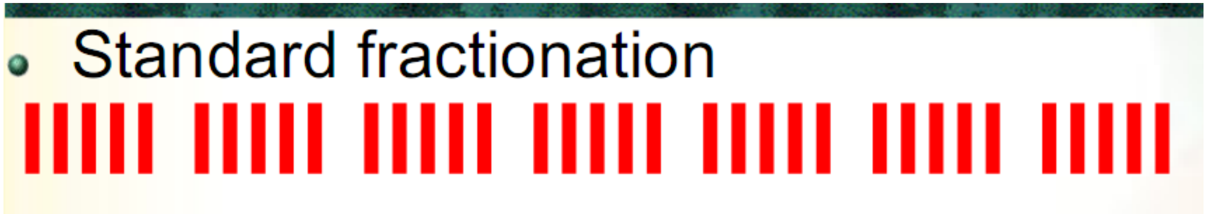
Introduction to Altered Fractionation and Radiobiology to Hypo-fractionation

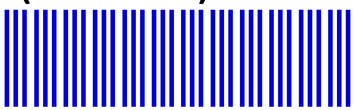


70 Gy - 35 fx - 7 wks

81.6 Gy - 68 fx - 7 wks

Concomittant Boost

(CHART)

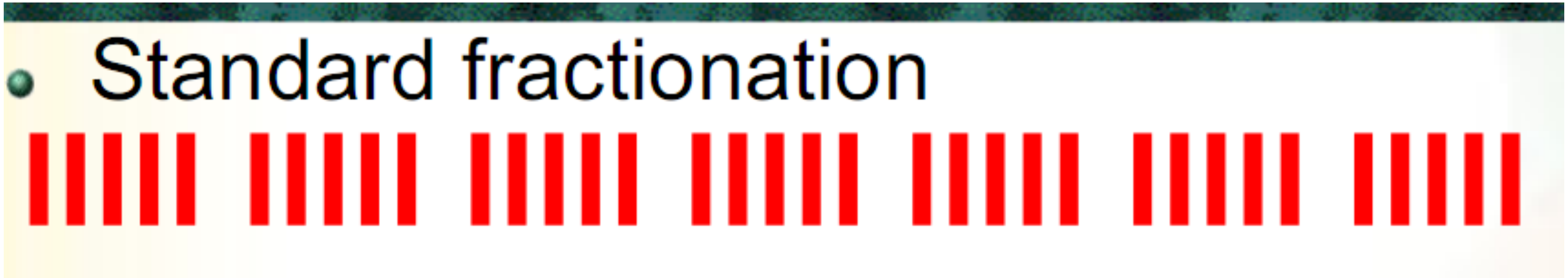


54 Gy - 36 fx - 12 days

Prof Manoj Gupta
Head, Rad Onc, AIIMS Rishikesh
ICRO PG Course, Trivendrum Dec 2023

INTRODUCTION TO ALTERED FRACTIONATION

Fractionation



70 Gy - 35 fx - 7 wks Dose per fraction 1.8 to 2 Gy

Altered Fractionation

Hyper fractionated Radiation

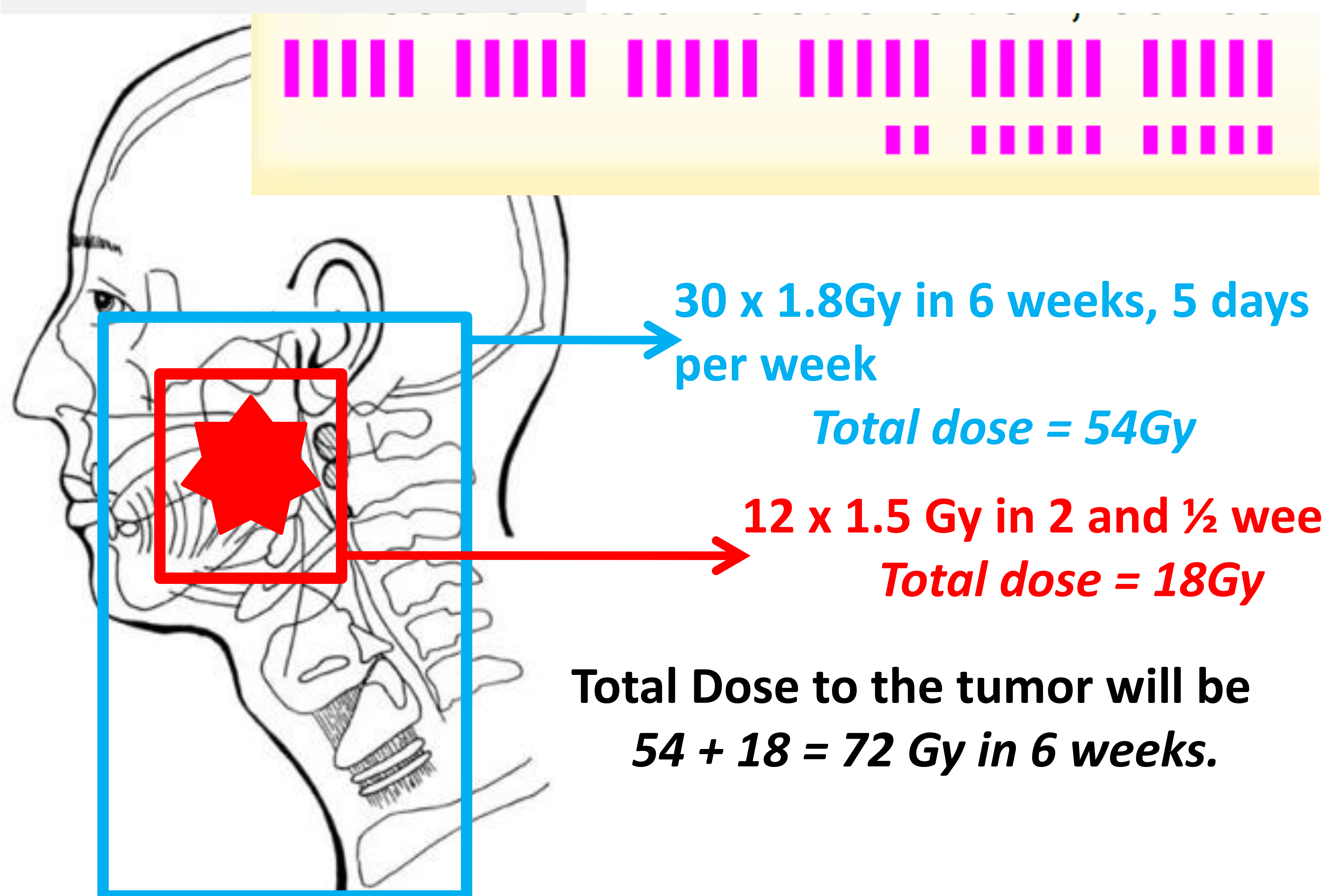
70 fractions of 1.15 Gy x twice daily, 6 hours apart, 5 days/week x 7 weeks→ 70 F x 1.15 Gy = 80.5 Gy

<u>Advantage</u>

1. Total dose is higher and so is the BED leading to high local control.
2. BED to late reacting tissue is less so might expect lower late side effects.

<u>Disadvantage:</u> Higher acute toxicities.

Concomitant boost



30 x 1.8Gy in 6 weeks, 5 days per week

Total dose = 54Gy

12 x 1.5 Gy in 2 and ½ week

Total dose = 18Gy

Total Dose to the tumor will be

54 + 18 = 72 Gy in 6 weeks.

Concomitant boost

Advantage

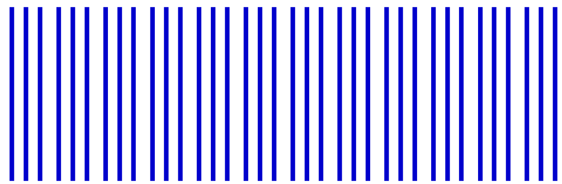
1. Total dose is higher and so is the BED leading to high local control.
2. Overall treatment time is shorter than conventional 7 weeks so lesser negative effect of accelerated Re-population.
3. BED to late reacting tissue is less so might expect lower late side effects.

Disadvantage:

Higher acute toxicities.

CHART

36 fraction of 1.5 Gy given 3 fraction a day, 6 hours apart, for 12 consecutive days, with an over all treatment time of 12 days, i. e. 36F x 1.5 Gy(3F/day) x 12 days



54 Gy - 36 fx - 12 days

Advantage

1. Overall treatment time is drastically reduced so no negative impact of accelerated repopulation.
2. BED to late reacting tissue is less so might expect lower late side effects.

Disadvantage:

Higher acute toxicities.

Accelerated Radiotherapy

66 Gy/33f/38 days - 6f/wk

Advantage

Overall treatment time is reduced by 7 days so less negative impact of accelerated repopulation.

Disadvantage:

Higher acute toxicities.

Hypofractionation

1. Palliative Hypofractions eg. 30 Gy/3w or 20 Gy/2w specially for bony metastasis.

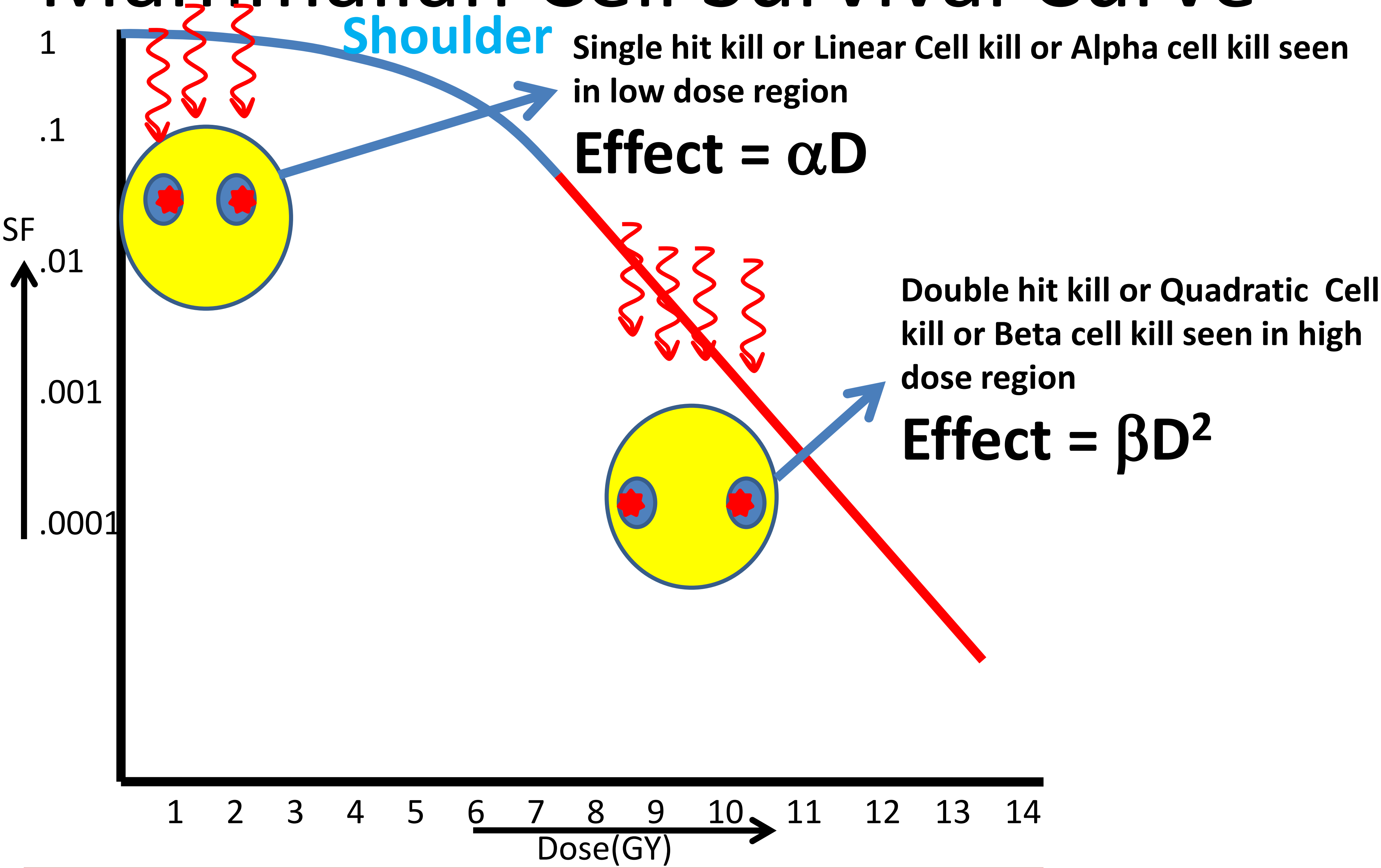
2. Curative Hypofractions like in Ca Breast and Ca Prostate or T1 Vocal Cord Tumors.

3. Extreme Hypofractions like SRS and SBRT

RADIOBIOLOGY OF HYPO-FRACTION

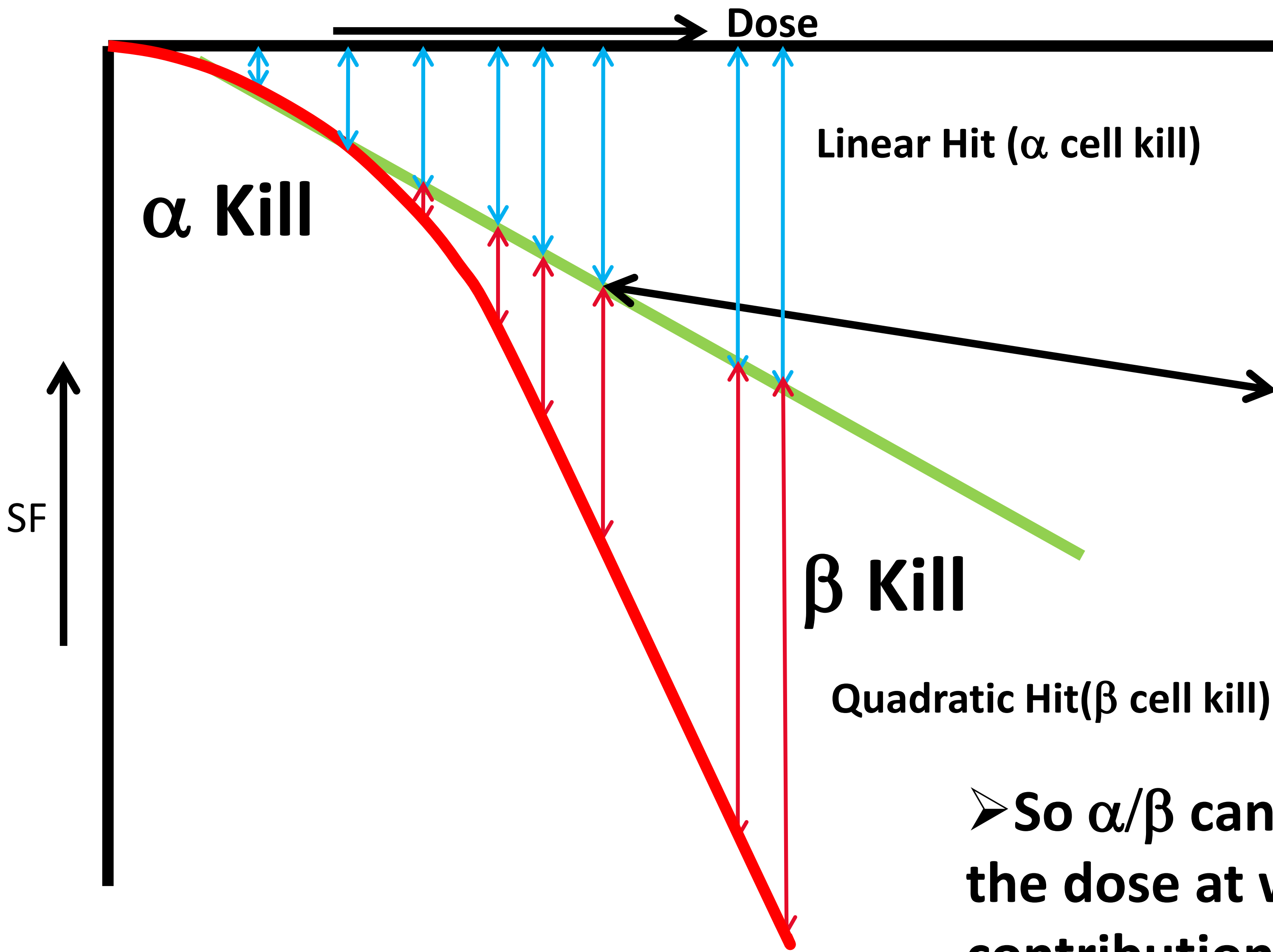
CELL SURVIVAL CURVE

Mammalian Cell Survival Curve



Linear-Quadratic Model

Linear Quadratic model (α/β Ratio)



Killing by SHE=Killing by two hit event

Linear = Quadratic

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

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

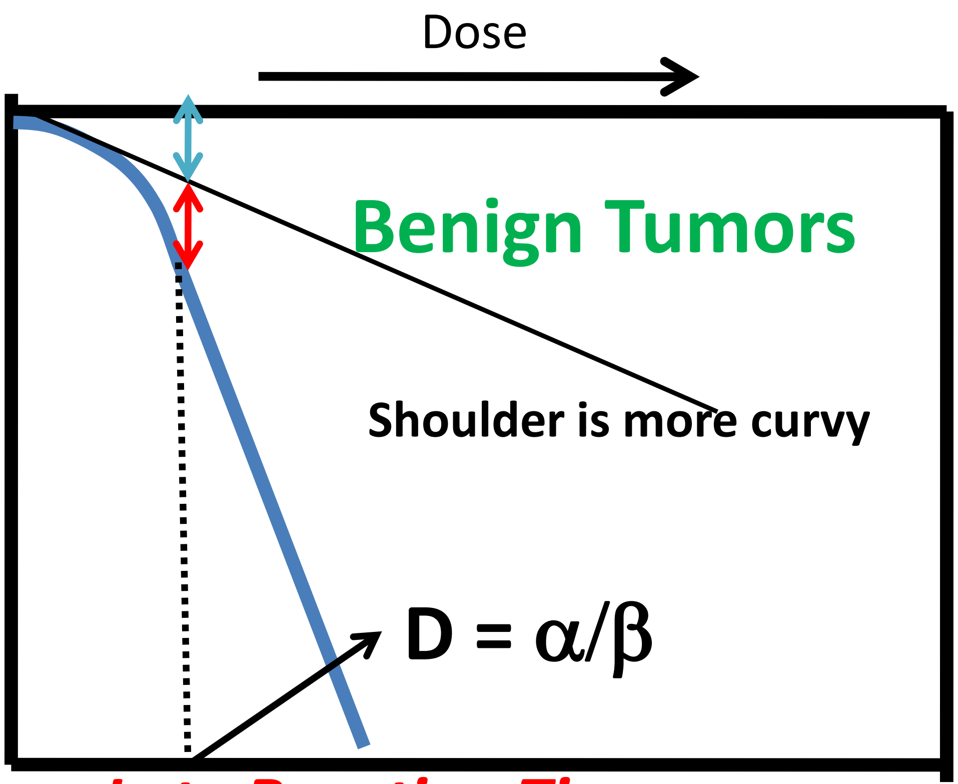
$$\alpha/\beta = D$$

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

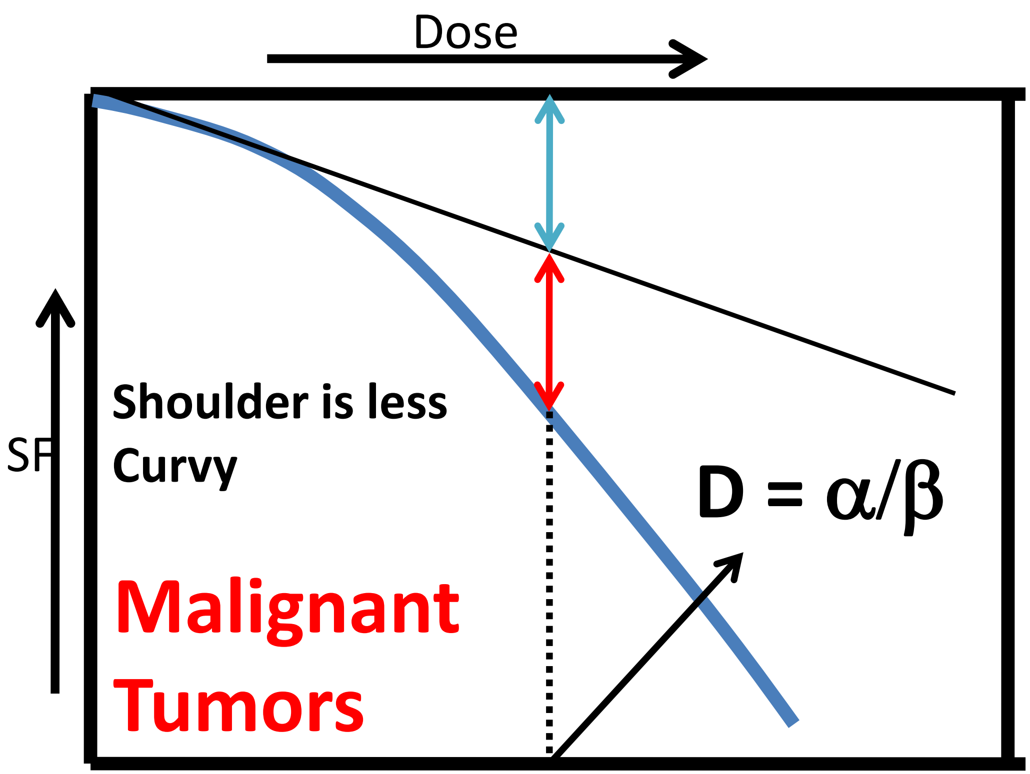
α/β Ratio defines "curviness" of survival curve

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



Late Reacting Tissue



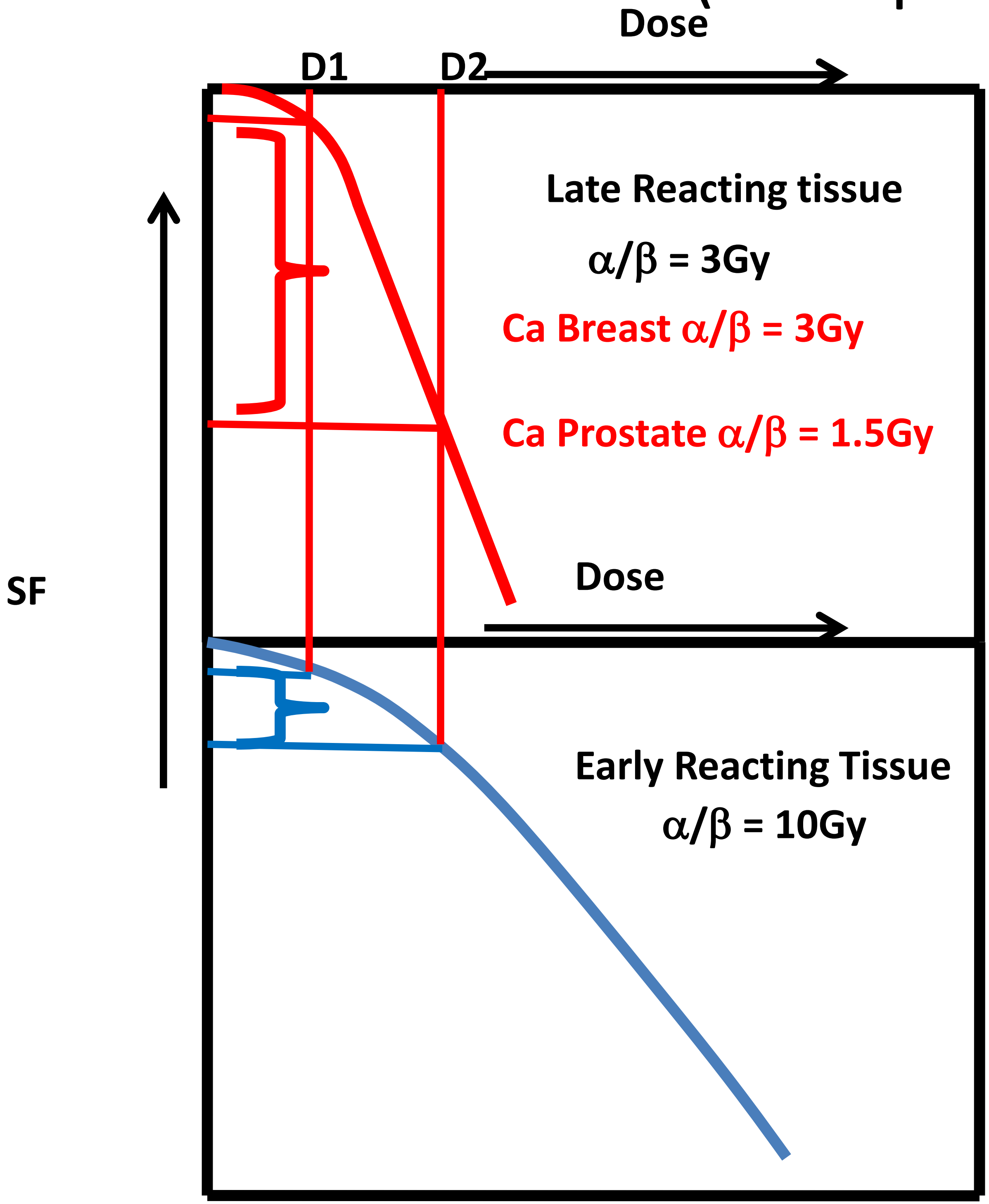
Early Reacting Tissue

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.

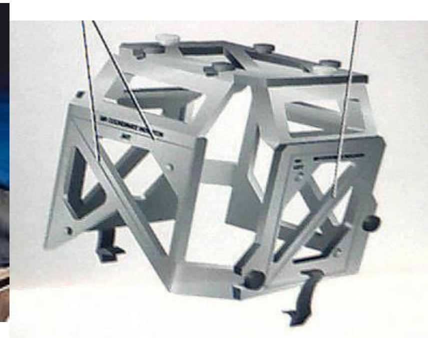
CURATIVE HYPO-FRACTION RT IN CA BREAST & CA PROSTATE

Fraction size (Dose per fraction)

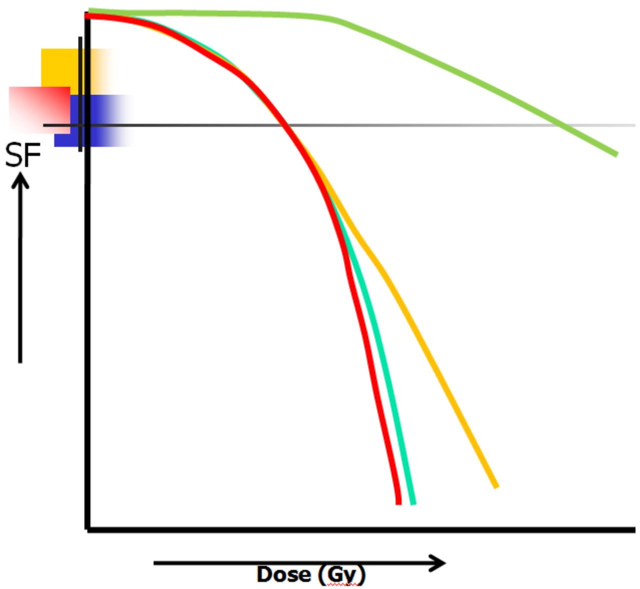


- **Increase in dose per fraction damages late reacting tissue more than early reacting tissues**

Radiobiology of Non Fractionated RT



❖20 Gy to 60 Gy given in single fraction or 2-5 fractions

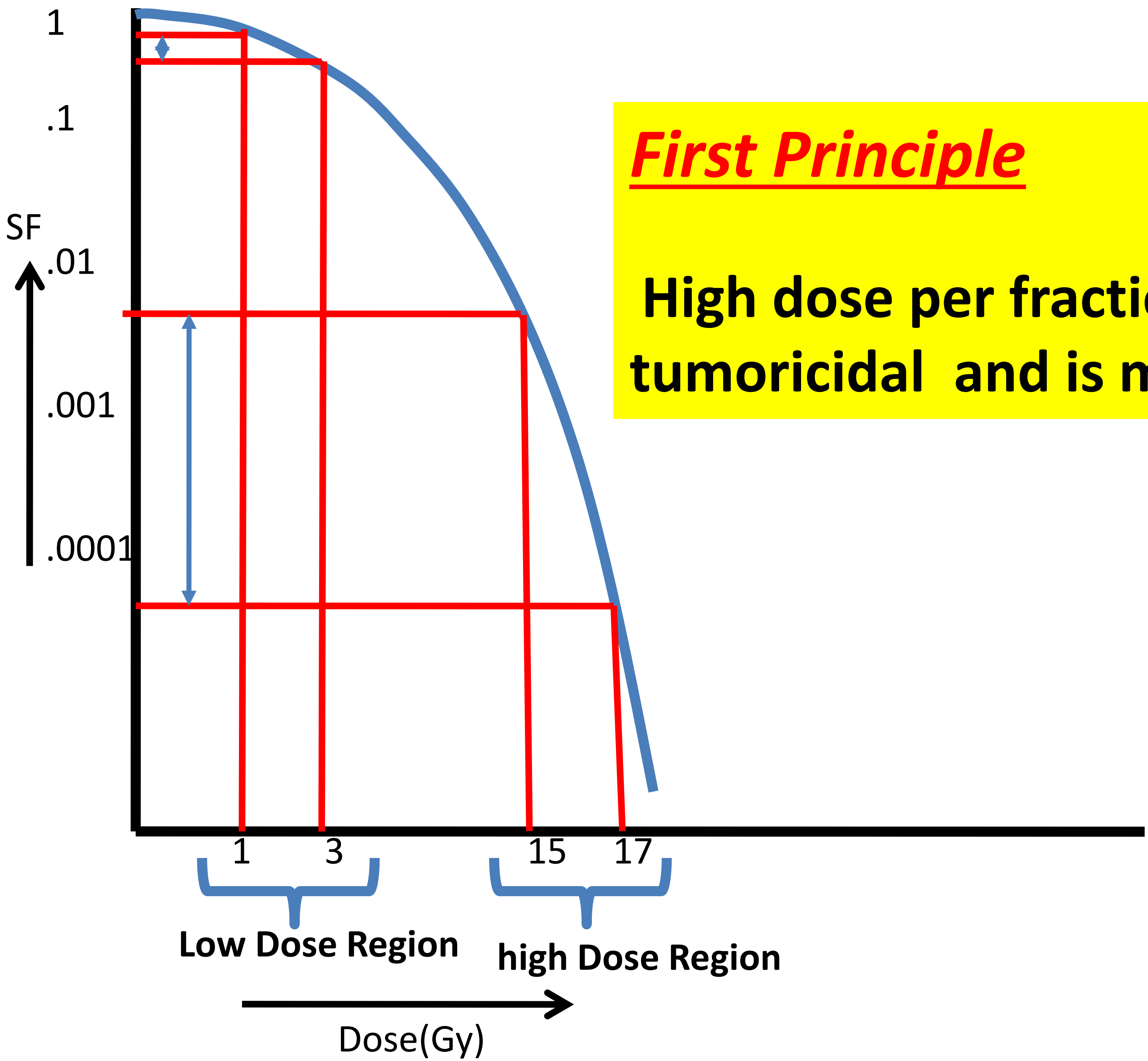


❖Benign and Malignant Diseases

RADIOBIOLOGICAL RATIONALE

Cell Survival Curve

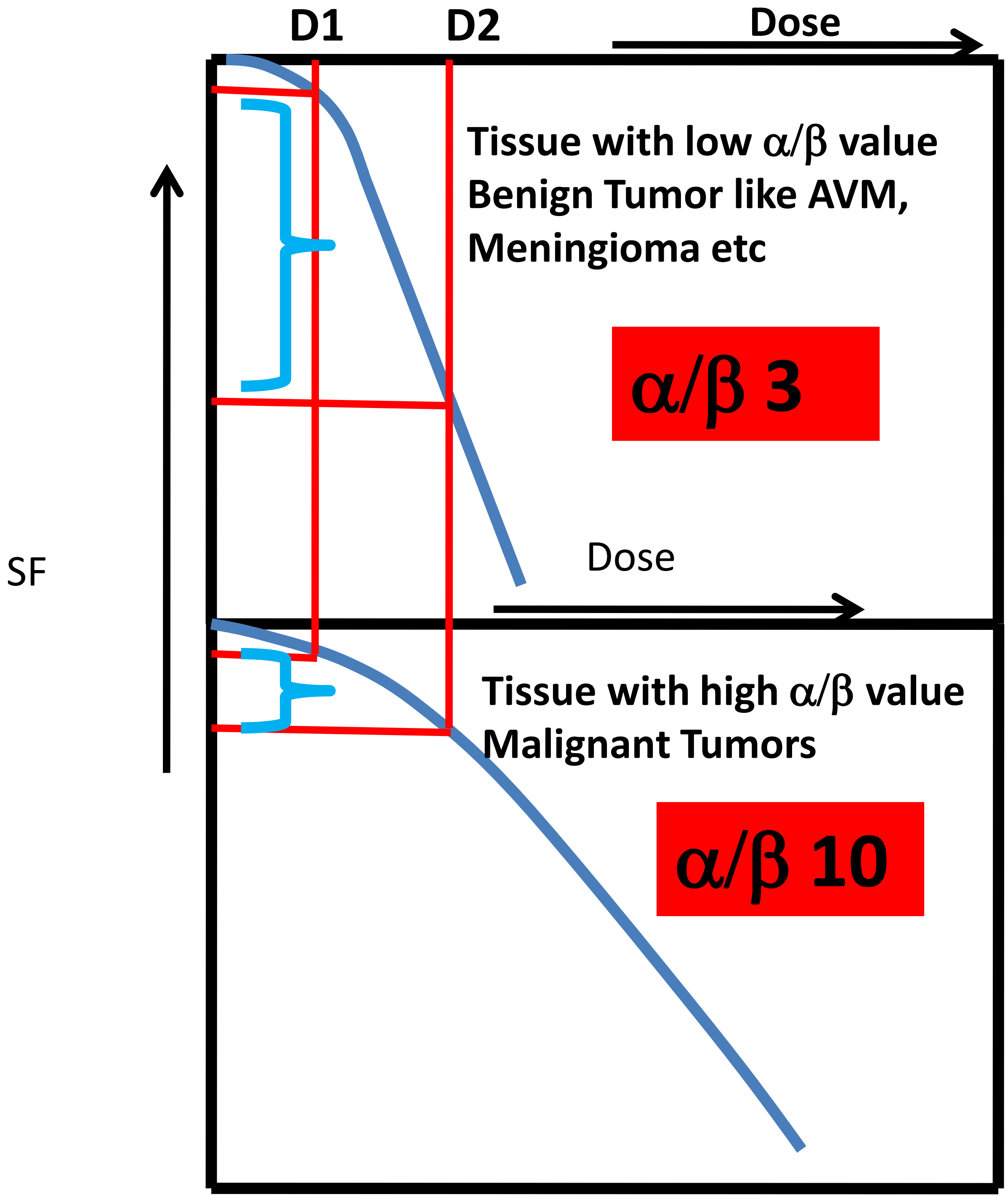
Effect of high dose on Cell Survival Curve



First Principle

High dose per fraction is more tumoricidal and is more damaging

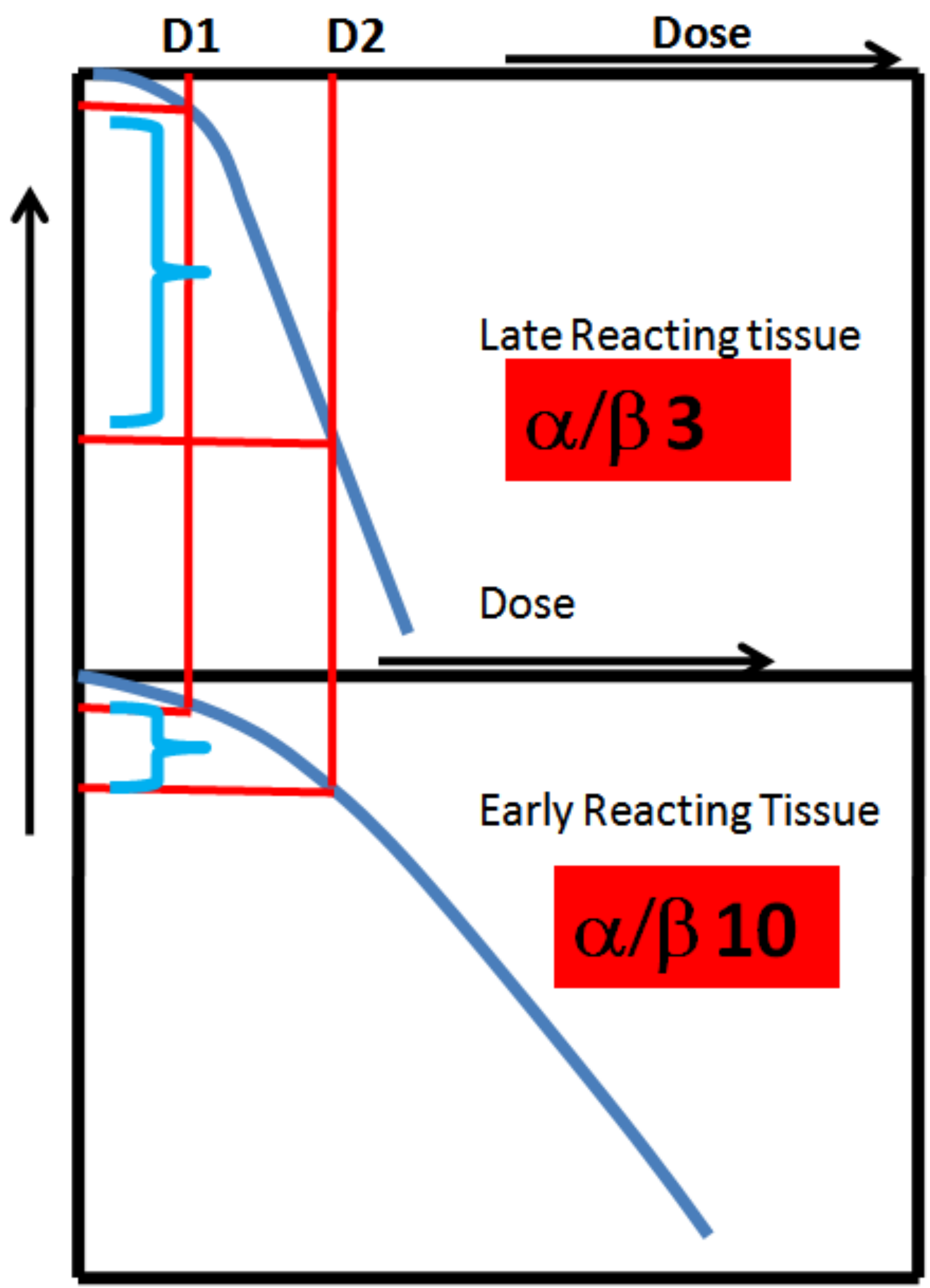
More Effective For Benign Tumors

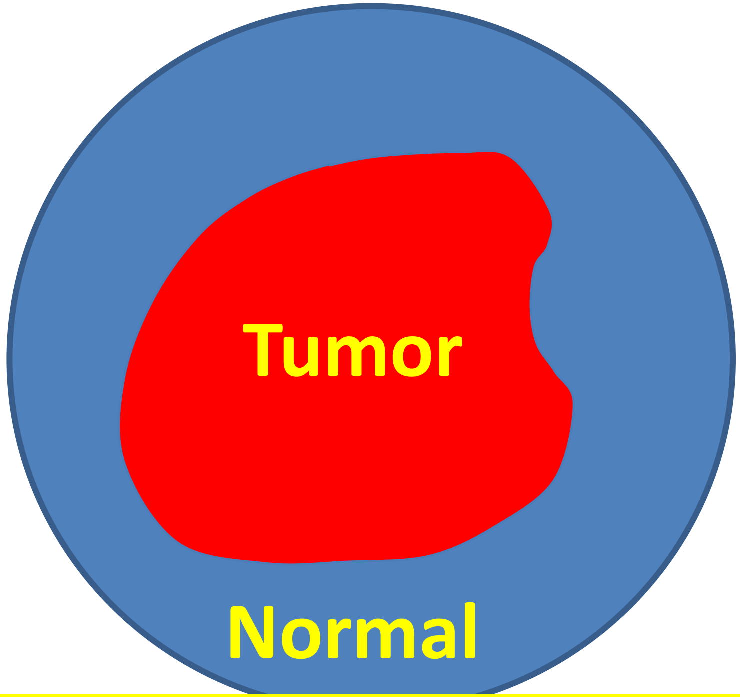


Second Principle

High dose per fraction is more damaging to Benign lesions with low α/β value like meningioma, AVM, acoustic neuroma etc

NonFractionatedRT More Damaging to Late Reacting Tissues



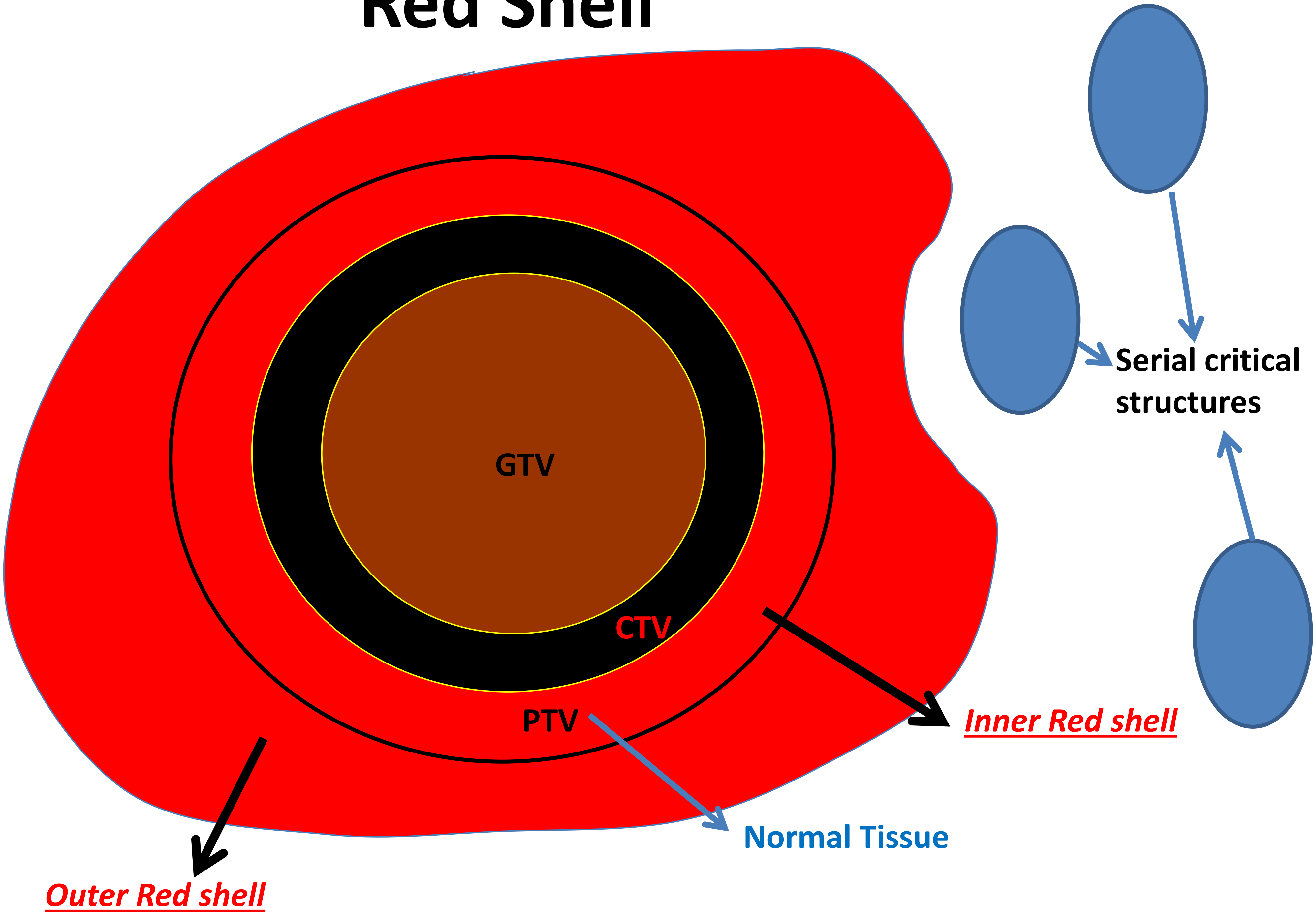


<u>Third *Principle*</u>

This is overcome by highly precise, highly conformal RT with minimum surrounding normal tissue in high dose

Red Shell

Red Shell


GTV
CTV
PTV
Inner Red shell
Outer Red shell
Normal Tissue
Serial critical structures

Clinical Significance of Red Shell

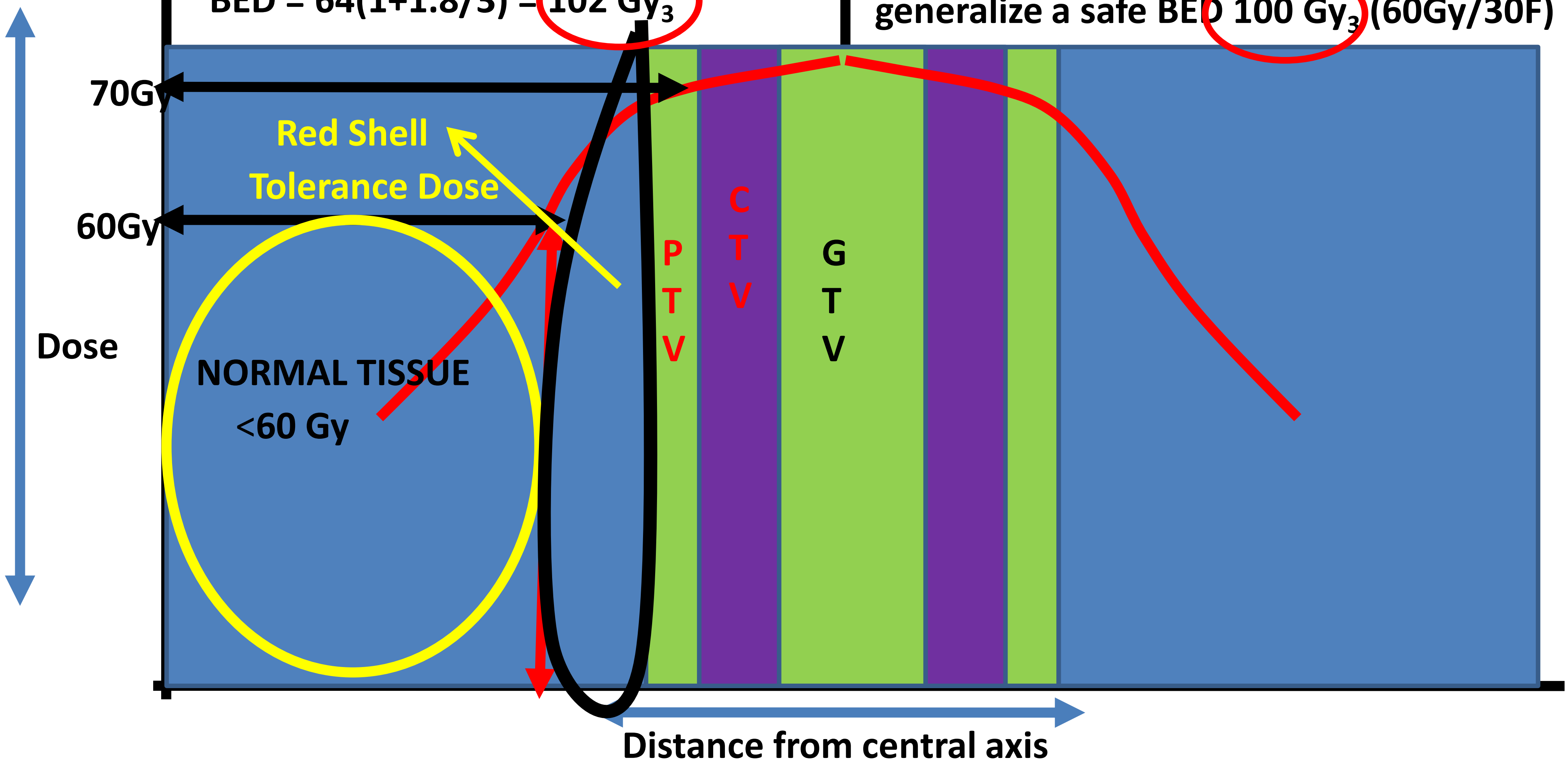
64 Gy in 35fx, d/f = 1.8 Gy

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

BED = 64(1+1.8/3) = 102 Gy_3

70 Gy/35fx/2Gy per fx

For surrounding normal tissue we generalize a safe BED 100 Gy_3 (60Gy/30F)



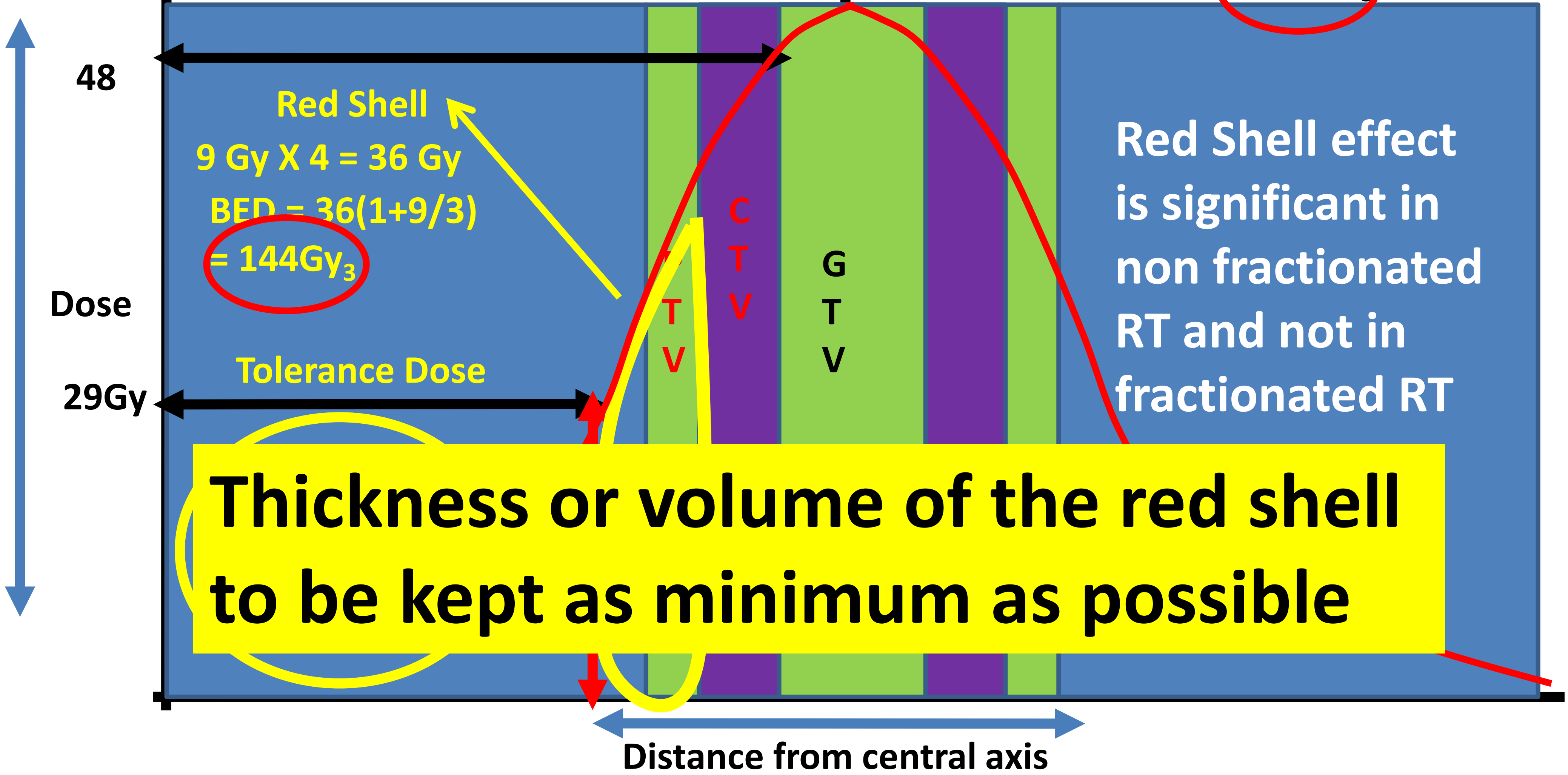
Fractionated Radiotherapy

Clinical Significance of Red Shell

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

Dose = 12Gy X 4

For surrounding normal tissue we generalize a safe BED 100 Gy_3 (29Gy/4F)



Non Fractionated Radiotherapy

Red Shell

- *So we can reduce the Volume of Red Shell thus damaging effect of Non fractionated RT on normal tissue by:-*
  - ❖ Keeping the dose gradient very steep.
    - ➢ By multiple non-coplaner beams and careful planning
  - ❖ Keeping the target volume minimum.
    - ➢ By Treating early lesions only
  - ❖ Reducing the PTV margins.
    - ➢ By Reducing uncertainties. Use of IGRT, 4D RT, gamma knife etc
  - ❖ Delivering total dose in more than 1 fraction.
    - ➢ By using 2-4 fractions

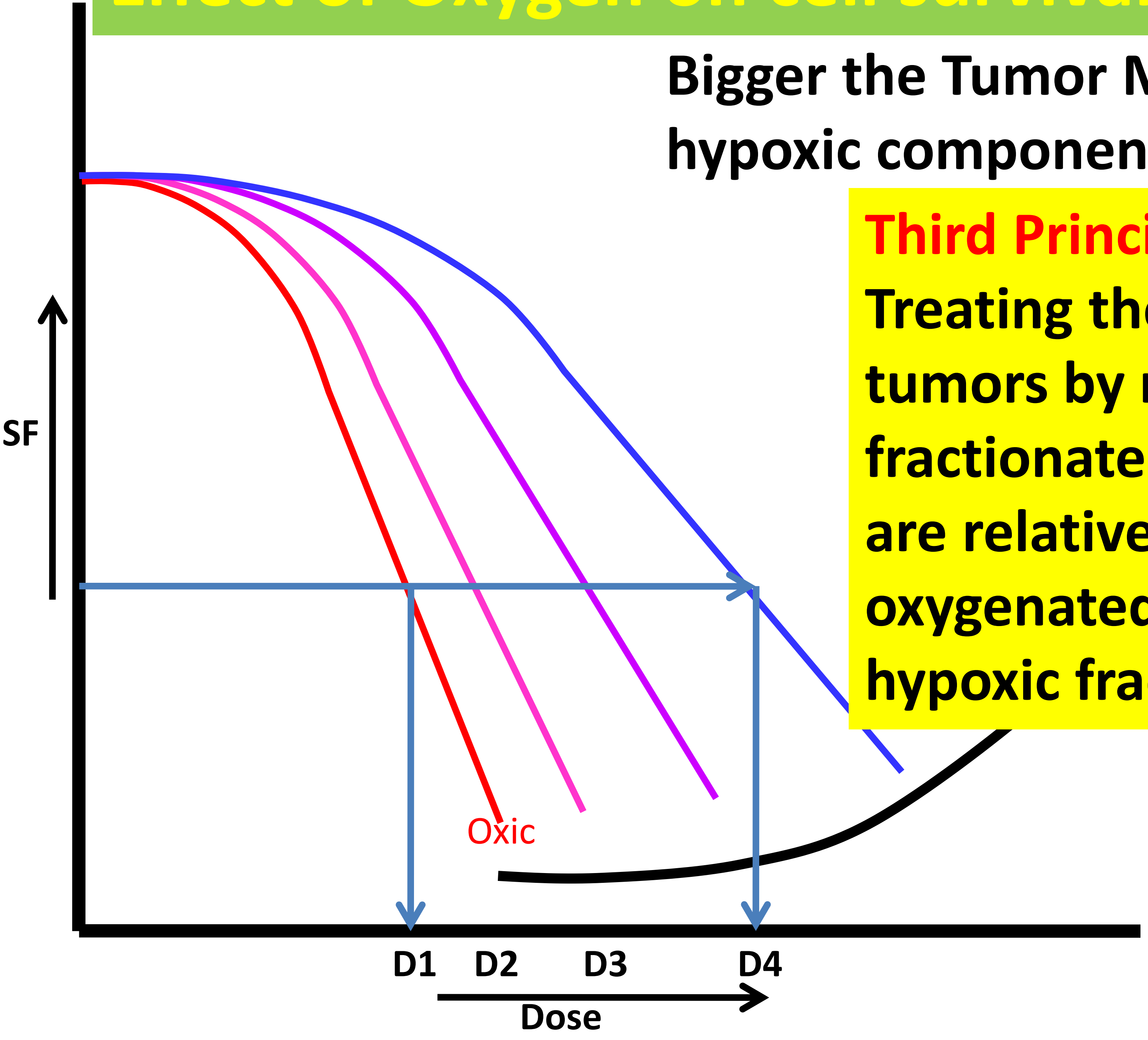
4 Rs of Fractionations

- Re-oxygenation
- Repair of Sub-lethal damage
- Re-population
- Re-distribution

REOXYGENATION

Effect of Oxygen on cell survival curve

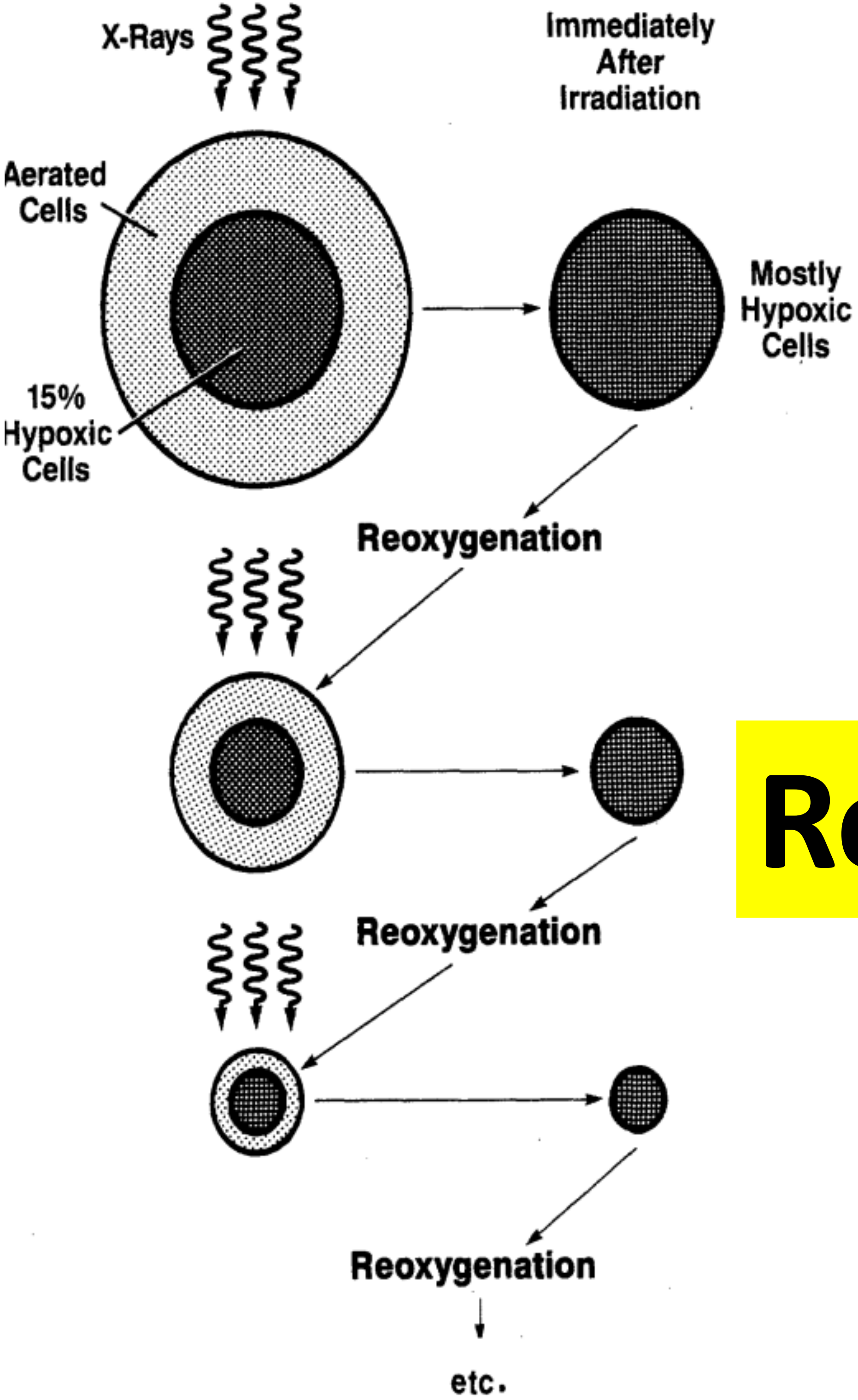
Bigger the Tumor More is the hypoxic component & vice versa



Third Principle

Treating the small tumors by non fractionated RT as they are relatively well oxygenated with little hypoxic fraction.

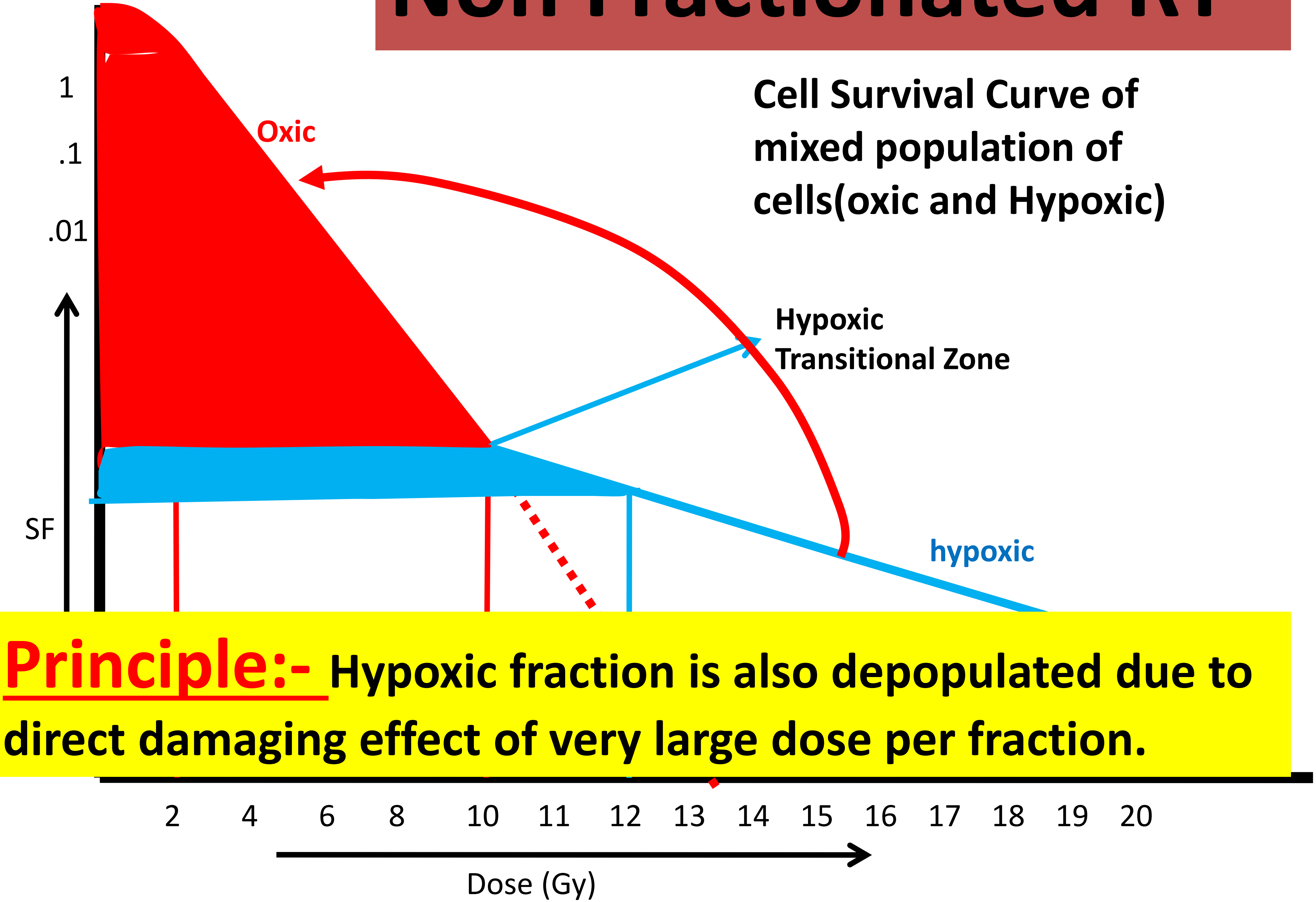
Fractionated RT



Reoxigenation

Authors: Hall, Eric J.; Giaccia, Amato J.
Title: *Radiobiology for the Radiologist, 6th Edition*

Non Fractionated RT



Principle:- **Hypoxic fraction is also depopulated due to direct damaging effect of very large dose per fraction.**

The ratio of HYPOXIC to AEROBIC IR doses needed to achieve the SAME biological effects is called Oxygen Enhancement Ratio.

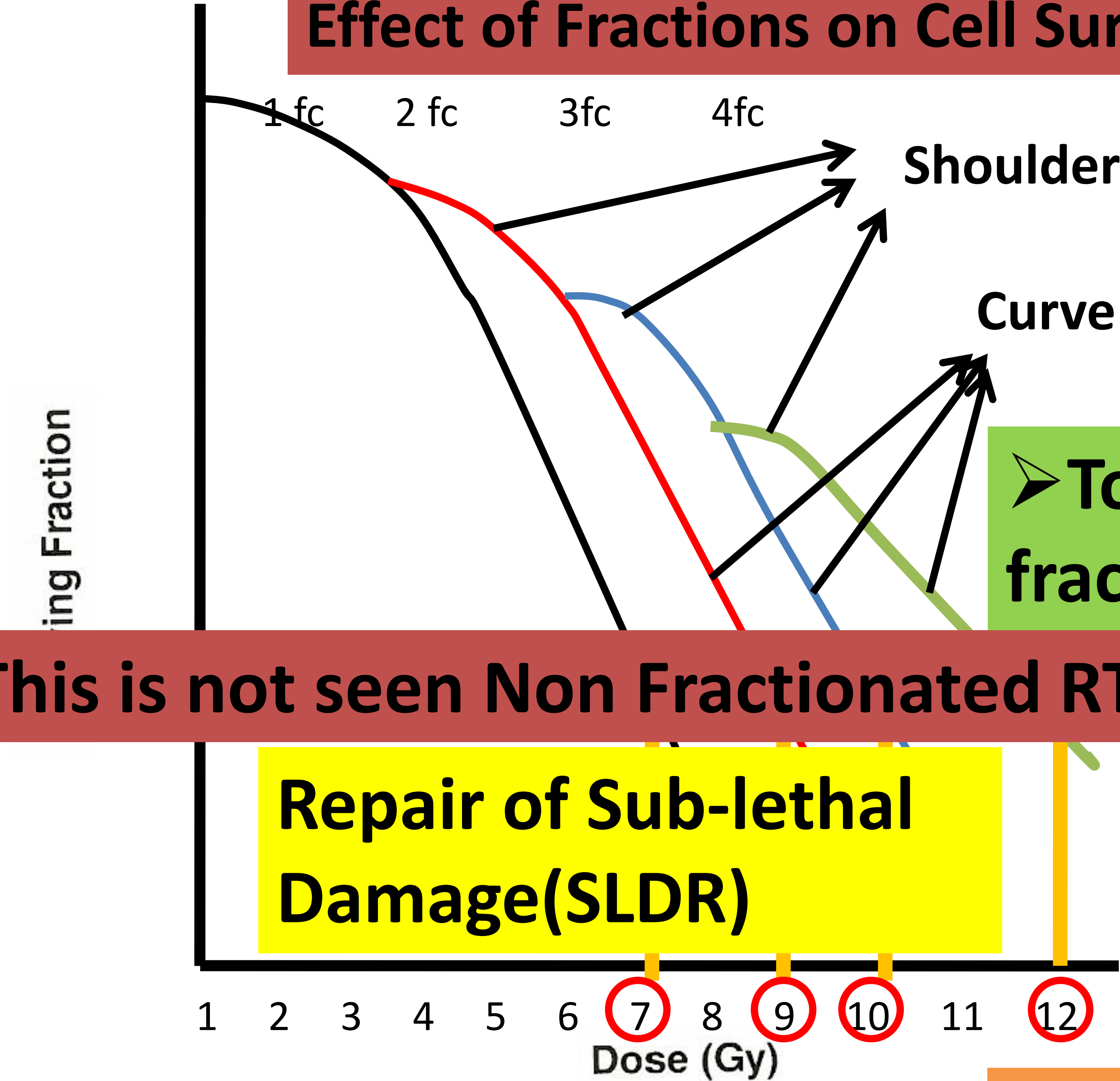
$$OER = \frac{D_0\ (\text{hypoxic})}{D_0\ (\text{aerobic})} \quad \begin{matrix} \longrightarrow 6\ \text{Gy} \\ \longrightarrow 2\ \text{Gy} \end{matrix}$$

= 2.5 to 3 for x-rays and γ-rays

SRS/SRT Dose is > 12 Gy

REPAIR

Effect of Fractions on Cell Survival Curve



- Total dose α no of fractions

This is not seen Non Fractionated RT as in SRS/SBRT

Repair of Sub-lethal Damage(SLDR)

Inter fraction repair

Completes in 4-8 hours

- Positive effect on normal tissue
- Negative effect on Tumor

Non Fractionated RT

Intra Fraction Repair with T1/2 = .2 -.4 hr may occur during SBRT as treatment time is prolonged

Late Reacting Tissue

Positive effect on normal tissue

Effect on the Tumor

Negative effect on Tumor

FFF beam is better than FF beam as delivery time is very short

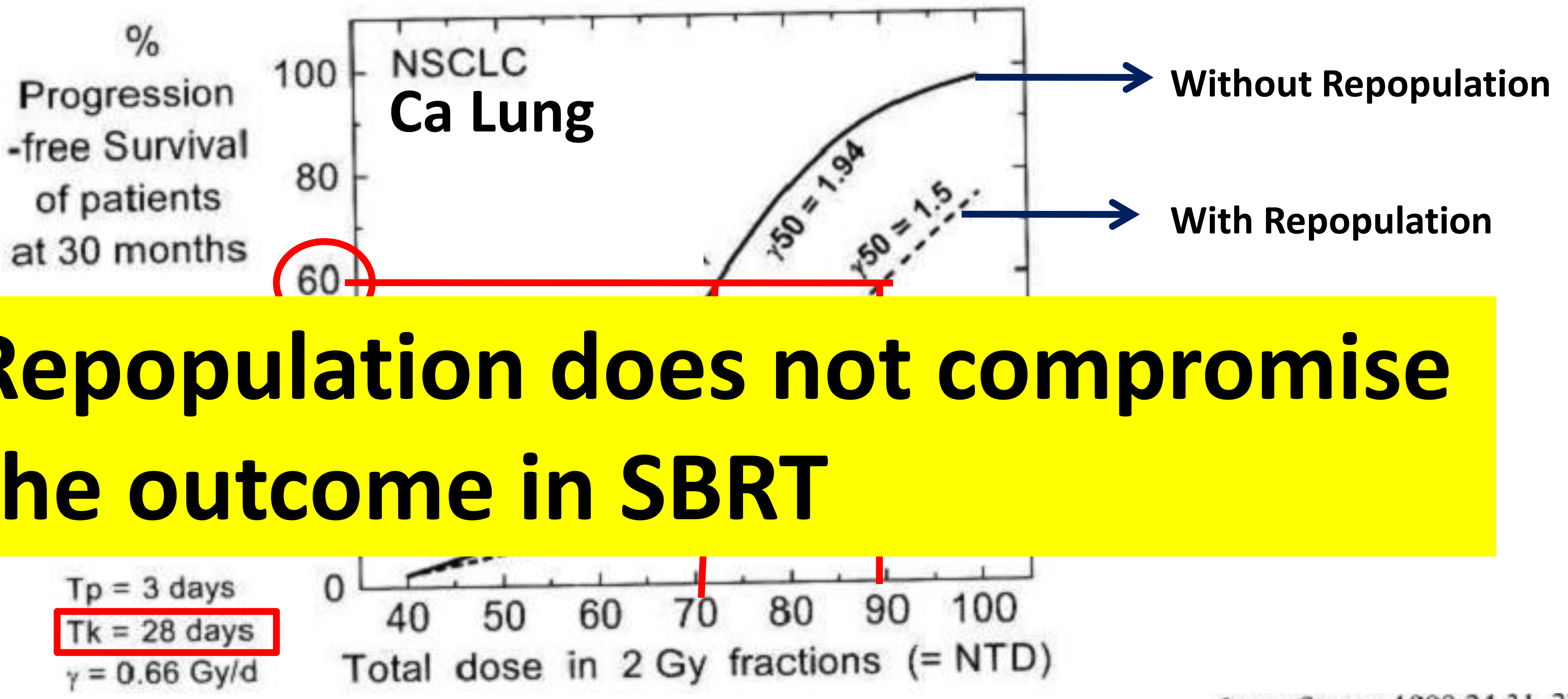
Benedict SH, Lin PS, *Int J Radiat Oncol Biol Phys* 1997;37:765–769.

REPOPULATION

Repopulation(NSCLC)

Repopulation in NSCLC starts at 28 days

Most of the SBRT lung regimen are completed by two weeks

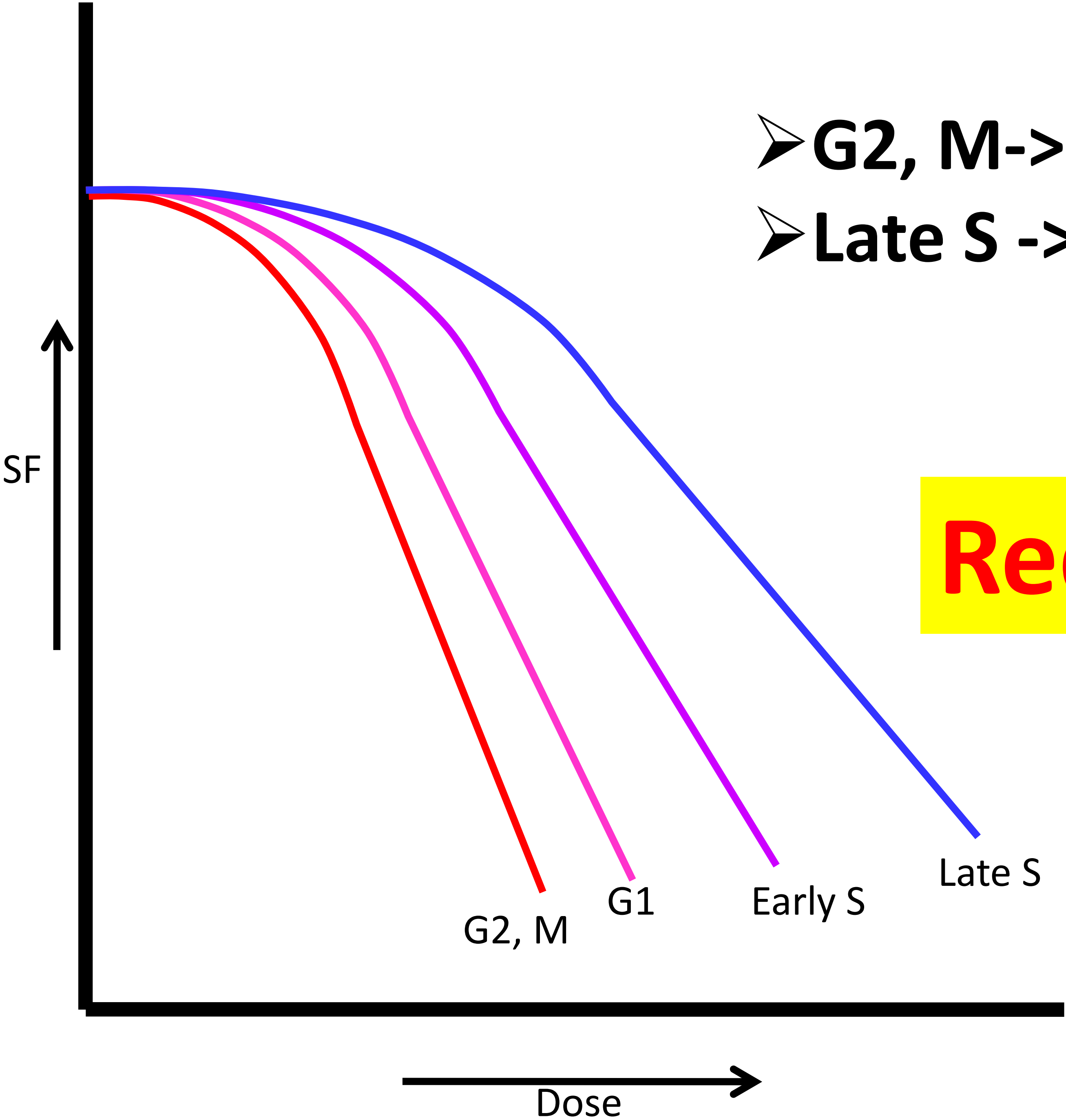


Repopulation does not compromise the outcome in SBRT

Martel MK, Ten Haken RK *Lung Cancer* 1999;24:31–37.

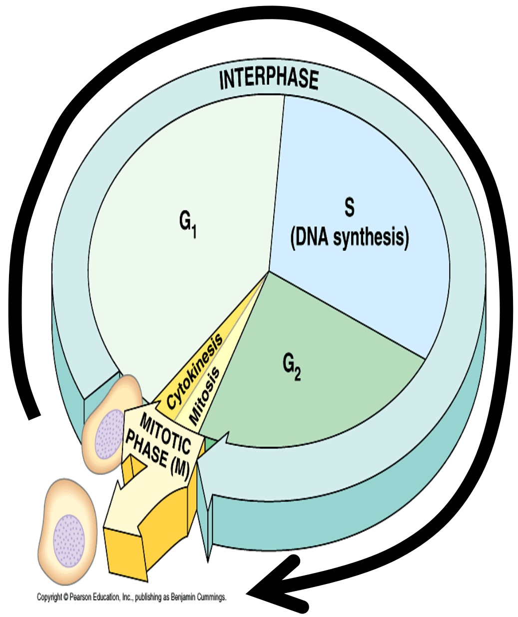
REDISTRIBUTION

Effect of cell cycle on cell survival curve



- G2, M-> most sensitive
- Late S -> most resistant

Redistribution.



Non Fractionated RT

- **Benign Tumors** not a issue like AVM or meningioma as they are not actively proliferating

- **Malignant Tumors** may have negative effect but over come by very large dose of non fractionated radiotherapy.

- G2, M-------Most sensitive
- Late S--------Most Resistant

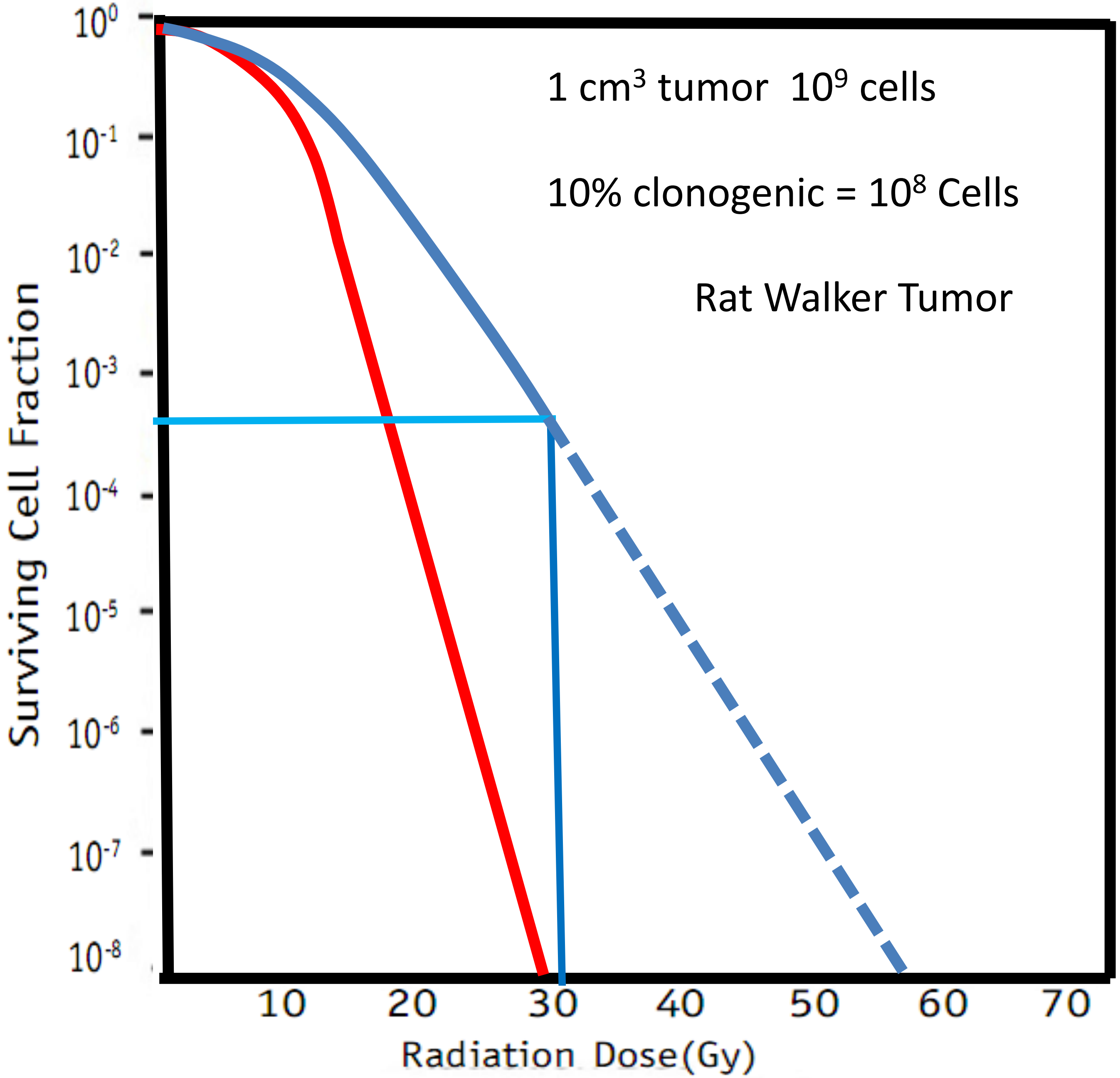
D_0 is 2 Gy

D_0 is 10 Gy

- There is 5 fold difference in survival after 200 rad

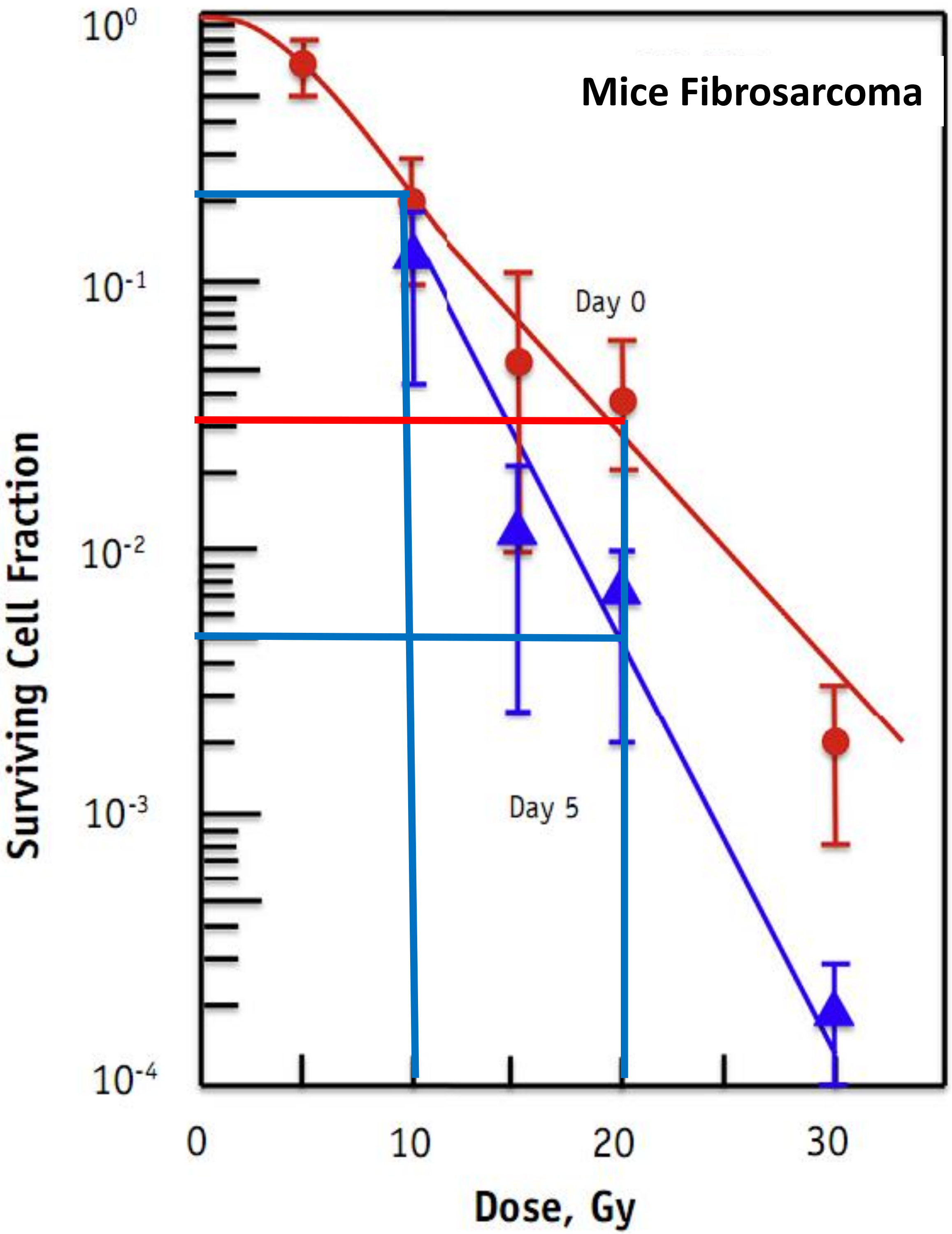
SRS/SRT Dose is > 12 Gy

New Biology of High dose RT



Apart from direct DNA damaging effect, other process of cell kills also triggered may be called as secondary cell deaths

International Journal of Radiation Oncology, Biology, Physics Vol. 110Issue 1p21–34Published online: March 2, 2019



New Biology of High dose RT

Two Messages

1. **Secondary cell death occurs at high dose per fraction.**
2. **Secondary death is triggered after 10 Gy**

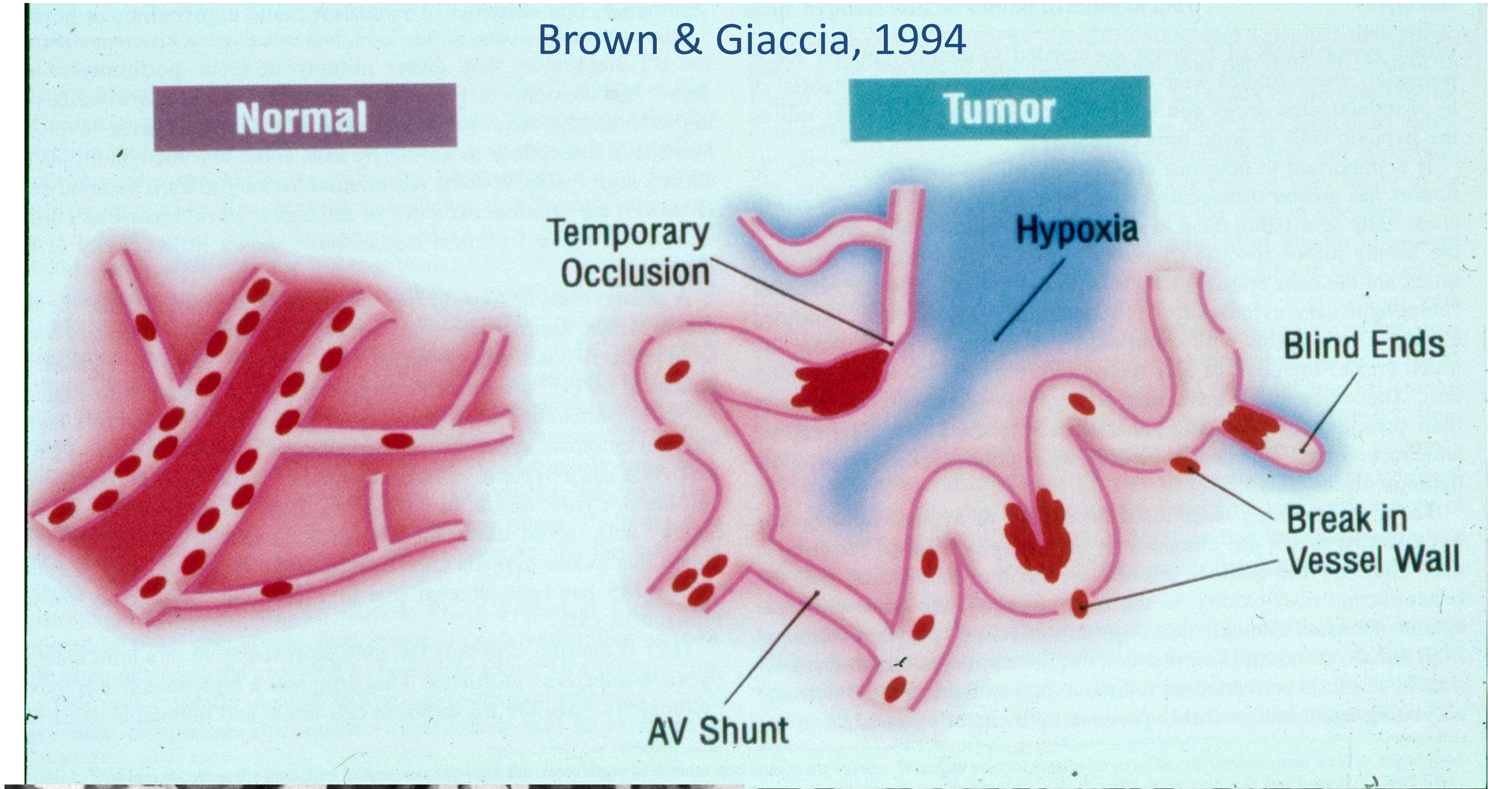
International Journal of Radiation Oncology, Biology, Physics Vol. 110Issue 1p21–34Published online: March 2, 2019

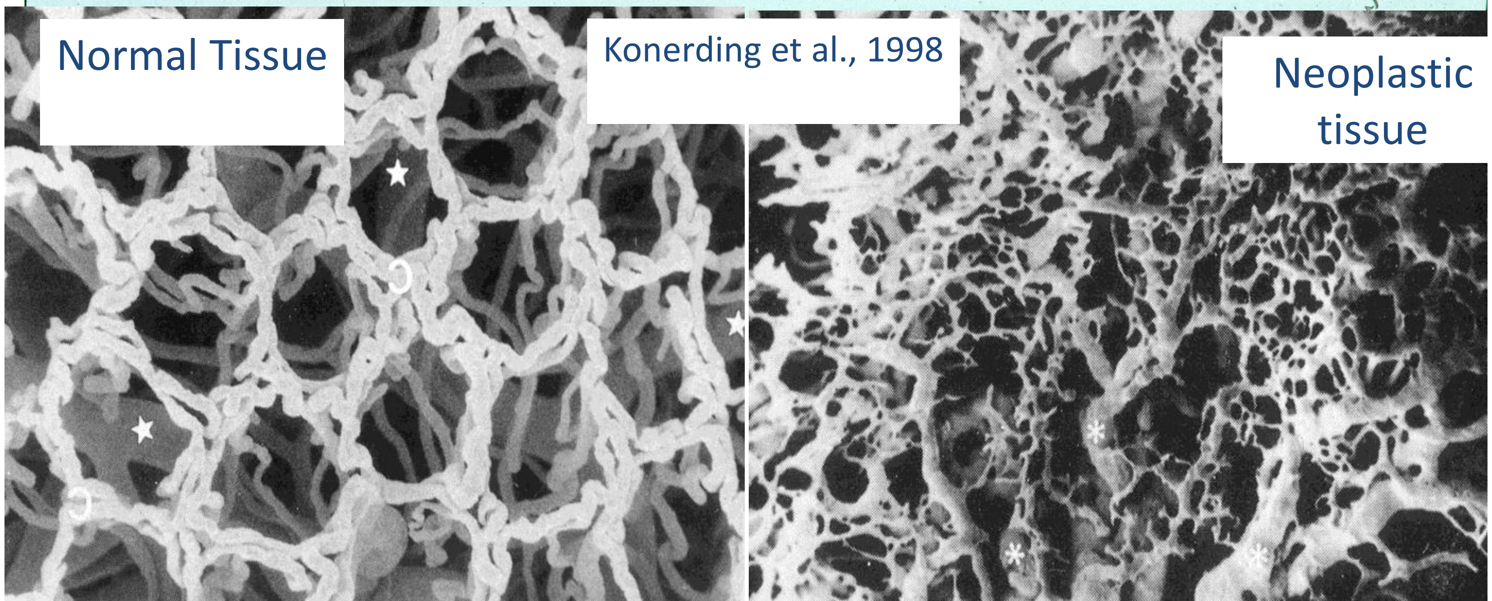
New Biology of High dose RT

- **Vascular/ Stromal damage at high dose.**
- **Stem Cell death at high dose.**

Tumor Vasculature

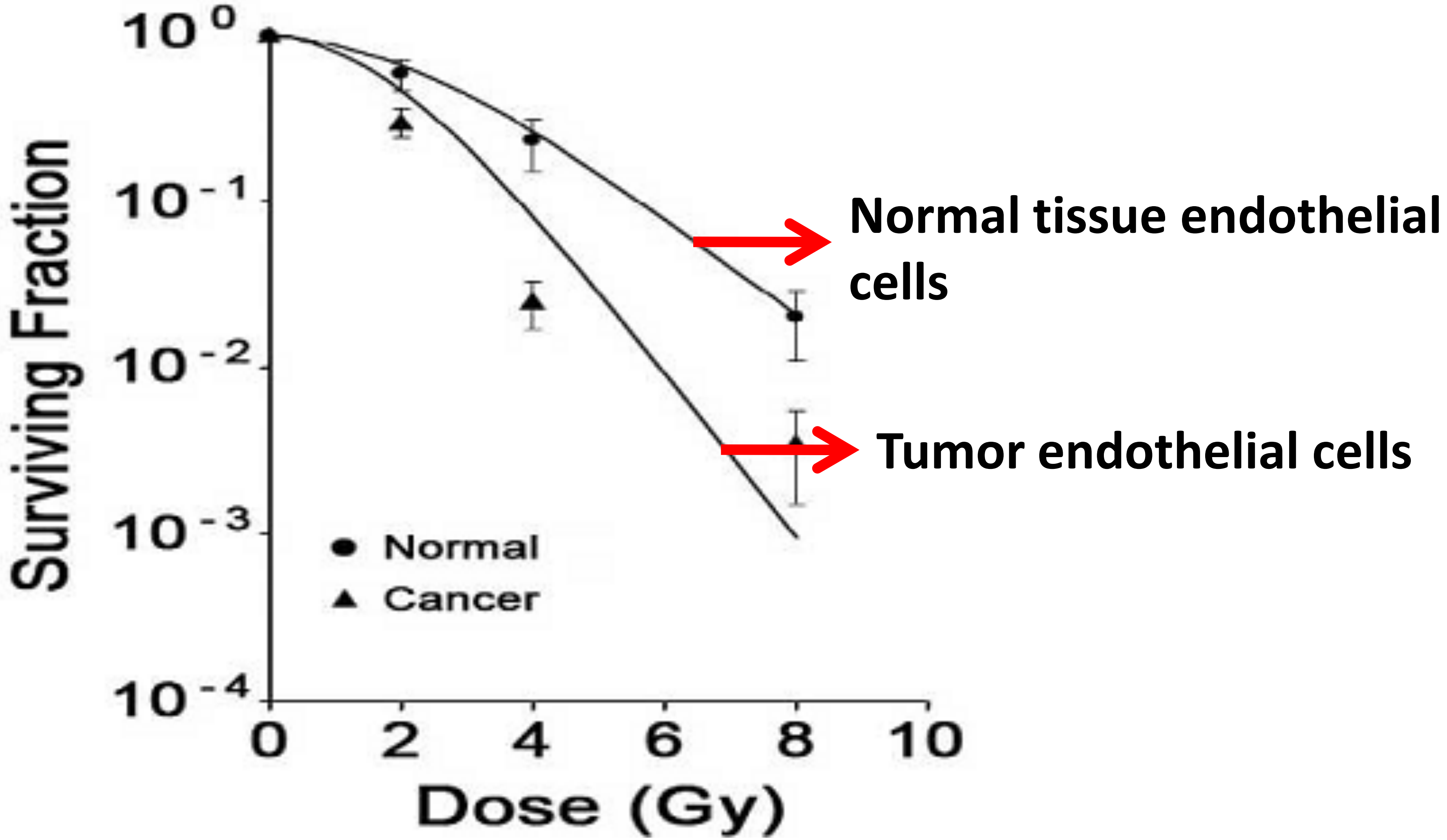
- The vascular network that develops in tumors is structurally abnormal
- Vessels are dilated, tortuous, elongated, with A-V shunts and blind ends
- The basement membrane is thin





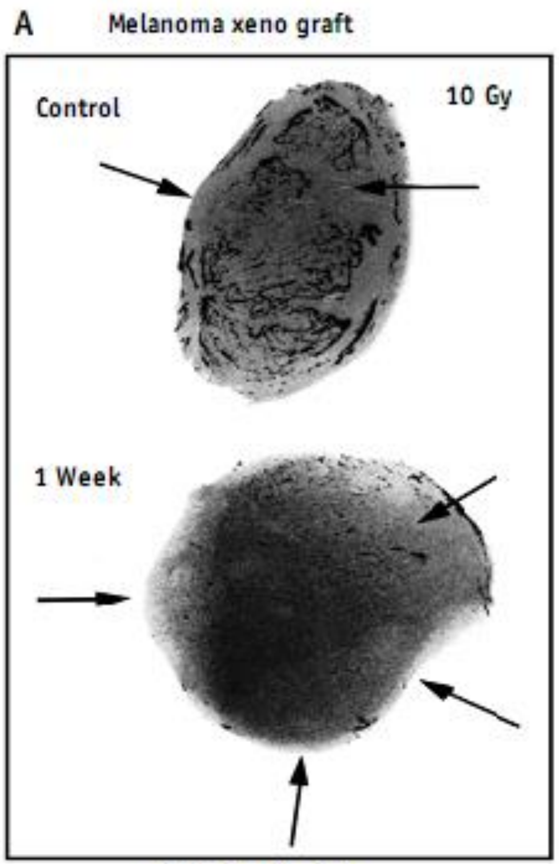
Pre clinical Evidence

Tumor vasculature is more sensitive

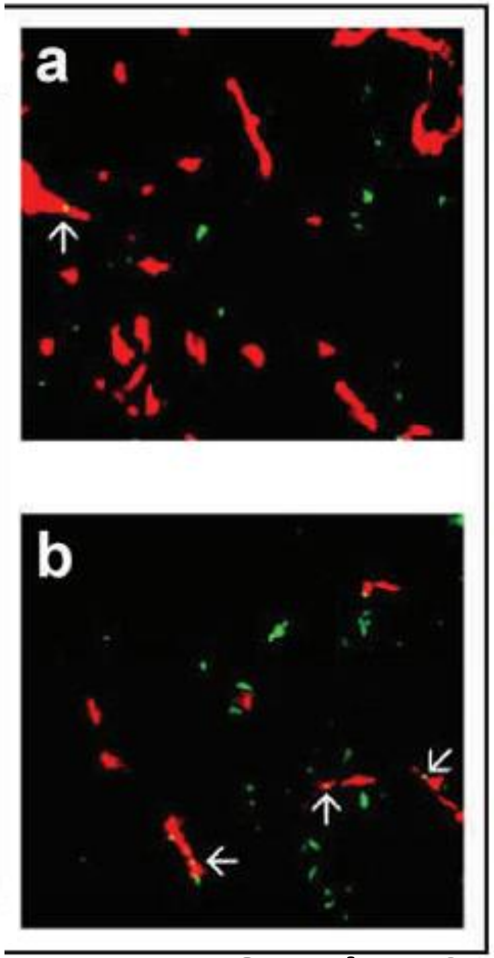


Heon Joo Park,[a,b] Robert J. Griffin,[c] RADIATION RESEARCH **177**, 311–327 (2012)

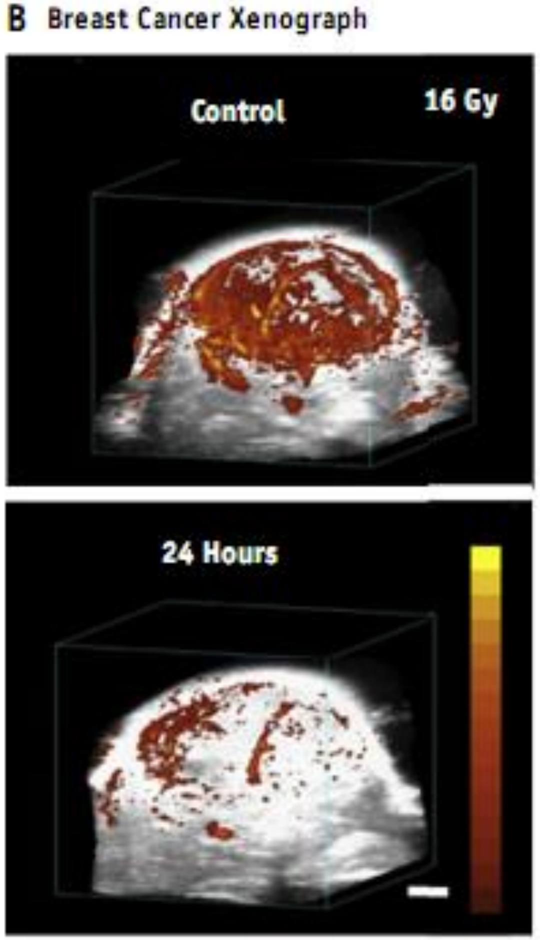
Vascular density in experimental tumor irradiated with high dose per fraction



OV. Solevik et al.



Human Ovarian Ca



A. Kaffas et al.

Pre RT

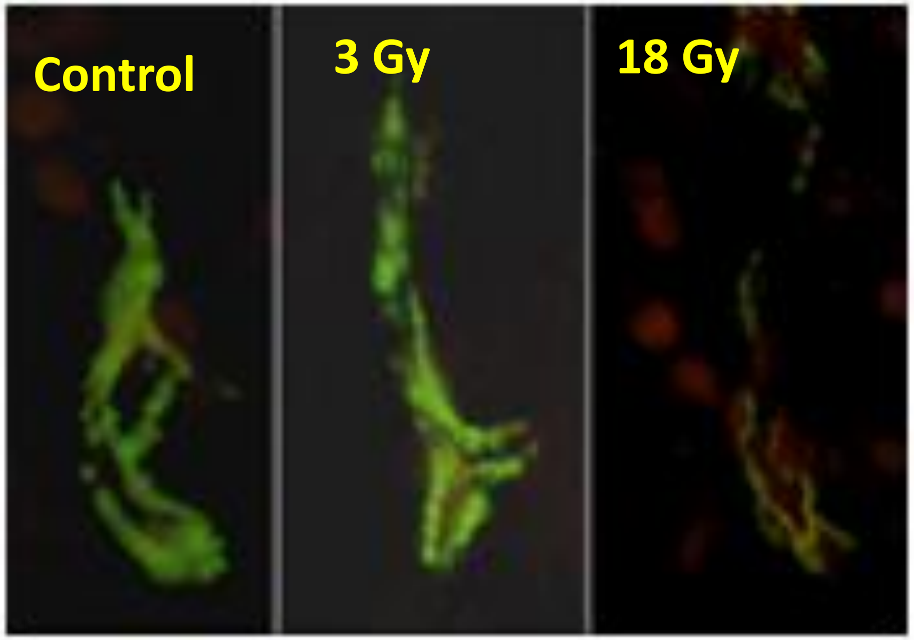
High dose RT

Post RT

Pre clinical Evidence

In vivo large animal and human evidence of apoptosis after high dose/fraction RT

Tumor endothelial apoptosis after 3 Gy or 18 Gy dingle fraction. Larue et al, Rad Res Mtg, 2008 (abst)



(L-R) control, 3 Gy fraction, 18 Gy fraction
Green = normal endothelium
Red = apoptosis

Extreme hypo fraction RT

↓

Endothelial Apoptosis

↓

Vascular Damage

↓

Cell Death

α and β cell kill

3rd process of cell kill

Stem Cell Death

CD 133+ Glioma cells are relatively radioresistant

CD 44+ breast cancer cell lines

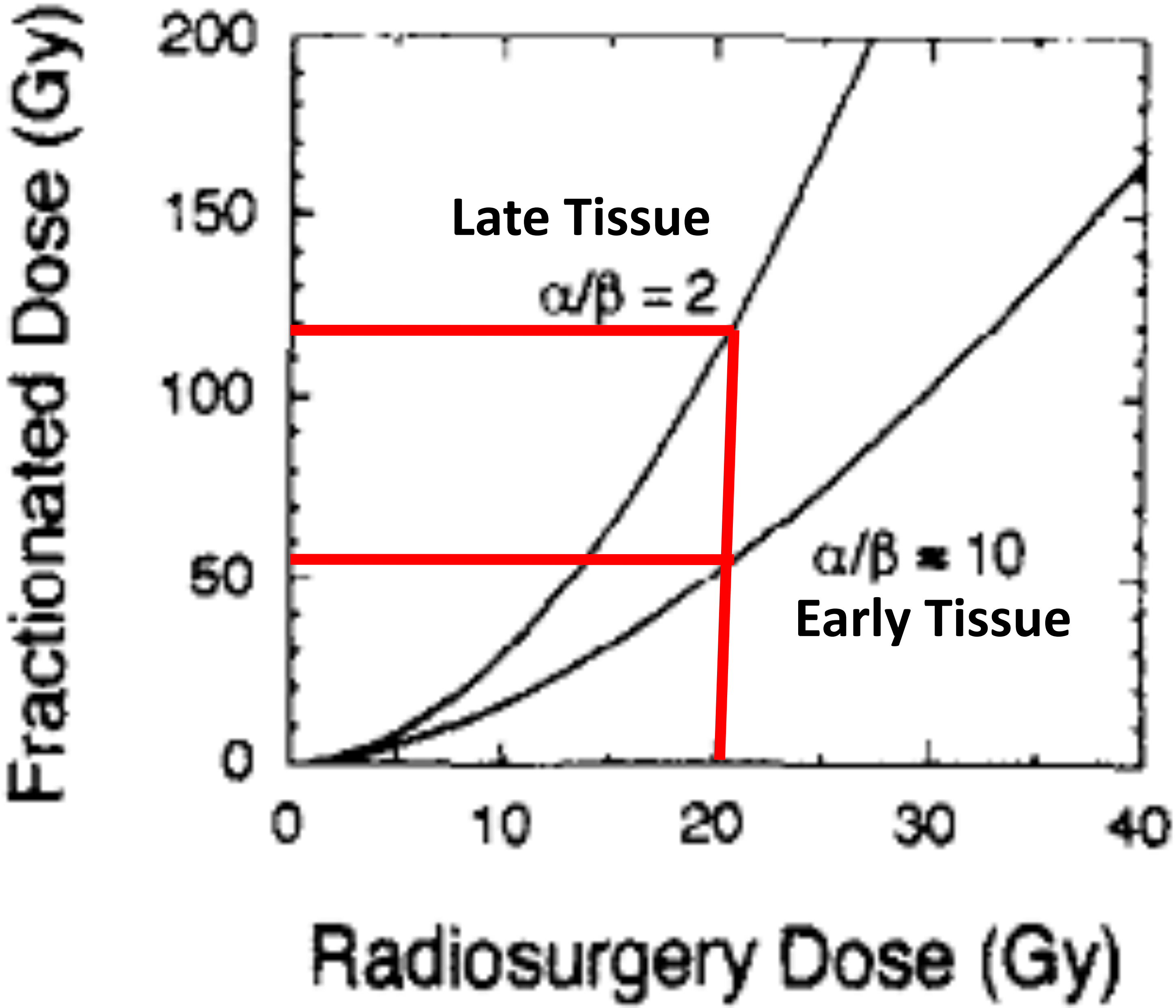
Cell death at High Dose RT

- **Direct cytotoxic damage related to DNA damage seen at all dose level and explained by LQ model**
- **Vascular/ stromal damage triggered at high dose level.**
- **Stem Cell Death triggered at high dose level.**

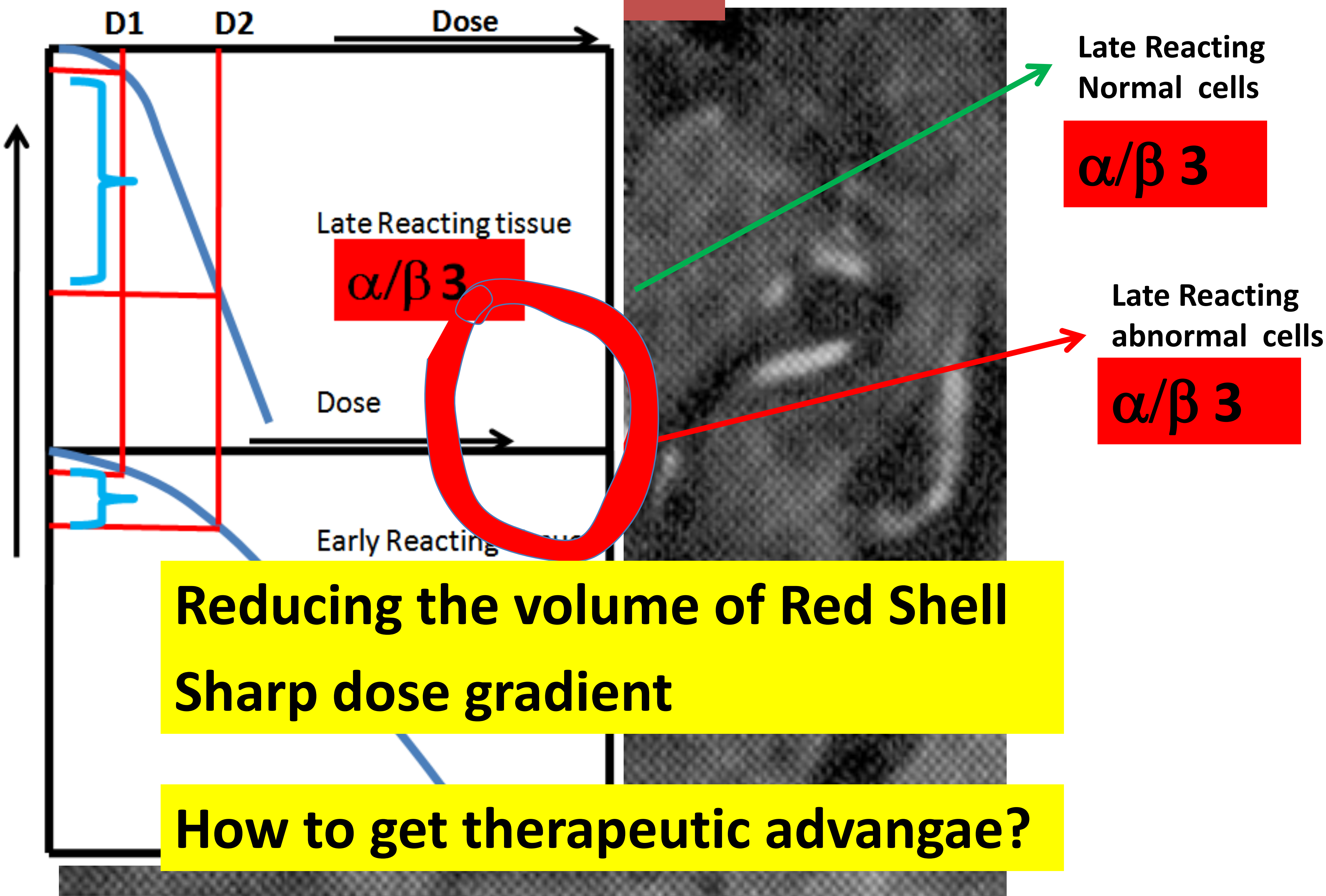
Intracranial SRS

Radio surgery dose vs. fractionated total dose at 2 Gy per Fx

D. A. LARSON *et al.* I. J. Radiation Oncology ● Biology ● Physics Volume 25, Number 3, 1993



Meningioma



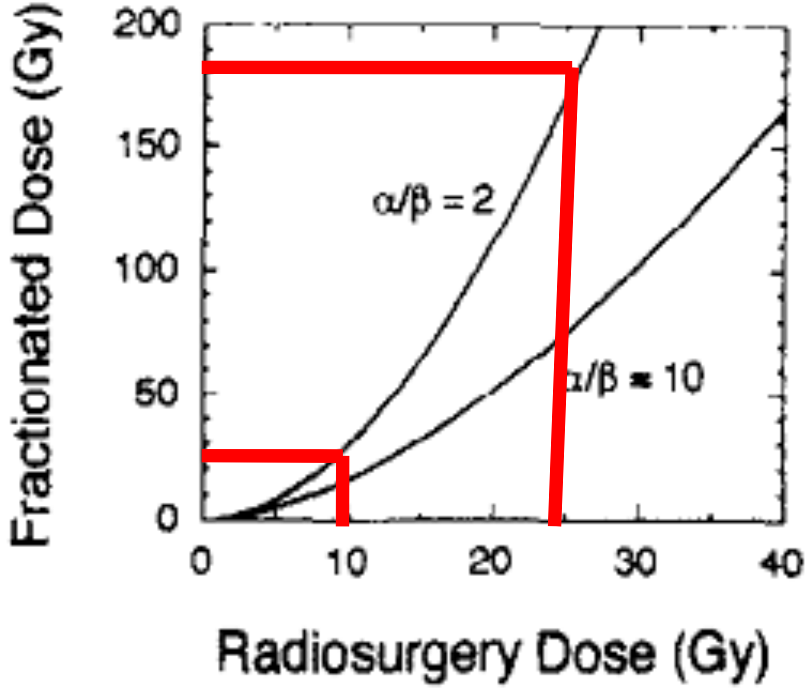
Reducing the volume of Red Shell

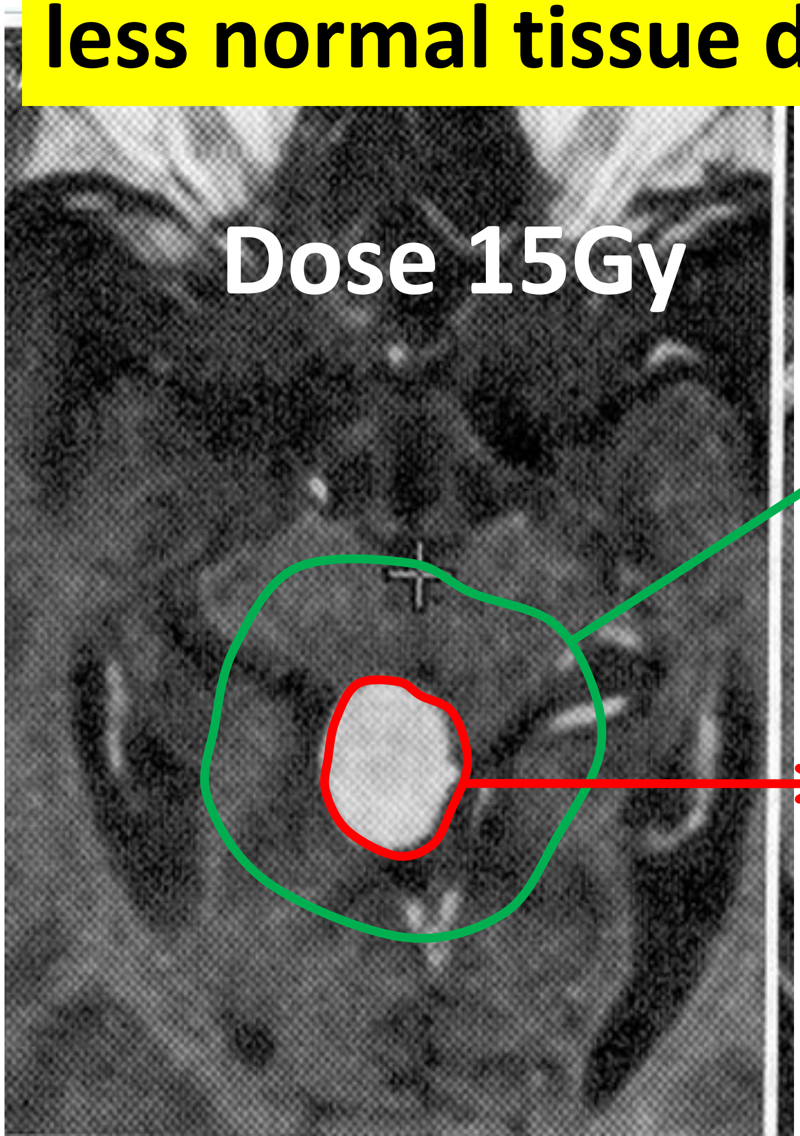
Sharp dose gradient

How to get therapeutic advangae?

Meningioma

Therapeutic Advantage with high tumor dose and less normal tissue doses





Late Reacting Normal cells

Dose outside the periphery will reduce to 10 Gy within few mm which will be EQD_2 30 Gy in fractionated regimen

Late Reacting abnormal cells

Dose = 15 Gy at Periphery will rise inside the periphery to 25-30 Gy which will be around EQD_2 200 Gy in fractionated regimen

Take Home

- Mainly rely on technical innovations to deliver highly precise dose of radiation to target with minimal dose to surrounding normal tissues.
- Lack of Repopulation is directly advantageous.
- The negative effect of other radiobiological principles of fractionated RT are countered by direct damaging effect of large dose per fraction.
- New Radiobiology not seen in fractionated RT are also triggered at large dose per fraction which also contribute in cell kill beside cell kill due to DNA damage.


Thank you


अखिल भारतीय आयुर्विज्ञान संस्थान, ऋषिकेश
All India Institute of Medical Sciences, Rishikesh