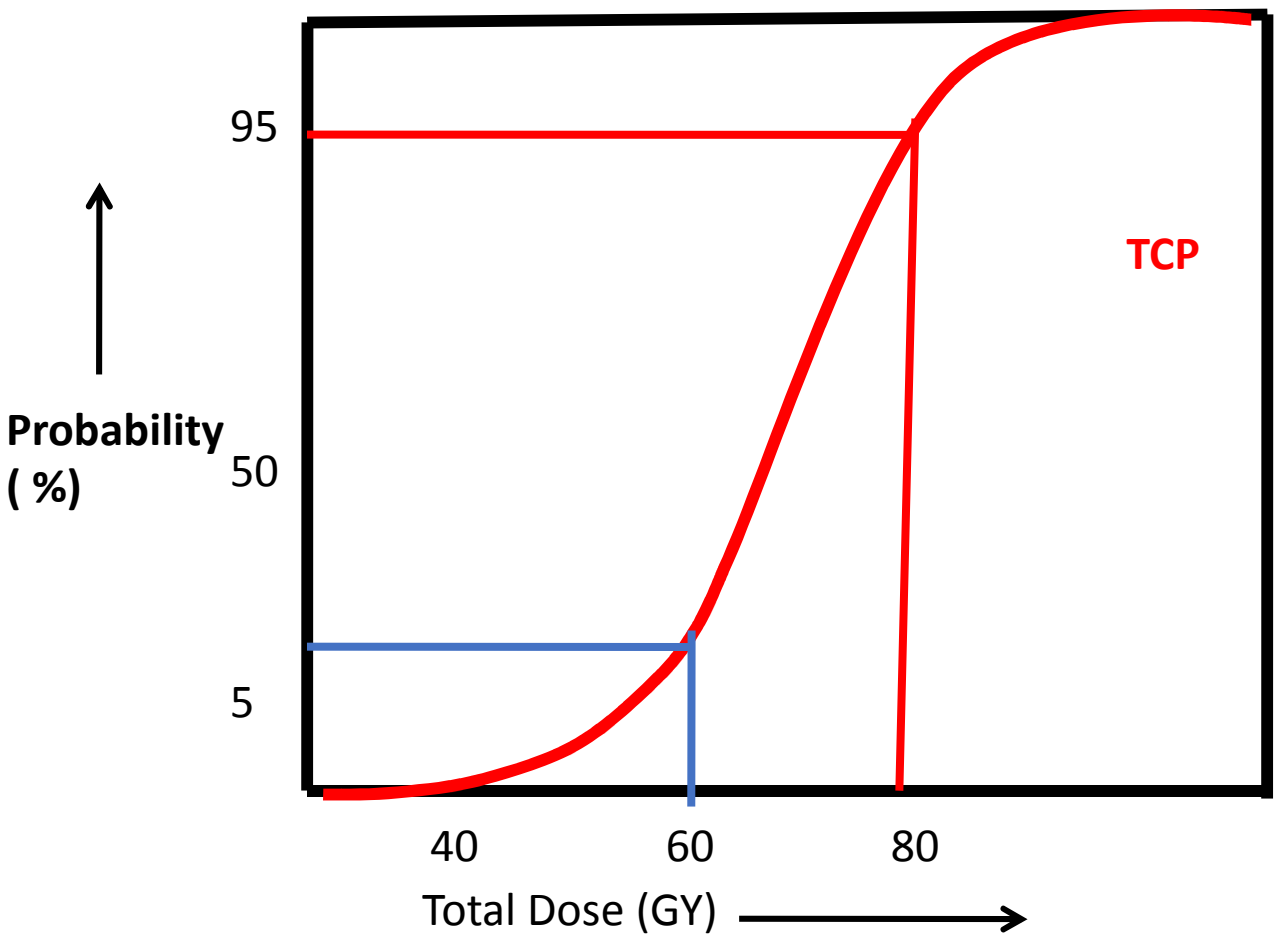
Tumour Control Probability (TCP)

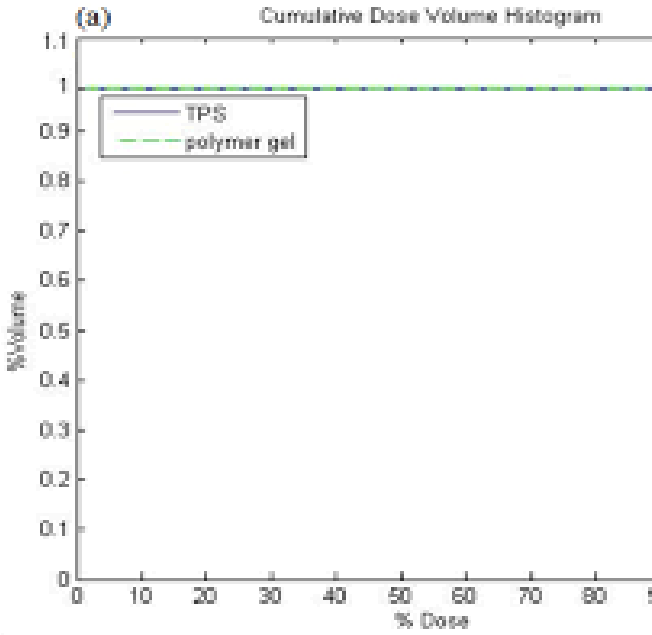
Normal Tissue Complication Probability (NTCP)



Tumor Control Probability (TCP)

100% prescribed dose should cover 100 volume of Tumour

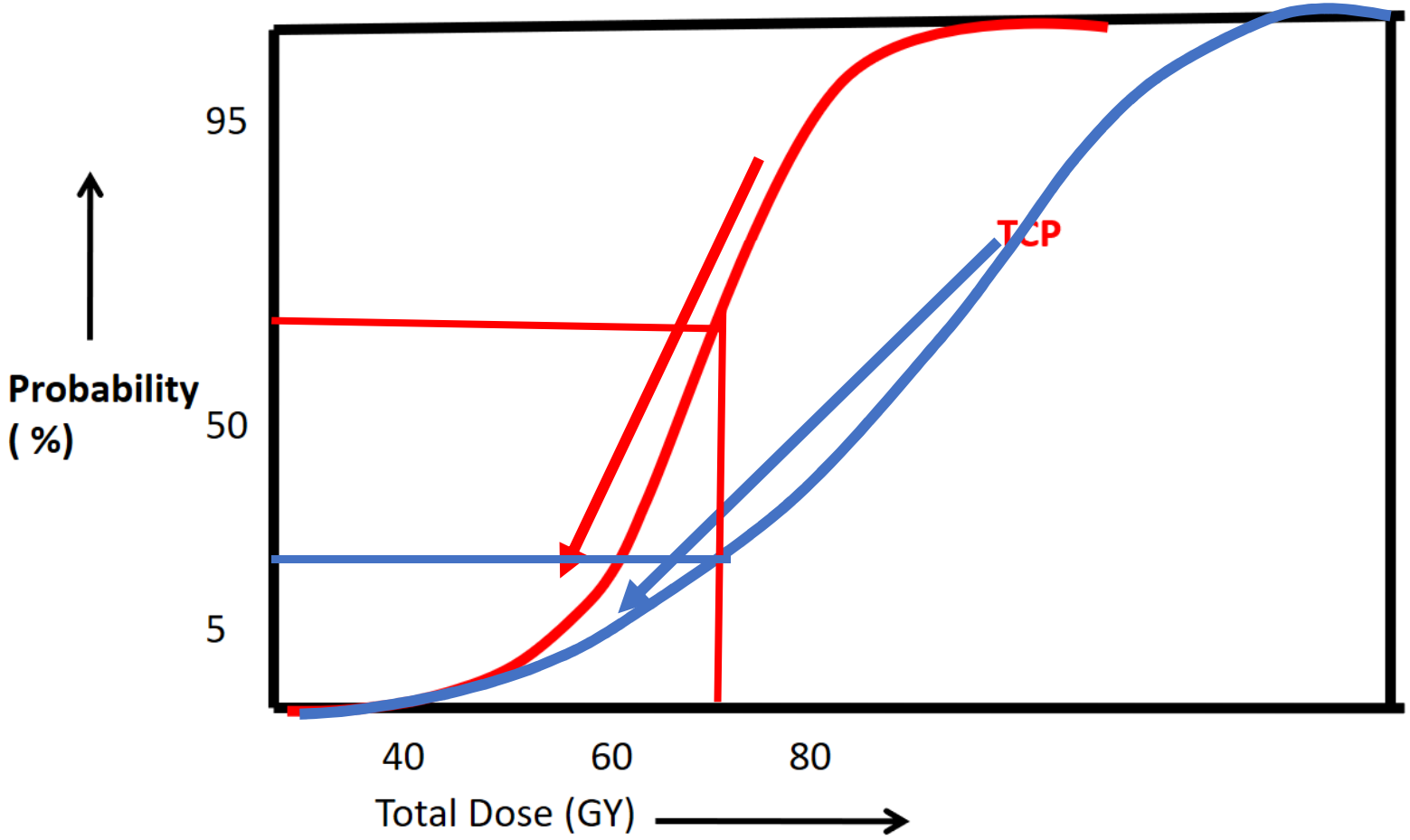




Sigmoid Curve for TCP

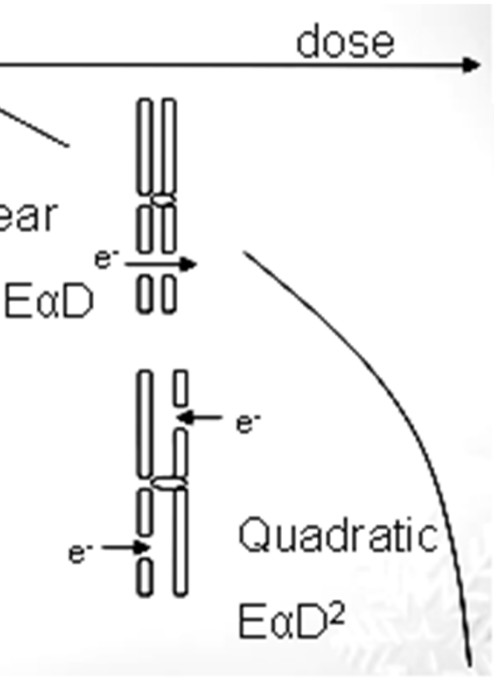
teepness of slope in clinical situation based on
linical data is less than obtained experimentally

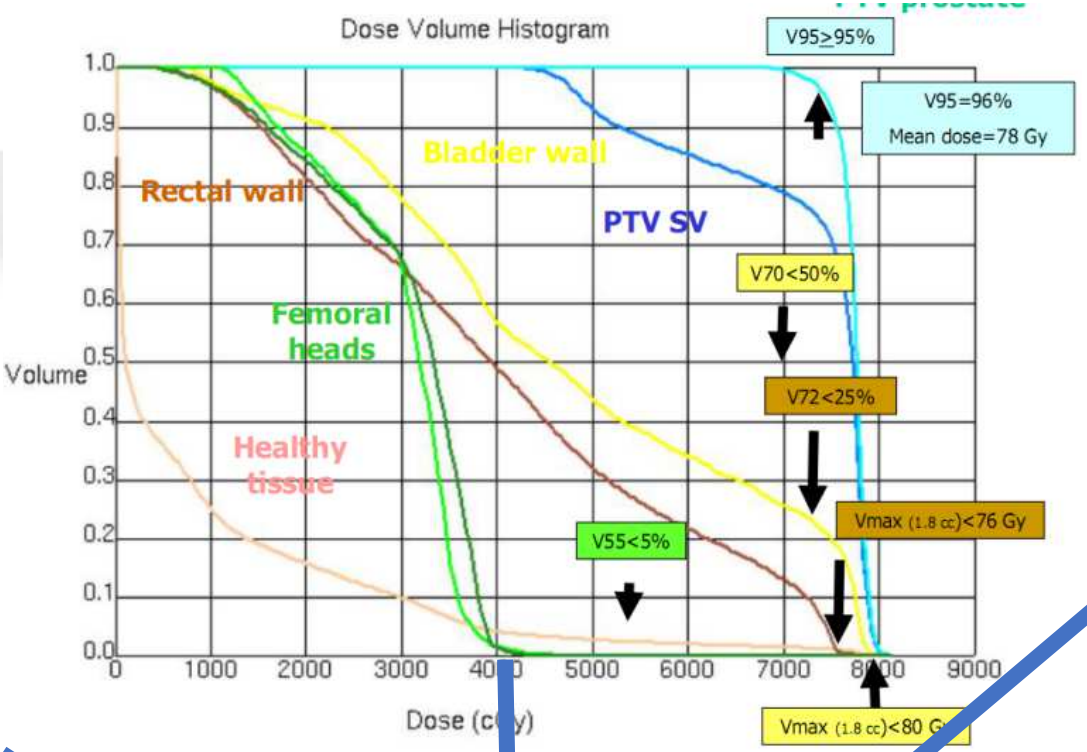
WHY ?

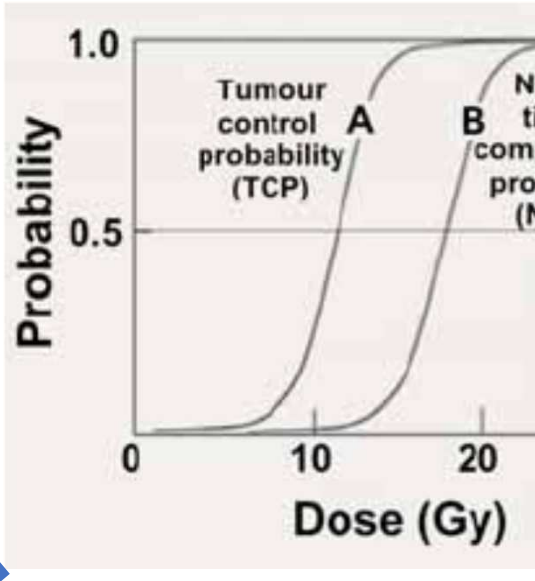


- **This was attributed to the difference in radio sensitivity of the cloanogenic cells in different patients k/as inter-patients heterogeneity.**
- **This is mainly due to variation in α values, which represent the intrinsic radiation sensitivity of an individual.**
- **Variation in number of clonogenic cells**
- **Variation in hypoxic fraction**
- **Variation in cell density**
- **etc.**

r-quadratic model







Biological Model

adiobiological Models

1. **There are number of radiobiological models developed for estimating normal tissue complication probability and tumor control probability but outcome of each model is not same.**
2. **Most of RB models are based on following presumptions.**

    a) **Cell survival after irradiation is bionomial and obeys Poissons statistics.**
    b) **Response of an organ is determined by the death or survival of its target cells. (functional sub units for normal tissue and clonogens for tumors)**
    c) **All the target cells respond identically.**
    d) **If BED of two radiation schedule is same then end point will be independent of dose per fraction.**

adiobiological Models

1. **TCP models:**
    a) **The complication free tumor control objective, P+**
    b) **Linear Quadratic Poissons cell kill model**

2. **NTCP models:**
    a) **Relative seriality model (s model)**
    b) **The k model**
    c) **The critical element model**
    d) **The critical volume model (Neimeirko)**
    e) **The Lyman, Kuthcer & Burman model (with fractionation & without fractionation effect)**
    f) **The parallel architecture model**
    g) **The Klepper & Klimanov mode**

Linear Quadratic(L-Q) Model

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

$F = N_s / N_o$ N_s = no of cell surviving N_o = no of initial cells

$$N_s / N_o = e^{-(\alpha D + \beta D^2)}$$

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

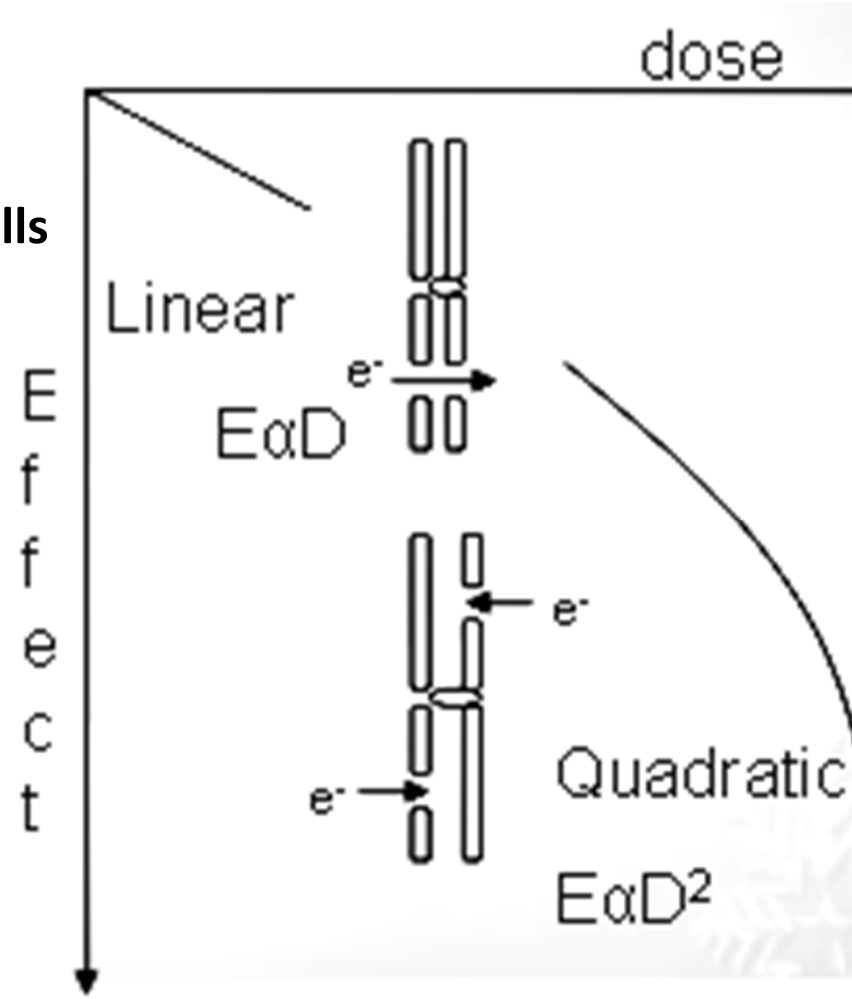
If n fx of dose d is given

$$N_s = N_o e^{-n(\alpha d + \beta d^2)}$$

$$N_s = N_o e^{-nd(\alpha + \beta d)}$$

$$N_s = N_o e^{-D(\alpha + \beta d)}$$

$$N_s = N_0 \exp\left[-\alpha D\left(1 + \frac{\beta}{\alpha} d\right)\right]$$



Tumor Control Probability (TCP)

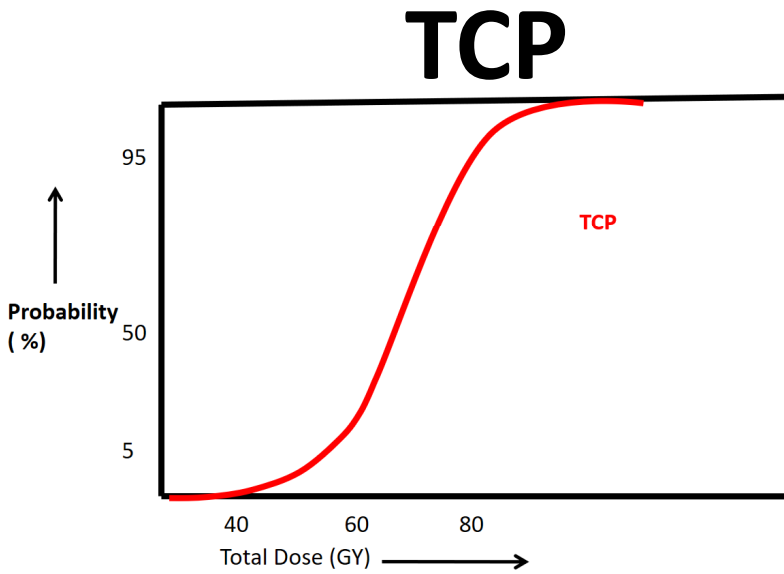
Poisson's Statistics $TCP = e^{-N_s}$ → **Average number of surviving**

$F = N_s / N_o$ N_s = no of cell surviving N_o = no of initial cells

$N_s = SF \times N_o$

$CP = e^{-SF \times No}$

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



$$CP = \exp[-N_0 \exp(-\alpha d - \beta d^2)]$$ **For single fraction of dose d**

or the case of n fractions, each of identical dose d such that $D_{tot} = d \times n$,

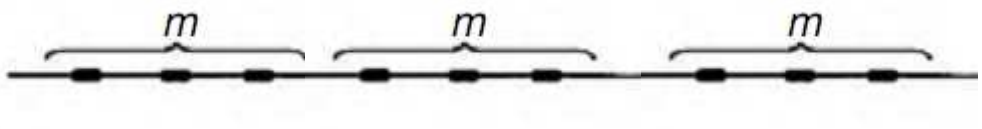
$$TCP = \exp\left\{-N_0 \exp\left[-\alpha D_{tot}\left(1 + \frac{\beta}{\alpha} d\right)\right]\right\}$$

rameters for TCP

- **Value of α and β.**
- **Number of cloanogenic cells**
- **Dose per fraction.**
- **Total dose.**
- **Standard deviation in α values.**
- **Inhomogeneous dose distribution.**
- **Inter fraction dose fluctuation due to set up uncertainties.**
- **Hypoxic component.**
- **Accelerated Repopulation**
- **Etc.**

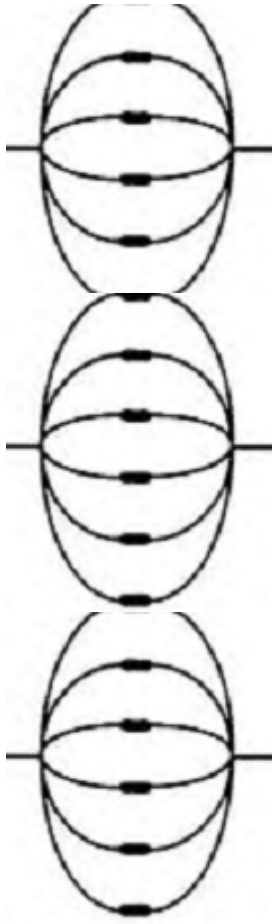
Normal Tissue Complication Probability (NTCP)

Functional Sub Unit (FSU) of Critical Organ



Serial like
Spinal Cord

Volume of the organ is not important and it is the dose which has got a threshold, eg, spinal cord dose < 45 Gy.



Parallel like kidney

Volume of the organ is important has got a threshold, eg, V20 of the lung should be < 30%.

Parallel FSU

- **Each FSU function independently.**
- **Clinical manifestation of radiation is evident only if small number of FSU survive.**
- **So there is always a threshold volume like V20 in lung etc. to be defined in radiation planning.**
- **Risk of complication depends upon the distribution of total dose in the organ and not on the hot spot at one place.**

Serial FSU

- **Function of the entire organ depends upon the function of each individual FSU.**
- **Inactivation of one FSU will result in clinical side effect.**
- **Risk of complication depends upon hot spot and not the dose distribution in entire organ.**
- **So Threshold dose is more important.**
- **Eg:- Spinal cord should get <45 Gy.**

Lyman–Kutcher–Burman (L–K–B) Empirical Model

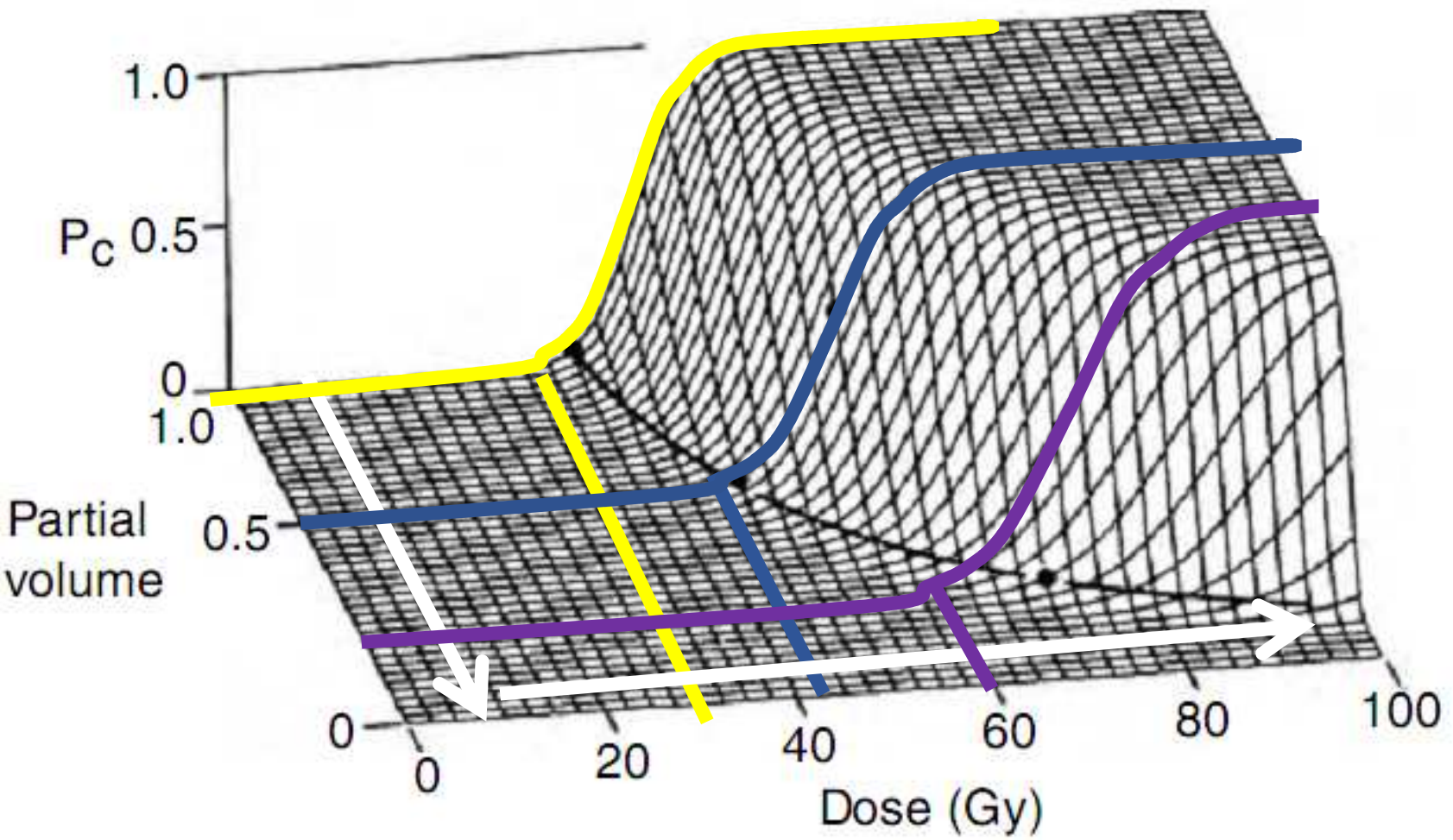
$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-t^2/2} dt$$

$$t = \frac{D - TD_{50}(V/V_{ref})}{m\, TD_{50}(V/V_{ref})}$$

$$TD_{50}(1) = TD_{50}(V/V_{ref})(V/V_{ref})^{n}$$

- $TD_{50}(1)$, the dose to the whole organ which would lead to complication in 50% of the population (note that $TD_{50}(V/V_{ref})$ is to be read as the TD_{50} at partial volume V/V_{ref});
- V_{ref}, a reference volume, which in many cases will be the (whole) organ volume;
- m, a parameter representing the steepness of the dose–response curve;

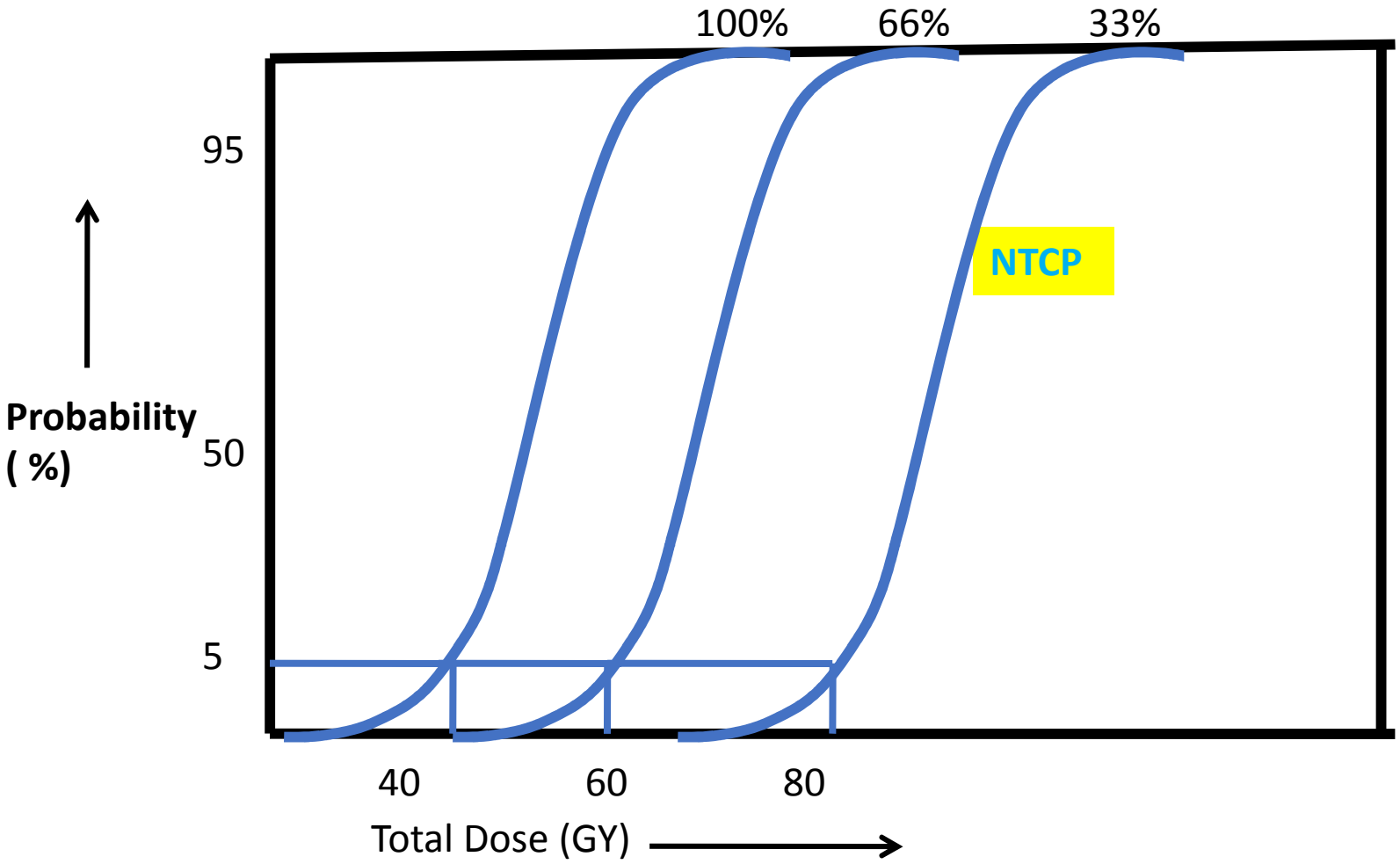
NTCP, Partial Volume and Dose Relationship for Heart



As partial volume decreases the sigmoid curve moves towards higher doses

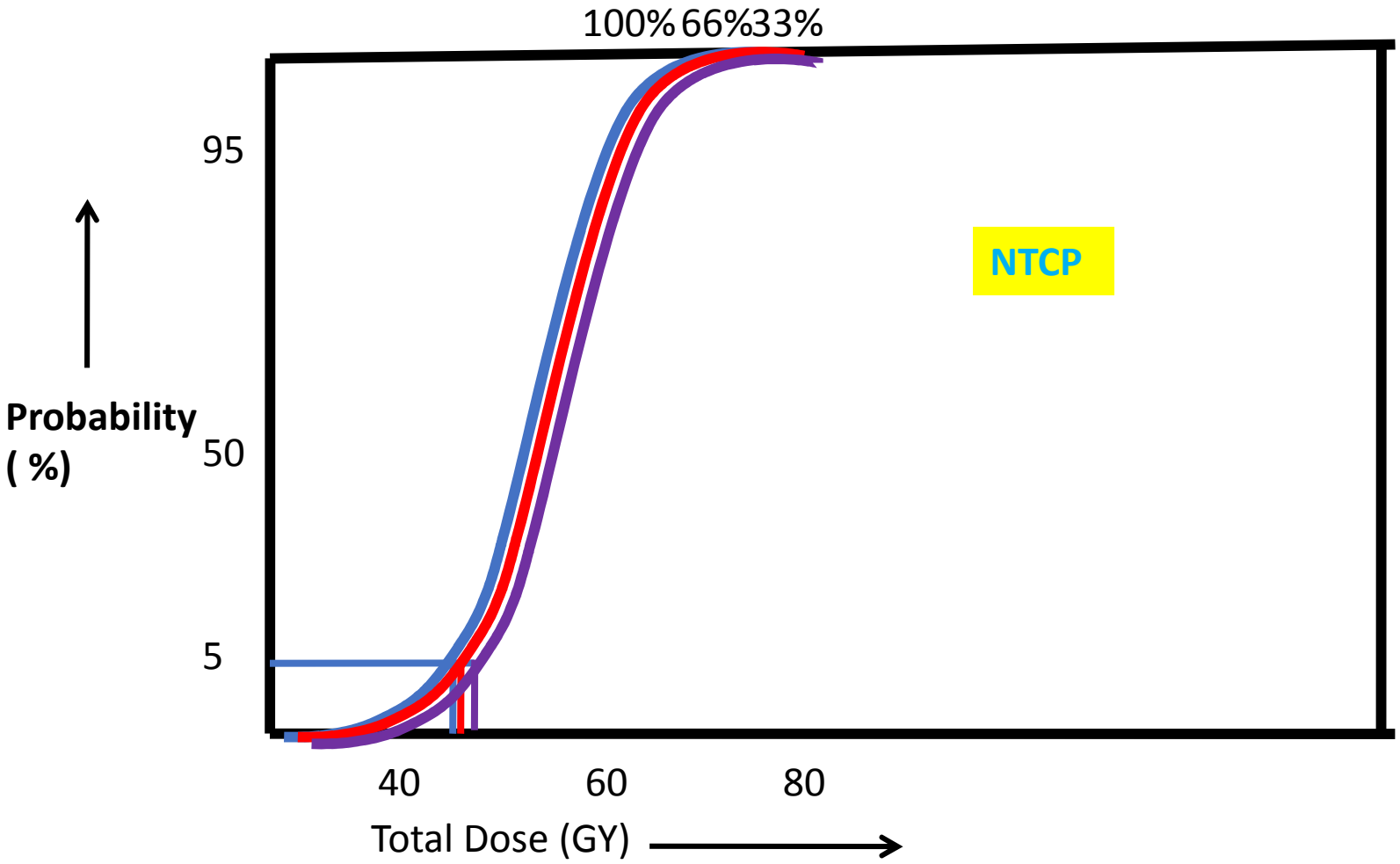
Volume effect for NTCP

This seen in parallel organ. Useful to have less no of fields so volume of the organ is kept low.



Volume effect for NTCP

This seen in Serial organs. Clinically useful to have many field so that dose distributed over lager volume but peak dose never reached.



What is RT Planning?

Basically radiotherapy planning has three stages.

1. **First is fluence optimization**
2. **Segmentation and dose calculation**
3. **Plan evaluation**

Optimization.

1. Biological cost functions based.

Target

Poisson Cell Kill LQ Model

EUD (Equivalent Uniform Dose)

2. Physical Cost Function Based.

Max Dose

Min Dose

Mean Dose etc.

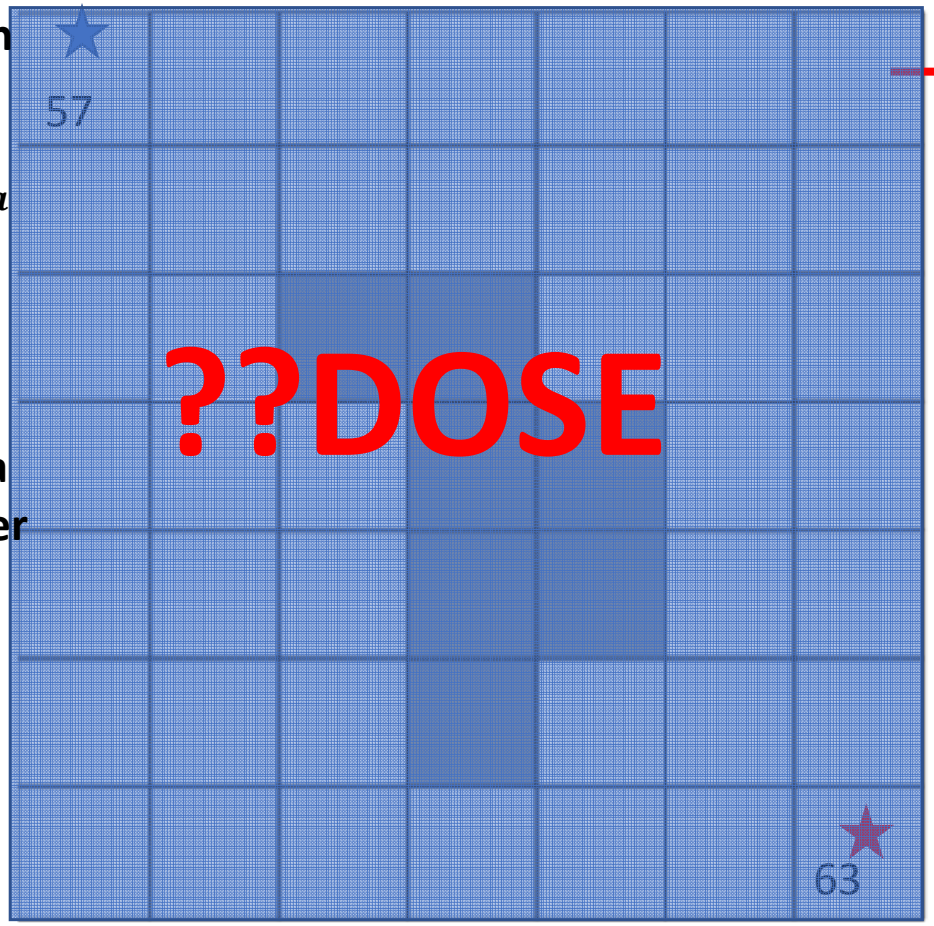
Equivalent Uniform Dose

EUD: the dose that, if distributed uniformly, will lead to the same biological effect as the actual non-uniform dose distribution. .....*Niemierko. MP. 1997*

lized EUD (gEUD) can
nulated as:

$$D = \left(\sum_i v_i \, D_i^a \right)^{1/a}$$

e fractional organ
e receiving a dose Dia
sue-specific parameter
escribes the volume



Voxel

Dose distribution +/- 5%

Dose = 60 Gy /30fx

70% control

Biological Cost functions

1. **There are three Biological based treatment planning system (BBTPS) available till date.**

    1. **Monaco**
    2. **Pinnacle &**
    3. **Eclipse.**

iological model used for treatment plan optimization in Monaco TPS (Elekta)

ructure Type	Name of model	Parameters	Comments
rget	Poissons statics cell kill model	Cell sensitivity (o.1-1.0 Gy^{-1}) a Parameter i.e. tissue specific parameter	Mandatory biological co function for targe no penalty for ho spots
AR	Serial complication model	Power law exponent (1-20)	Effective fo controlling maximum orga dose (Point dose)
AR	Parallel complication model	Power law exponent (1-4)	Effective fo controlling mea organ dose (Volum is important)

ological model used for treatment plan optimization in PINNACLE (Philips)

tructure Type	Name of model	Parameters	Comments
arget	Min EUD	Volume parameter (a<1)	Penalizes for too l EUD
rget	Target EUD	Volume parameter (a<1)	Penalizes for a deviation fr desired EUD
AR	Max EUD	Volume parameter (a≥1)	Penalizes for too h EUD, use for bo serial and para structures

ological model used for treatment Plan Evaluation in PINNACLE (Philips)

ol name	Structure type	Name of model	Parameters/input
CP/NTCP litor	Target OAR	Empirical TCP model Lyman-Kutcher model	D50, m D50, m, n
ological sponse panel	Target OAR Multiple targets Multiple OARs Target & OARs	Poisson/LQ-based TCP model Kallman s-model Composite TCP Composite NTCP Probability of complication free tumor control	D50, γ, α/β

Biological model used for treatment plan optimization & plan evaluation in Eclipse (varian)

ructure Type	Name of model	Parameters	Comments
rget	Min EUD	Volume parameter (a)	Penalizes for too low va
rget or OAR	Max EUD	Volume parameter (a)	Penalizes for high value
rget	TCP Poisson-LQ	D50, γ, α/β , seriality(s), $T_{1/2}$ for short Vs long repair time, repopulation times: T_{pot} and T_{start}	To control TCP
AR	NTCP Poisson-LQ	D50, γ, α/β , seriality (s), $T_{1/2}$ for short Vs long repair time, repopulation times: T_{pot} and T_{start}	To control NTCP
AR	NTCP-Lyman	D50, m,n,α/β , $T_{1/2}$ for short Vs long repair time, repopulation times: T_{pot} and T_{start}	To control NTCP

recaution while using RB models

1. **Most NTCP models do not include dose per fraction effects. If the plan under evaluation is very different from that in dataset used to derive parameter estimates, both sets of data should be normalized to the same dose per fraction using LQ model formalism.**

1. **If not corrected model can produce overestimates in NTCP if hyperfractionated and significantly underestimates if hypofractionated.**

1. **Currently available TCP/NTCP models incorporated in BBTPS are not well documented and are not supplied with databases of reliable model parameters, so therefore have not generalized for clinical use.**

ESTRO School

3rd ESTRO-AROI GYN Teaching Course

14th-17th March 2019

Department of Radiation Oncology

All India Institute of Medical Sciences, Rishikesh INDIA

Richard Pötter
ESTRO Course Director

Umesh Mahantshetty
AROI Course Director

Manoj Gupta
ESTRO-AROI Course Organizer

Lecture theatre- 4 Academic Block AIIMS Rishikesh, 249203 India

Thanks

Greetings From Rishikesh