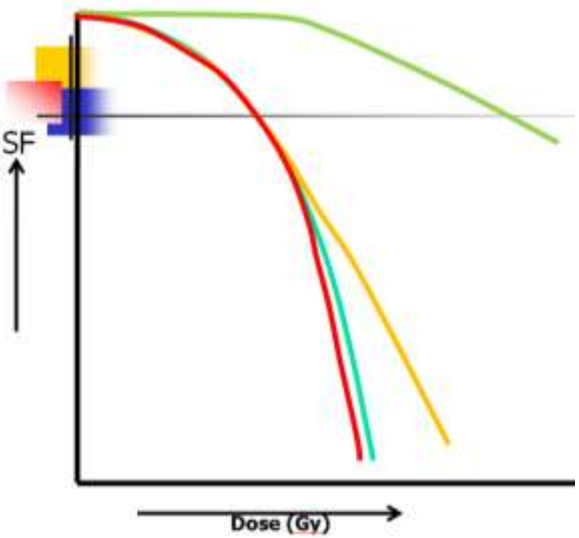
Radiobiology of Non Fractionated RT




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



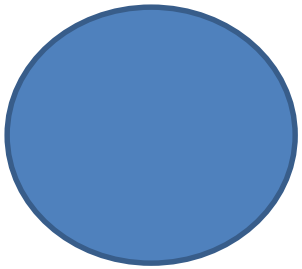
- Benign and Malignant Diseases

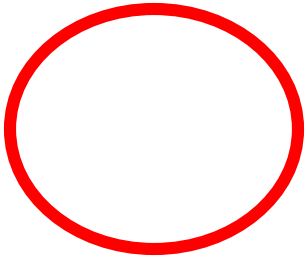
Prof Manoj Gupta
Head, Rad Onc
AIIMS Rishikesh
ICC, Mumbai Nov 2023

SRS and SBRT

1. Small Target usually tumor <3cm

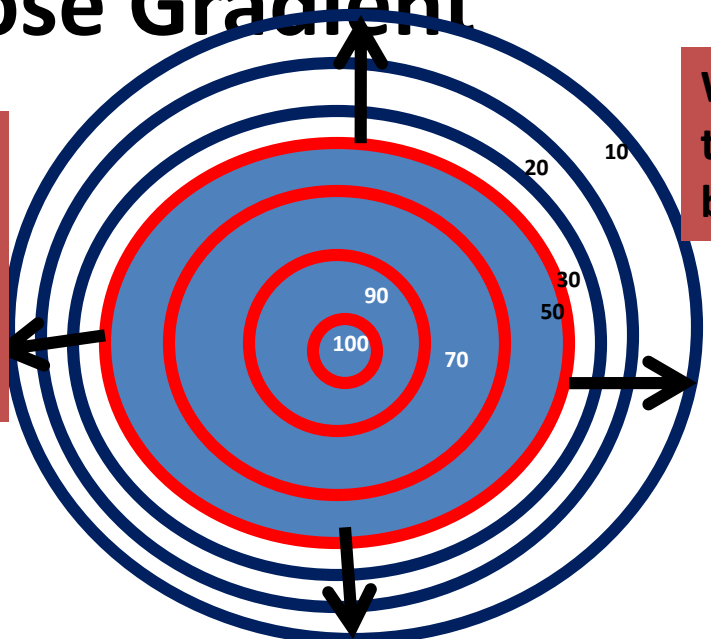
2. Highest degree of conformality.





3. Steep Dose Gradient

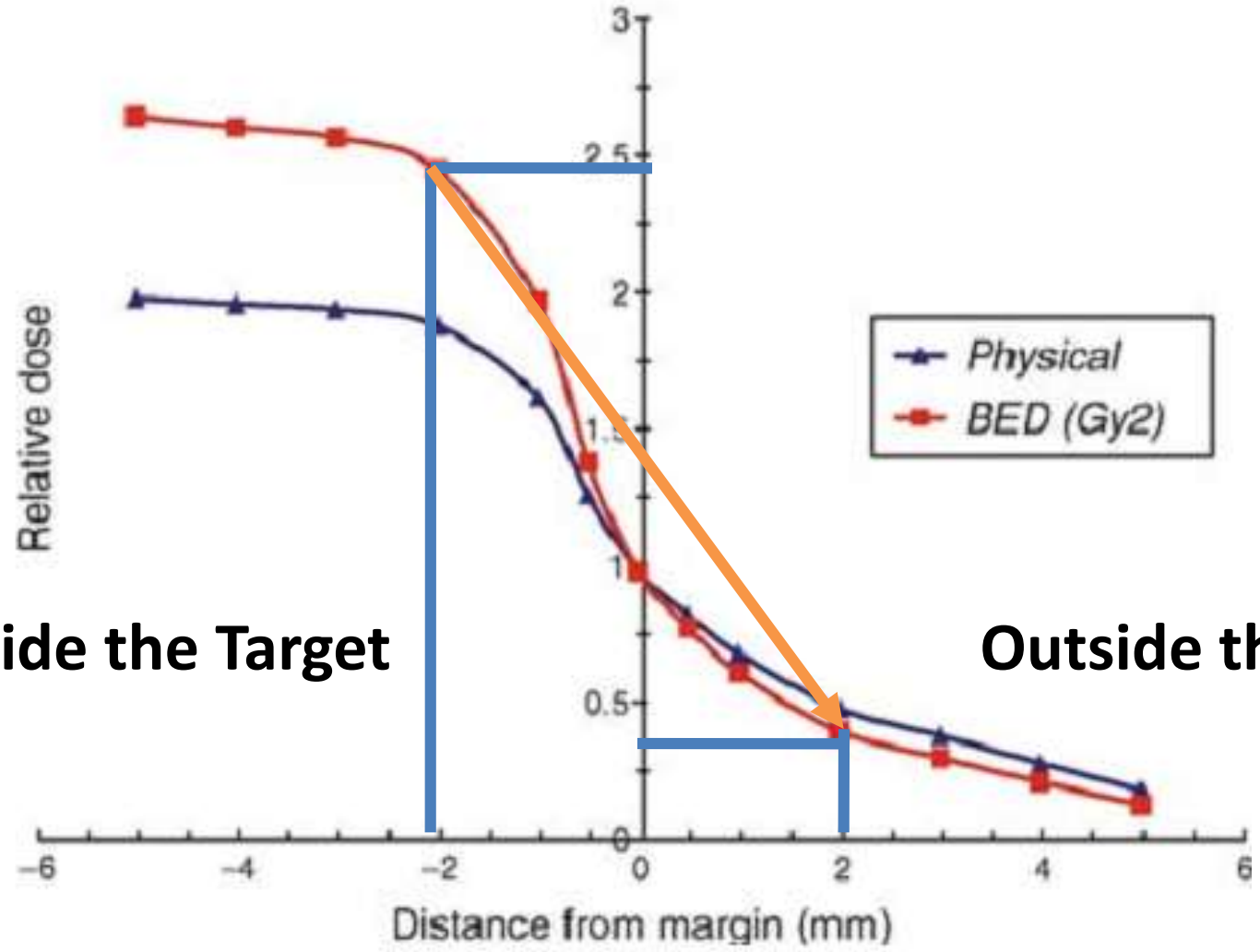
Within the target periphery the dose increases from 50% to 100% resulting into inhomogeneous dose distribution



Within mm outside the target periphery the dose become insignificant

Steep Dose Gradient

Dose Gradient from 50% isodose line at margin of target



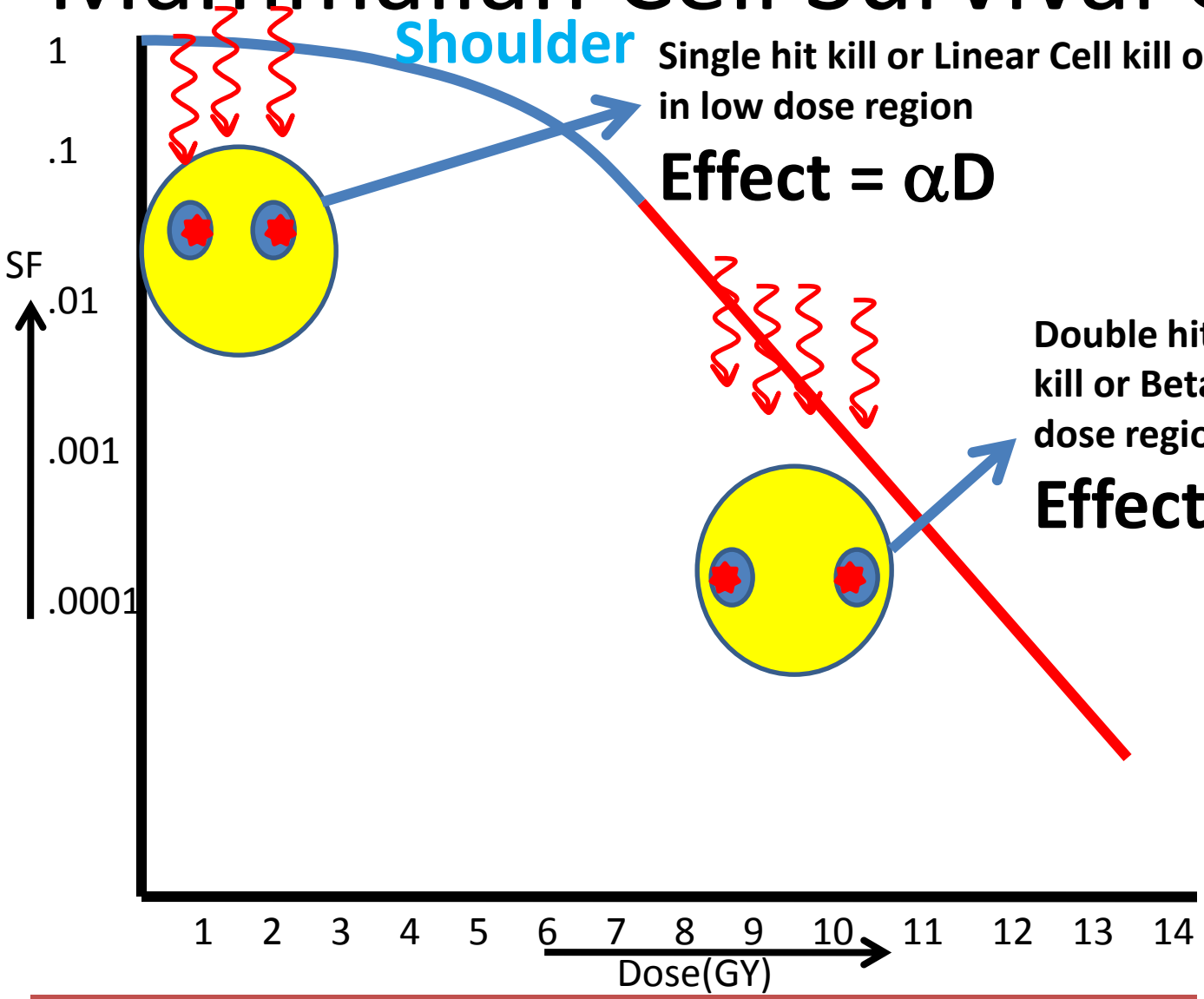
Inside the Target

Outside the Target

Road Map

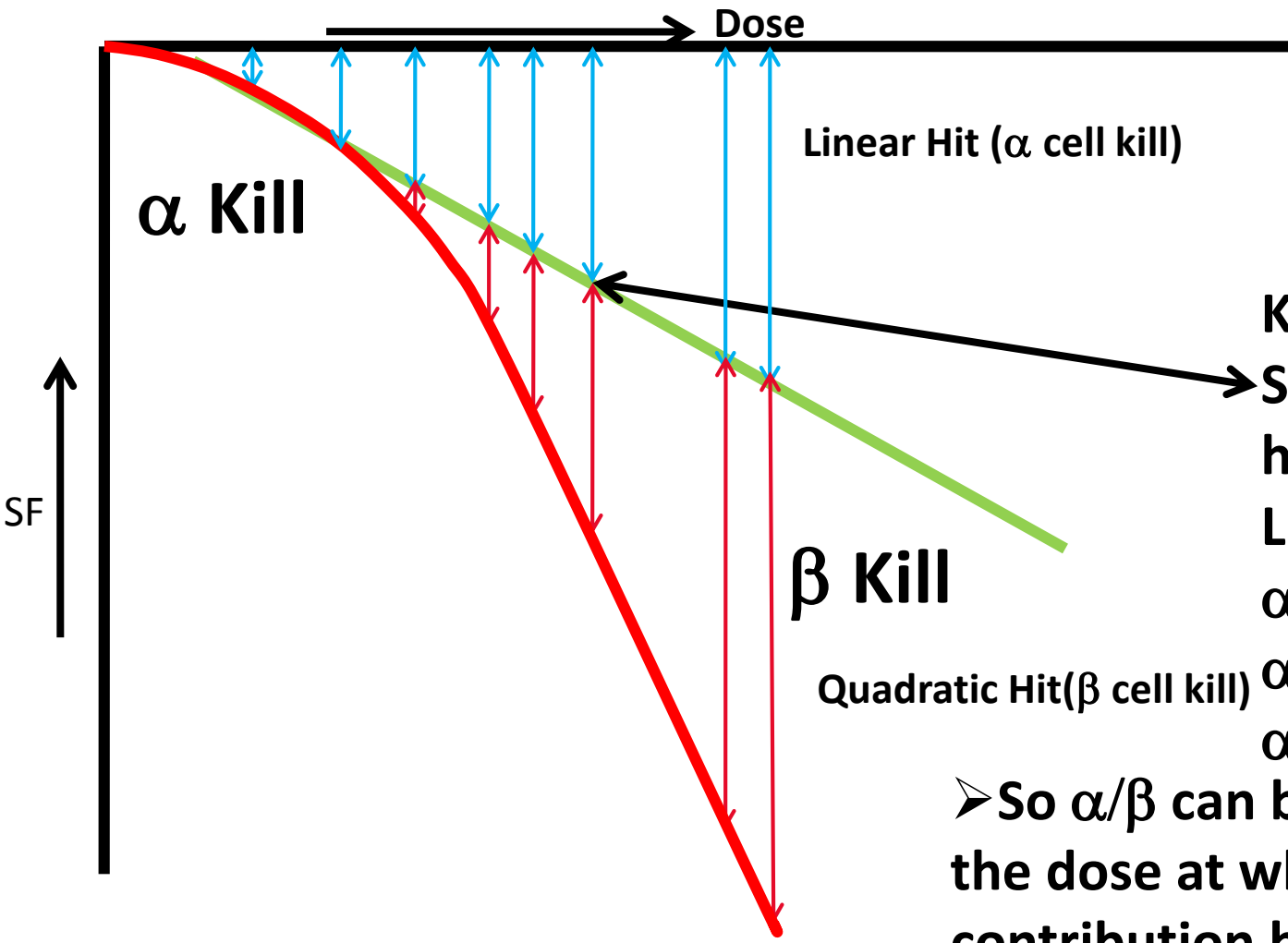
- L-Q Model of Cell Survival Curve
- Cell Survival Curve & SRS/SBRT
- Role of classical “Four Rs”
- New Biology at High Dose
- Intracranial SRS

Mammalian Cell Survival Curve



Linear-Quadratic Model

Linear Quadratic model (α/β Ratio)



Killing by SHE=Killing by two hit event

Linear = Quadratic

$\alpha D = \beta D^2$

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

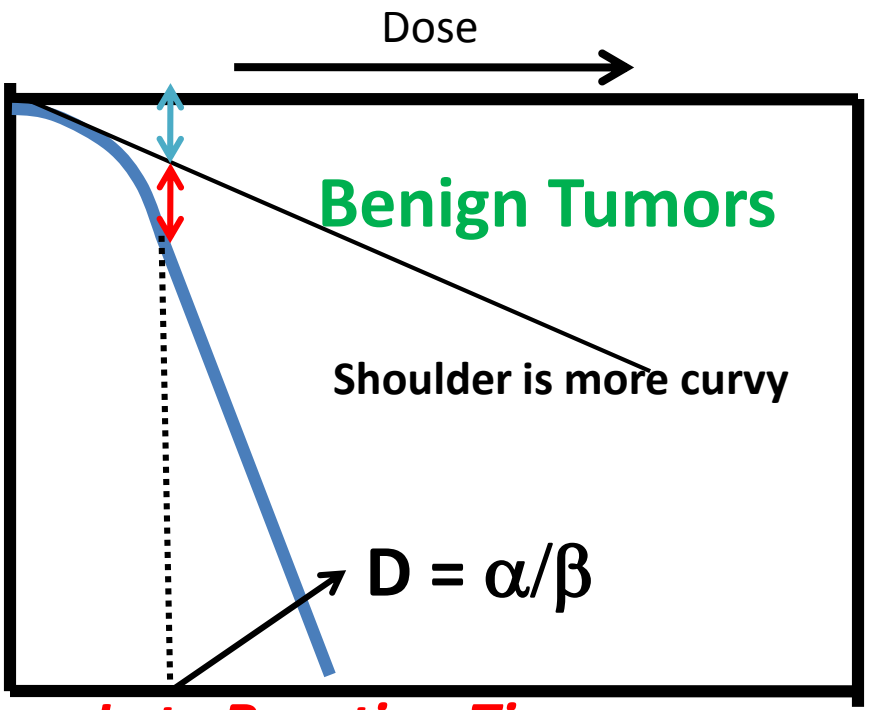
$\alpha/\beta = D$

➢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

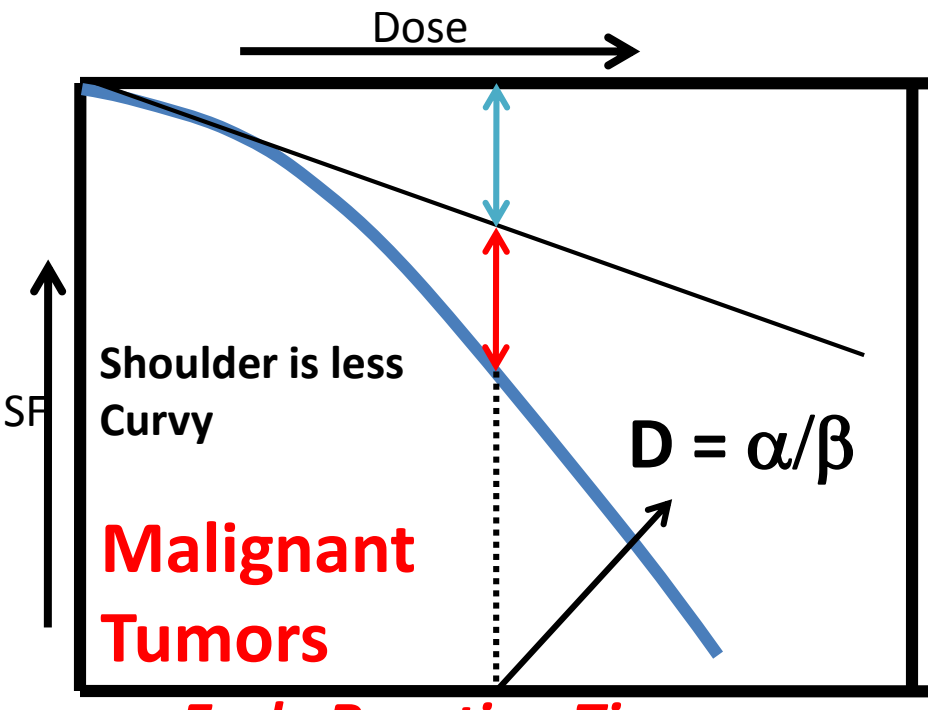
Small α/β ratio indicate more curvy nature of the shoulder As seen in late responding tissue

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



Late Reacting Tissue

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



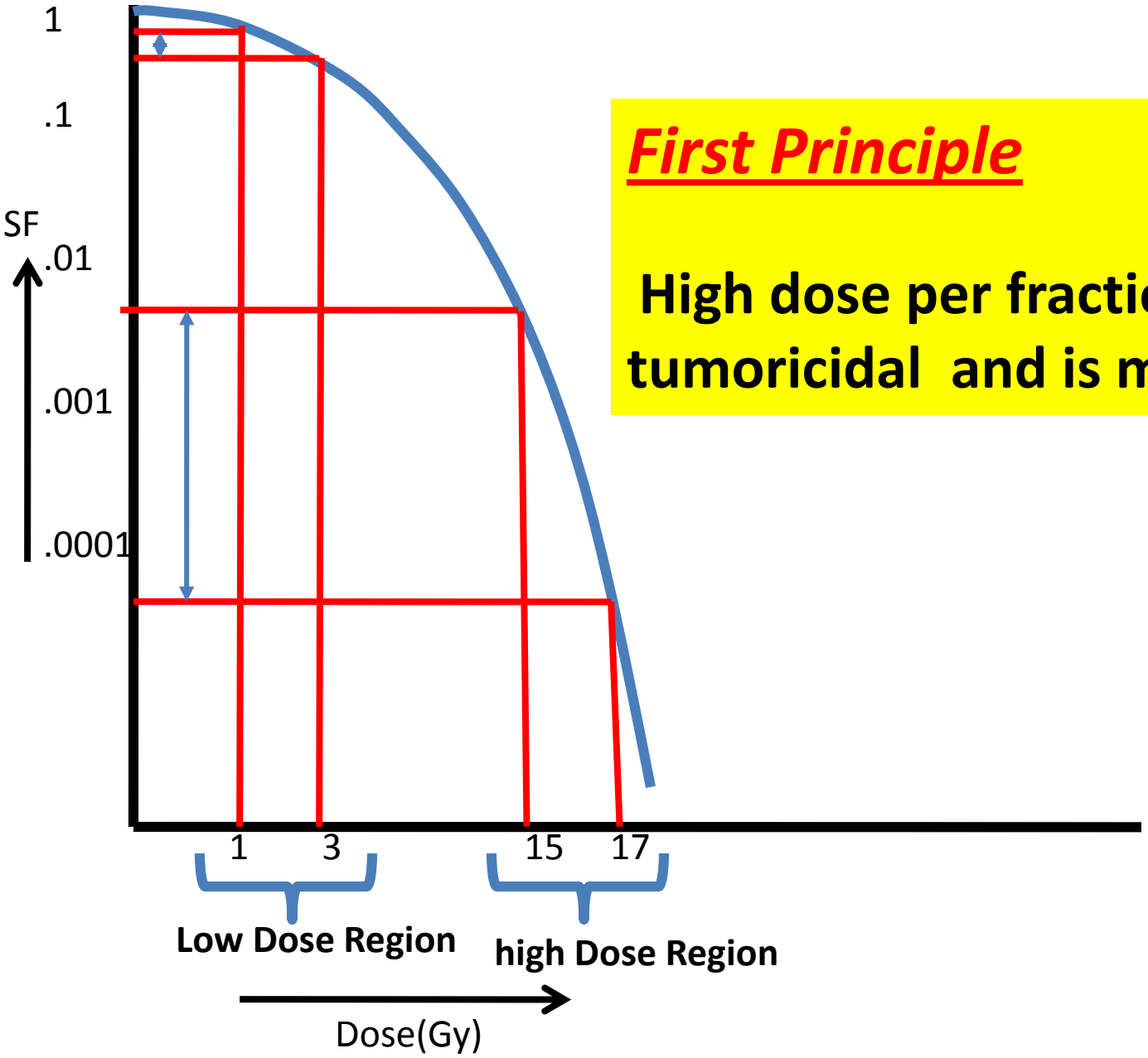
Early Reacting Tissue

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

RADIOBIOLOGICAL RATIONALE

Cell Survival Curve

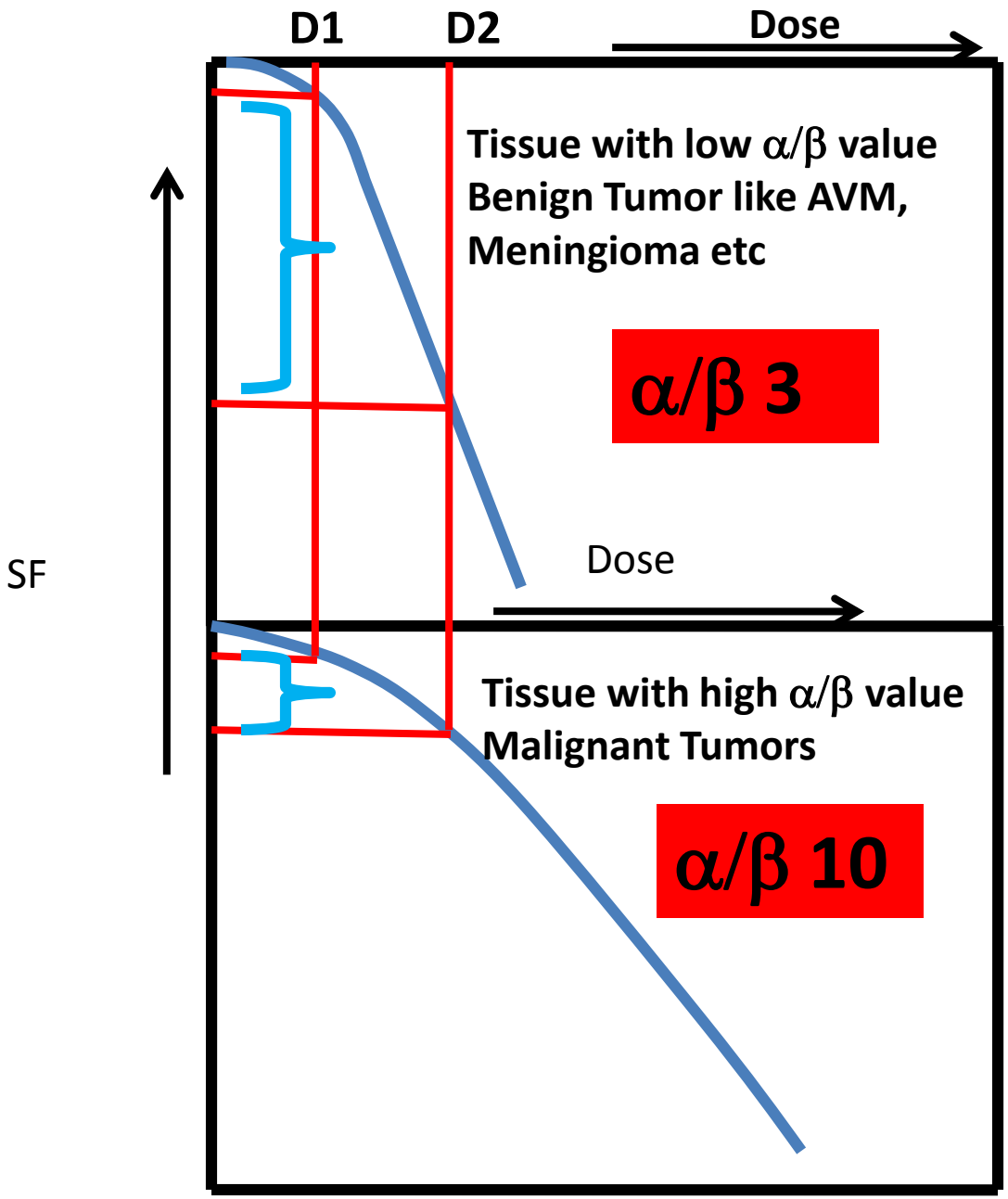
Effect of high dose on Cell Survival Curve



First Principle

High dose per fraction is more tumoricidal and is more damaging

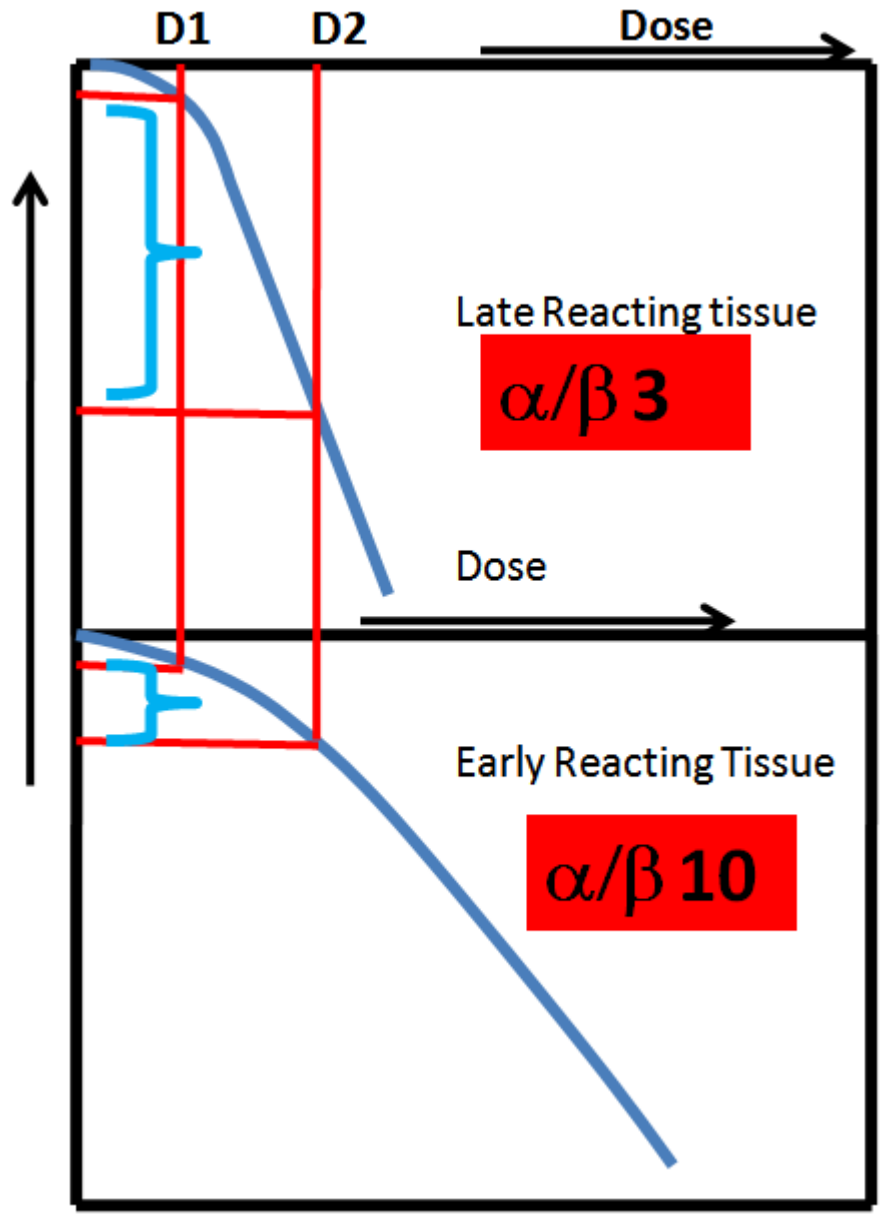
More Effective For Benign Tumors

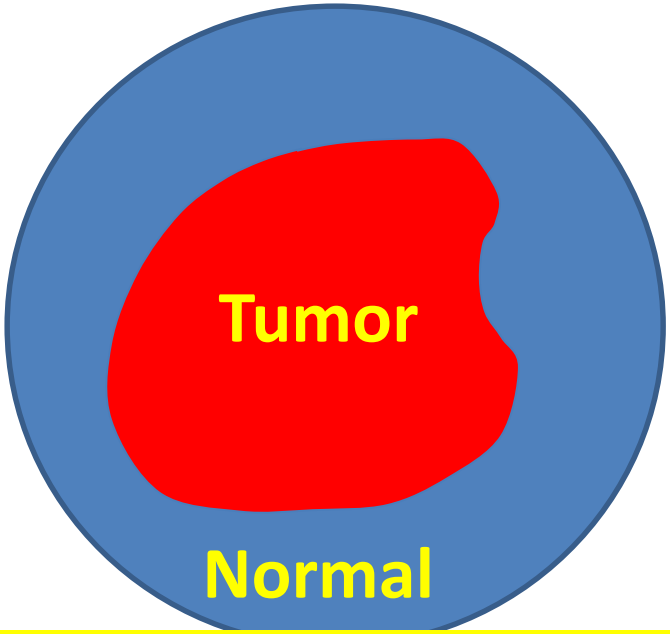


Second Principle

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



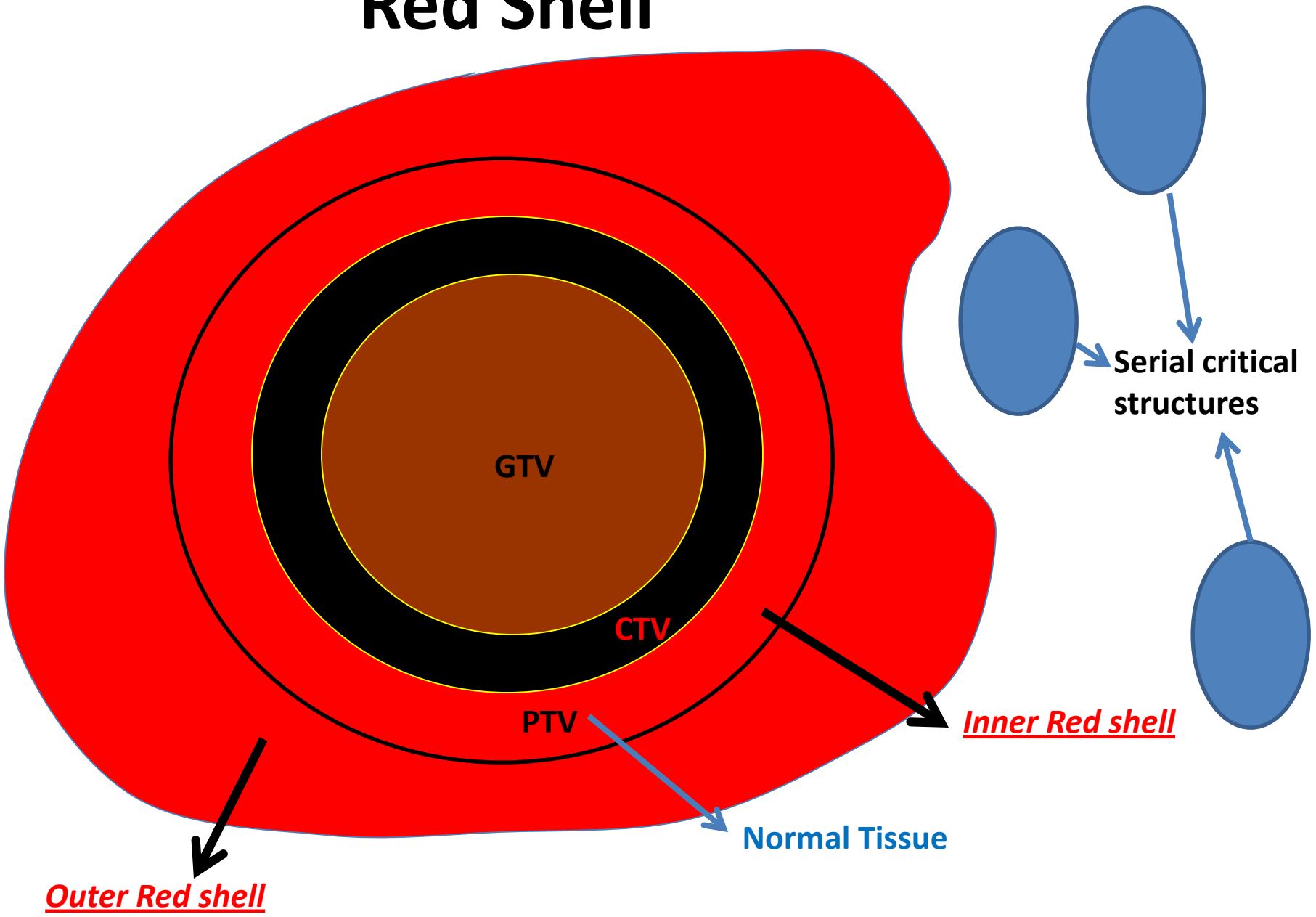


Third *Principle*

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
Normal Tissue
Outer Red shell
Serial critical structures

Clinical Significance of Red Shell

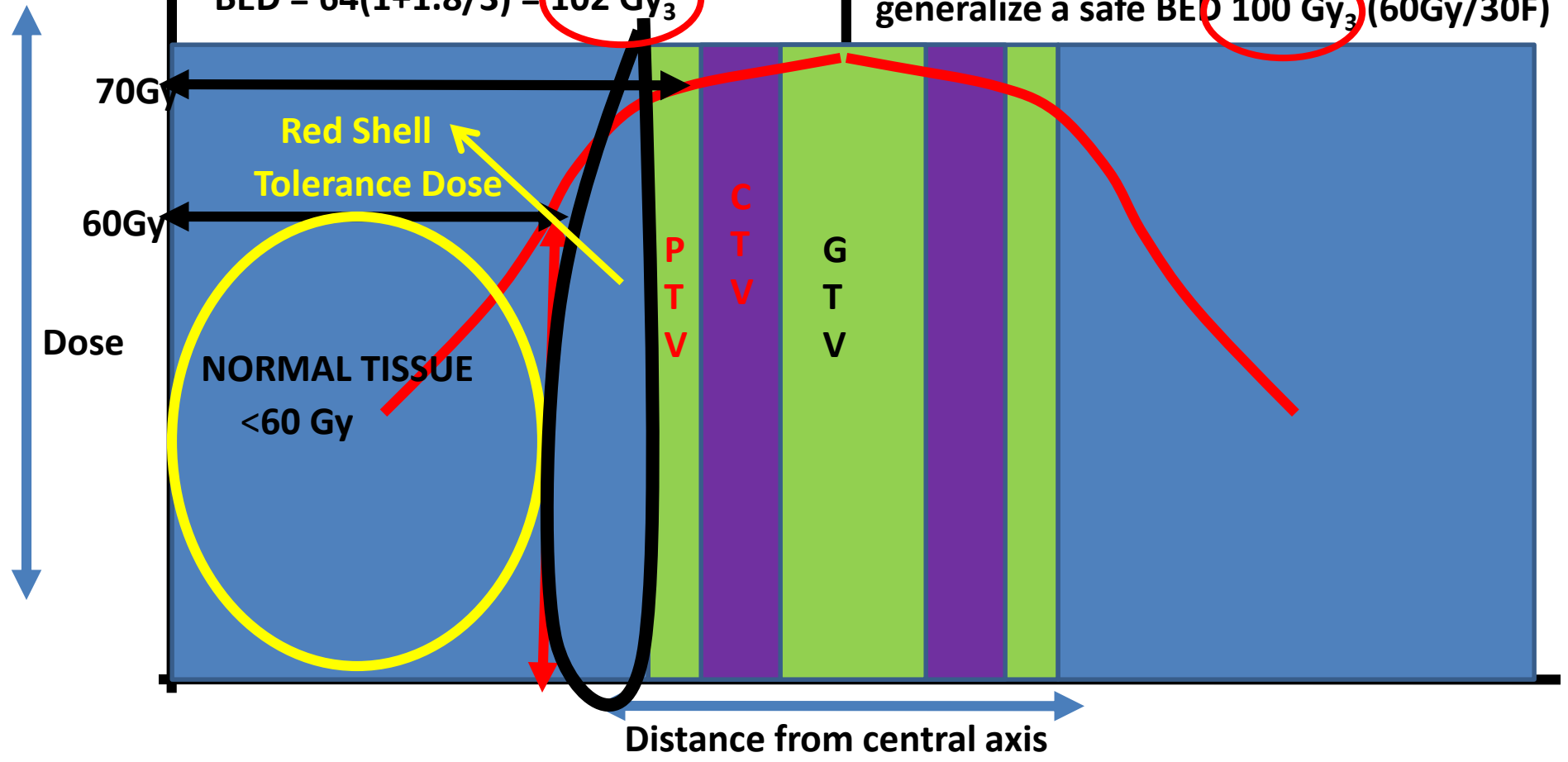
64 Gy in 35fx, d/f = 1.8 Gy

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

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

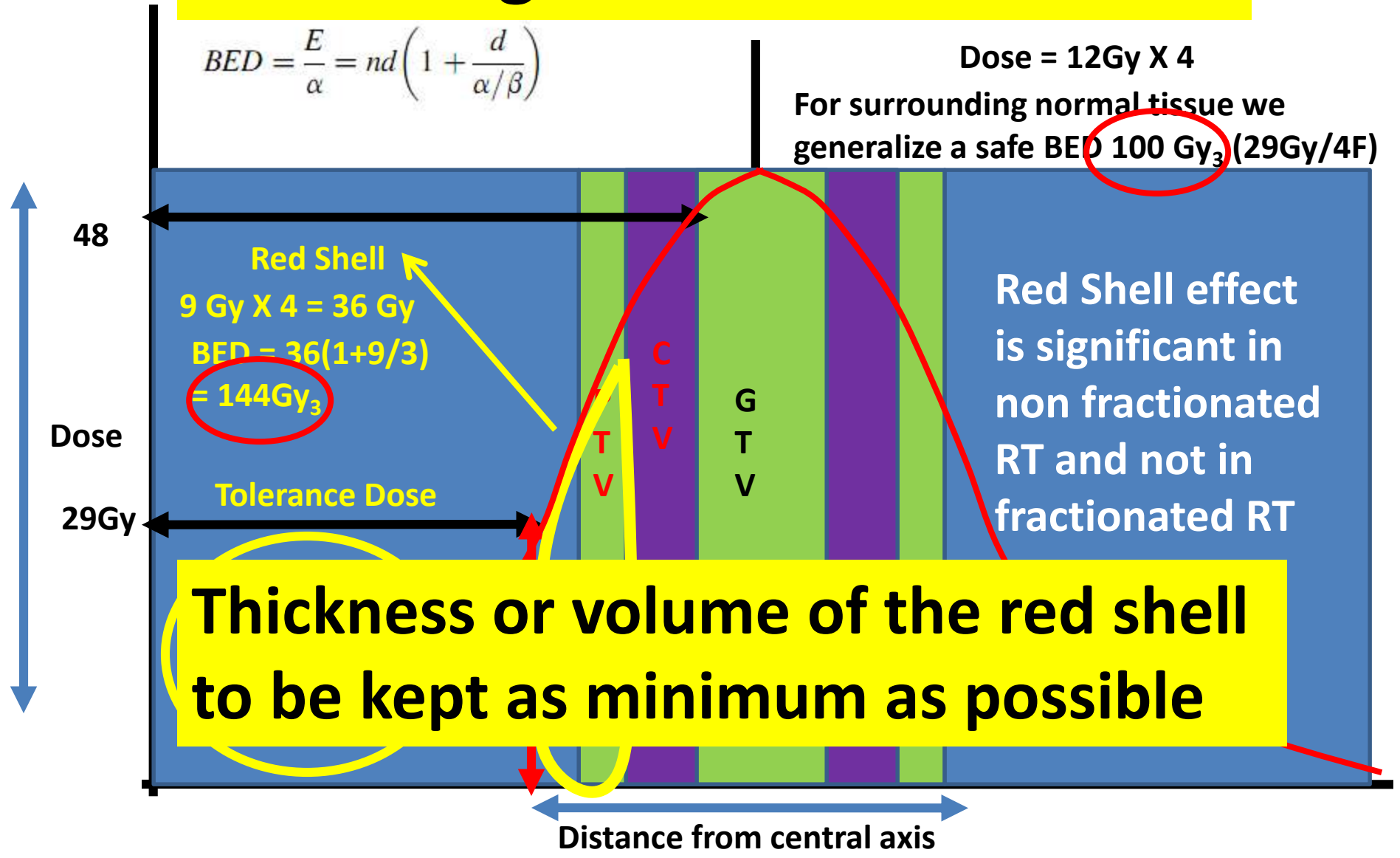
70 Gy/35fx/2Gy per fx

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



Fractionated Radiotherapy

Clinical Significance of Red Shell



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**

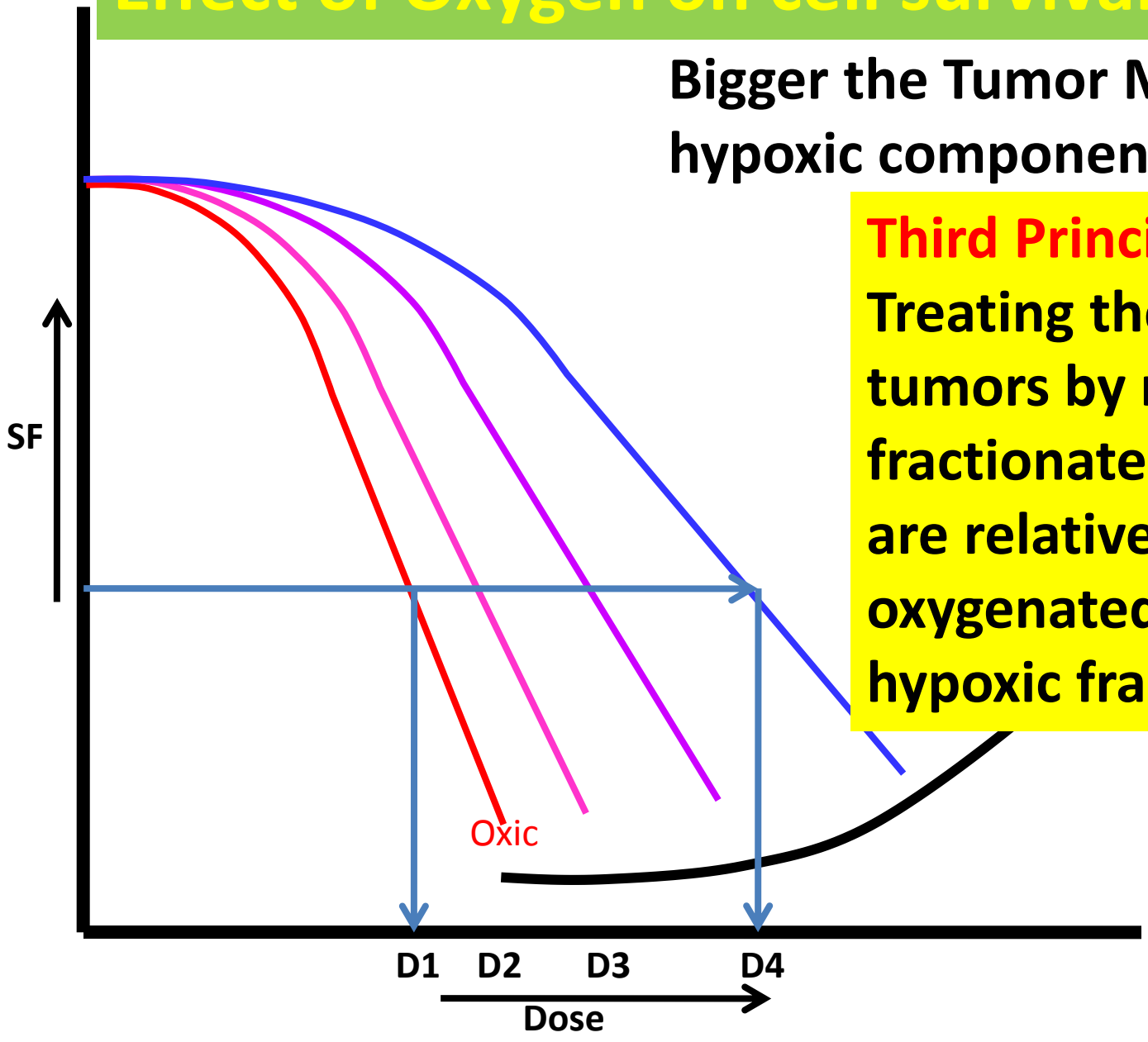
4 Rs of Fractionations

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

REOXYGENATION

Effect of Oxygen on cell survival curve

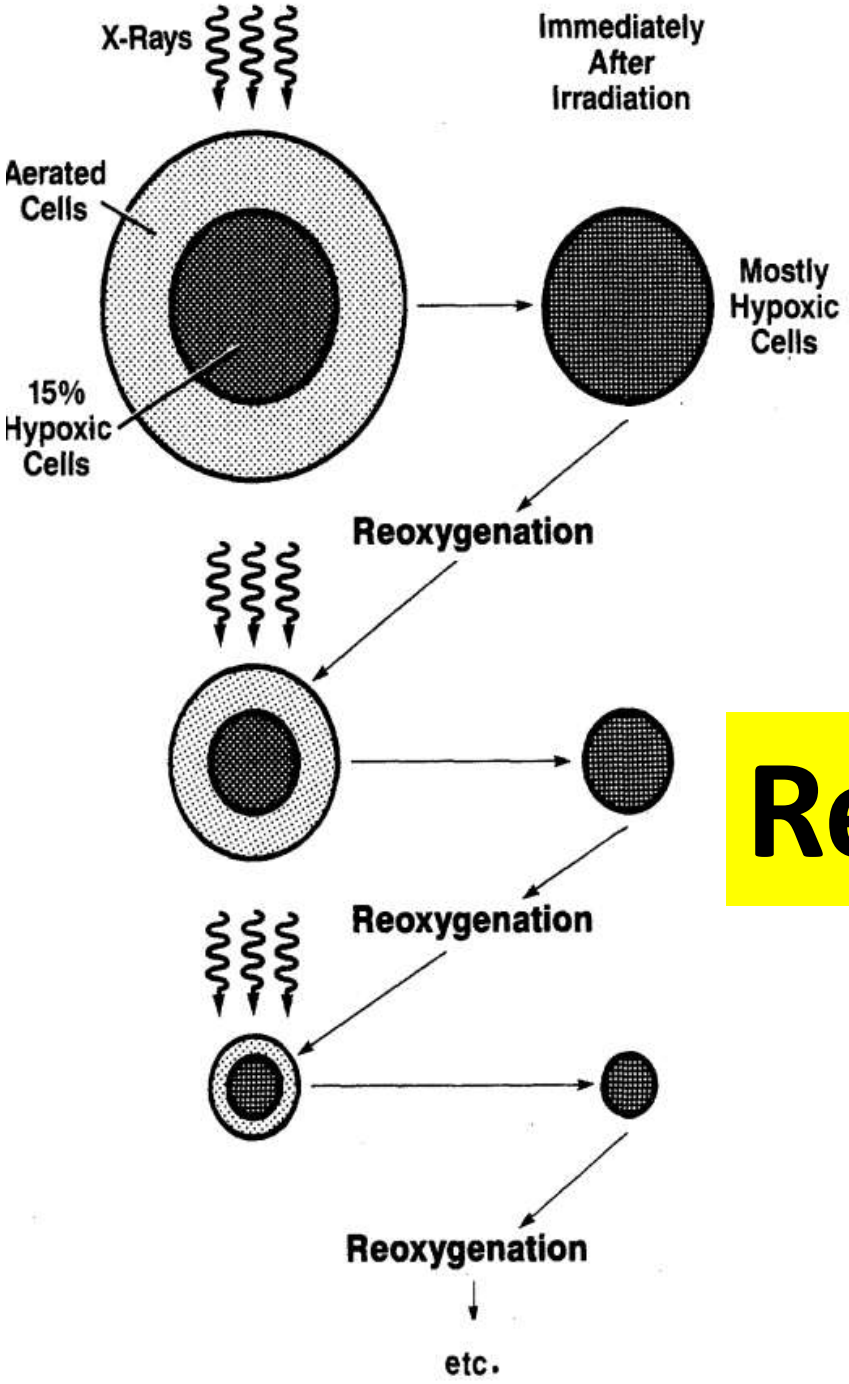
Bigger the Tumor More is the hypoxic component & vice versa



Third Principle

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

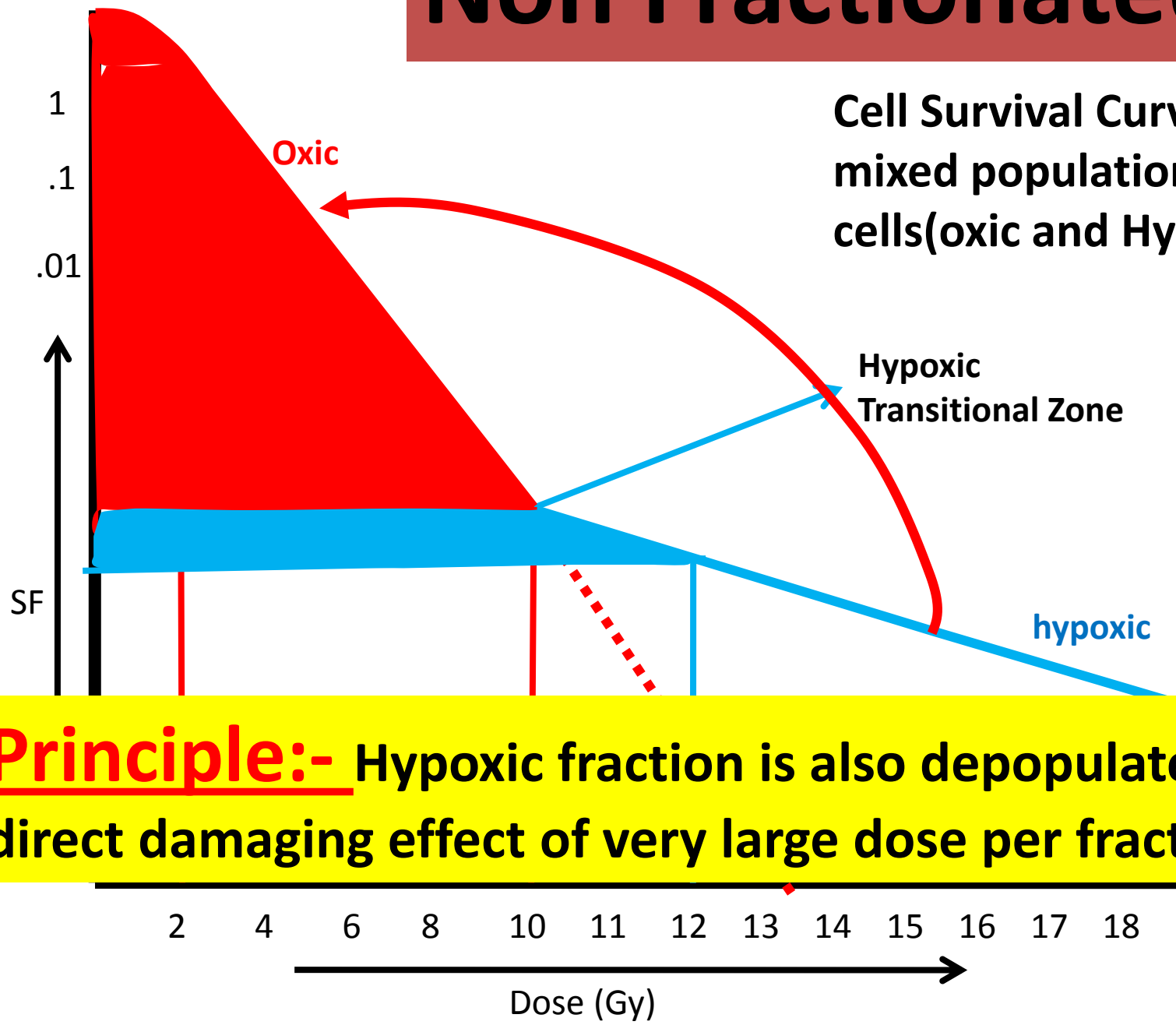
Fractionated RT



Reoxigenation

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

Non Fractionated RT



Cell Survival Curve of mixed population of cells(oxic and Hypoxic)

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.

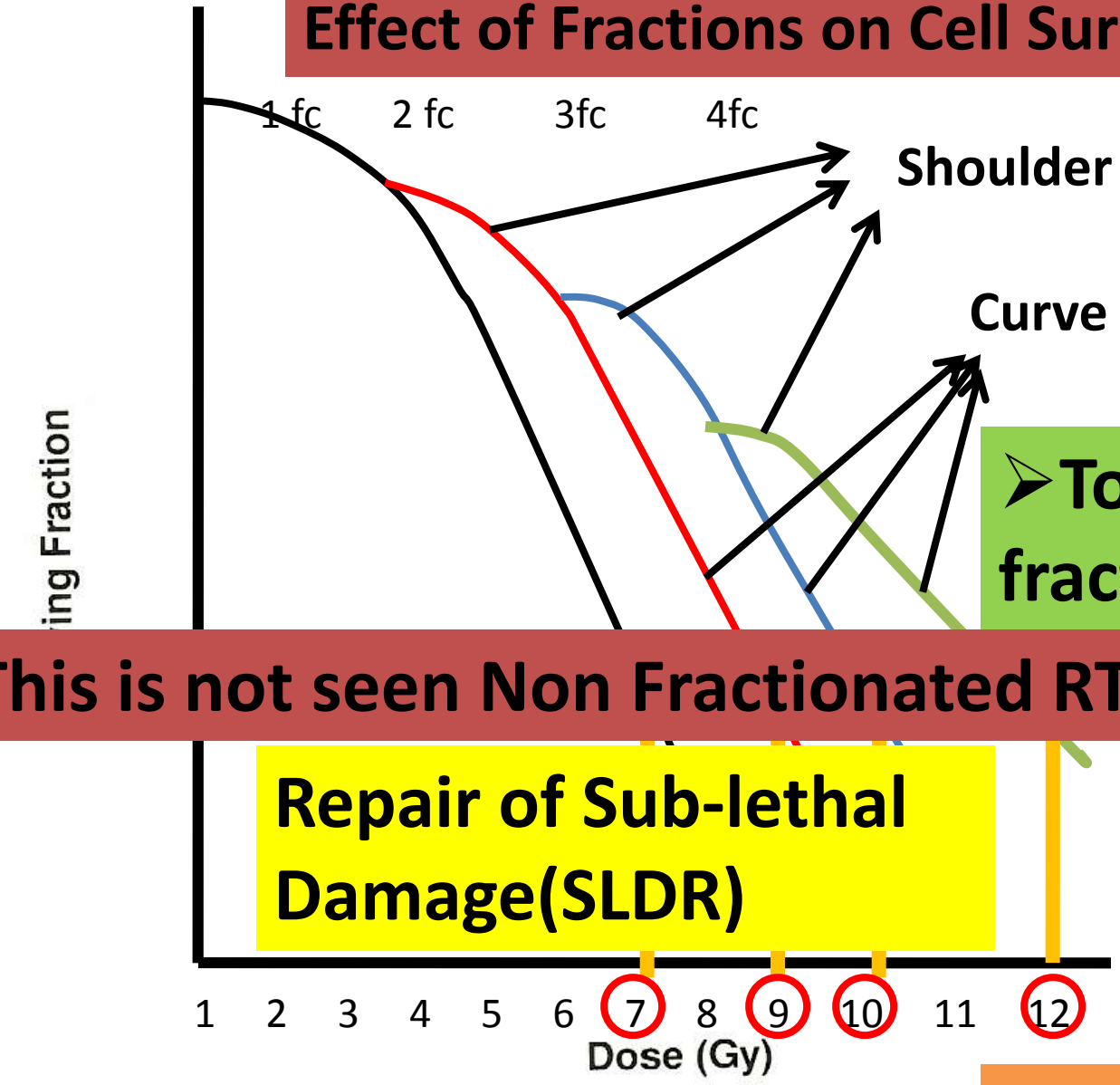
$$OER = \frac{D_0 \text{ (hypoxic)} \longrightarrow 6 \text{ Gy}}{D_0 \text{ (aerobic)} \longrightarrow 2 \text{ Gy}}$$

= 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

Fractionated SRS/SBRT

Question

Consecutive Days or Alternate Days

Complete Repair of SLD

Early Reacting Tissues	4 to 8 Hours
Late Reacting Tissues	12 to 24 Hours

Bentzen *et al*, *Radiother Oncol* **53**, 219, 1999

Fractionated SRS/SBRT

questionnaires between a SBRT schedule of 36.25 Gy in 5 fractions in five consecutive days with those treated with the same dose administered every other day. While late urinary toxicity showed only a tendency toward improvement with more protracted treatment (19% versus 5%), late moderate or severe rectal toxicity showed a statistically significant difference also in favor of the longer treatment (38% versus 0%; $p = 0.0035$).

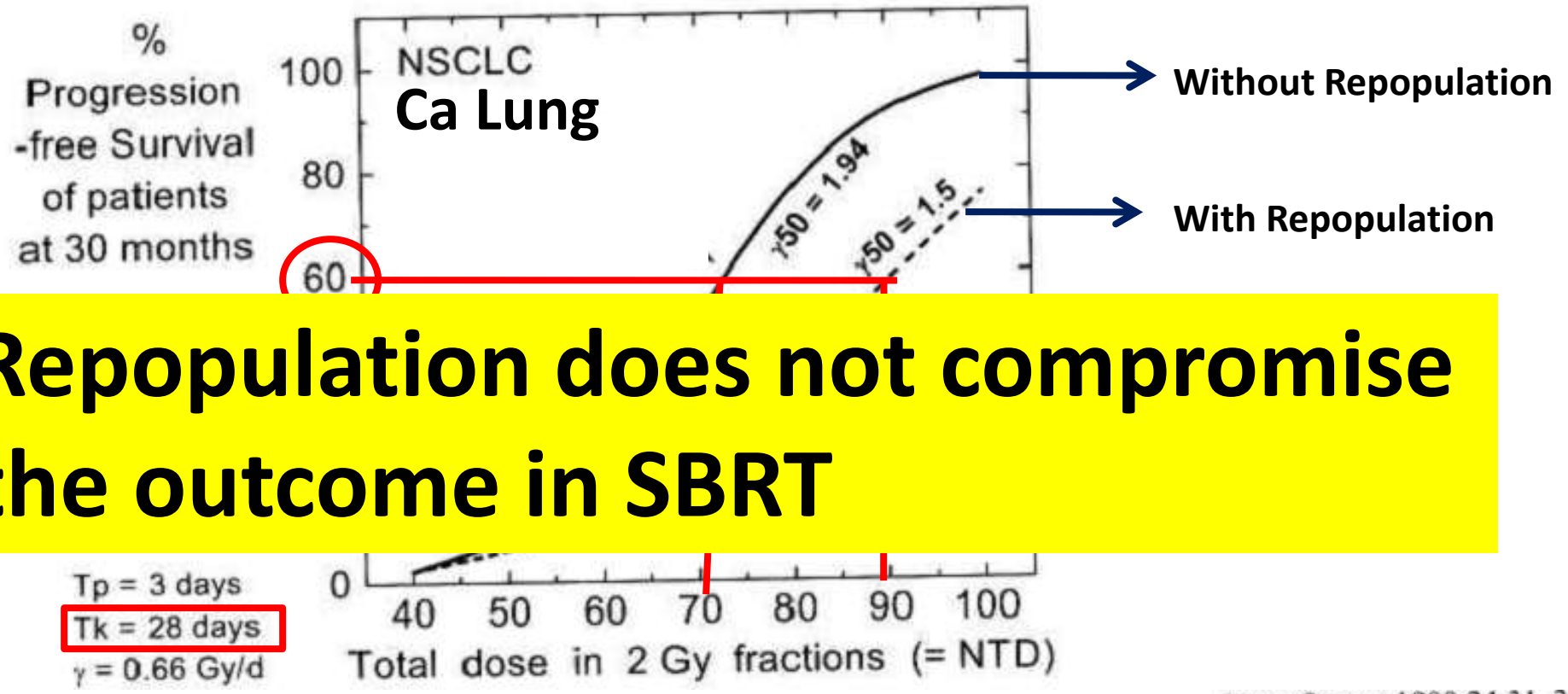
REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 22 (2017) 86–95

REPOPULATION

Repopulation(NSCLC)

Repopulation in NSCLC starts at 28 days

Most of the SBRT lung regimen are completed by two weeks



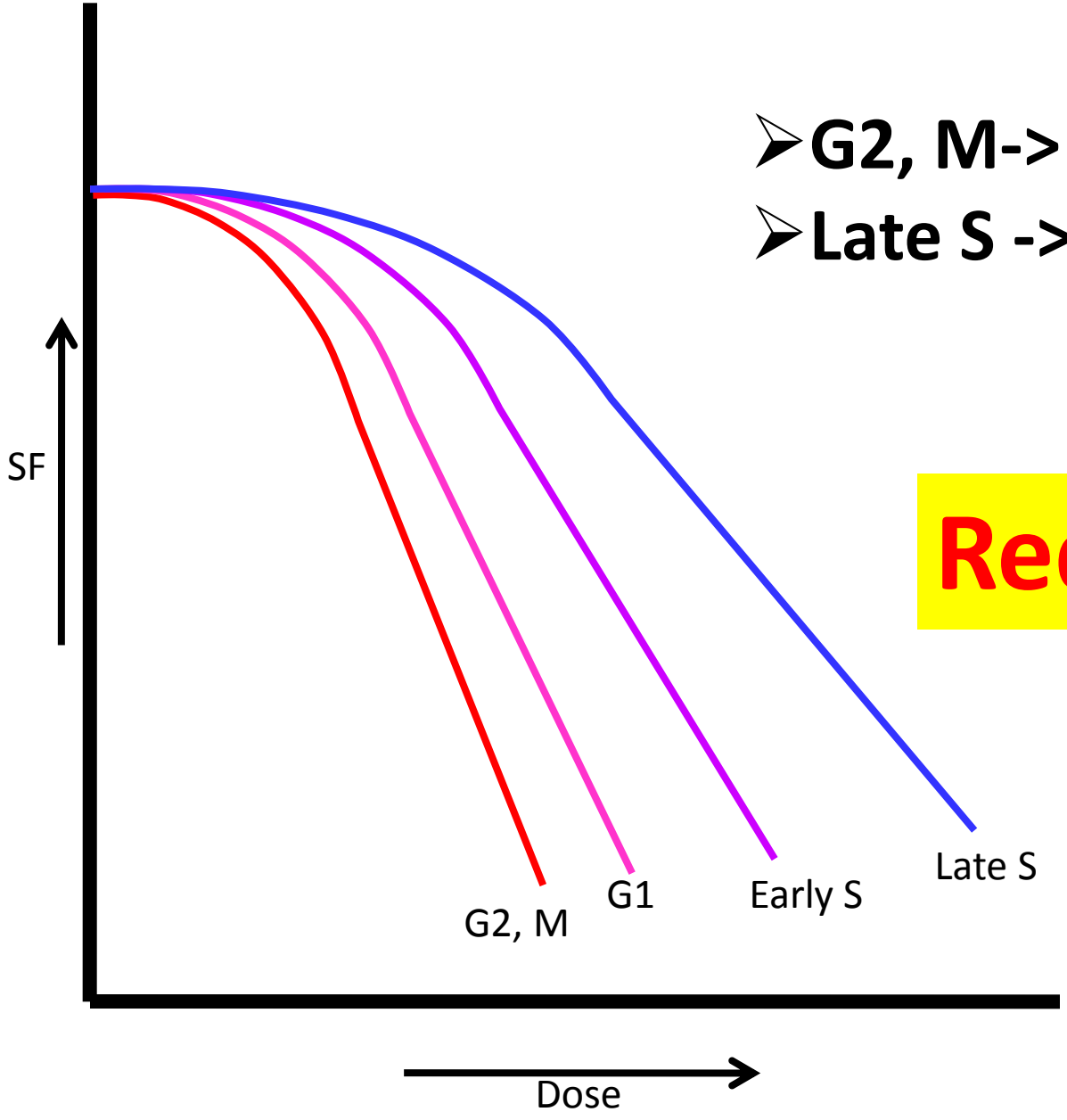
Repopulation does not compromise the outcome in SBRT

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

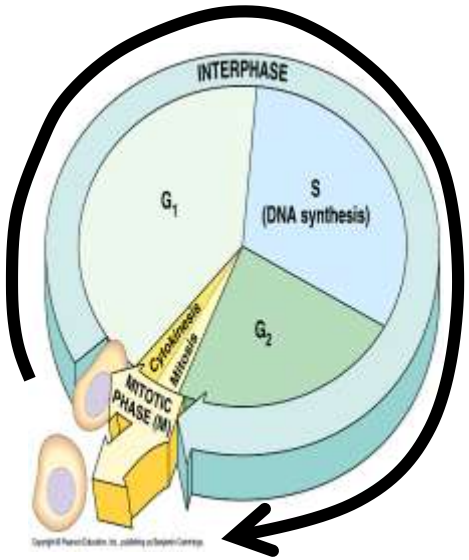
REDISTRIBUTION

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

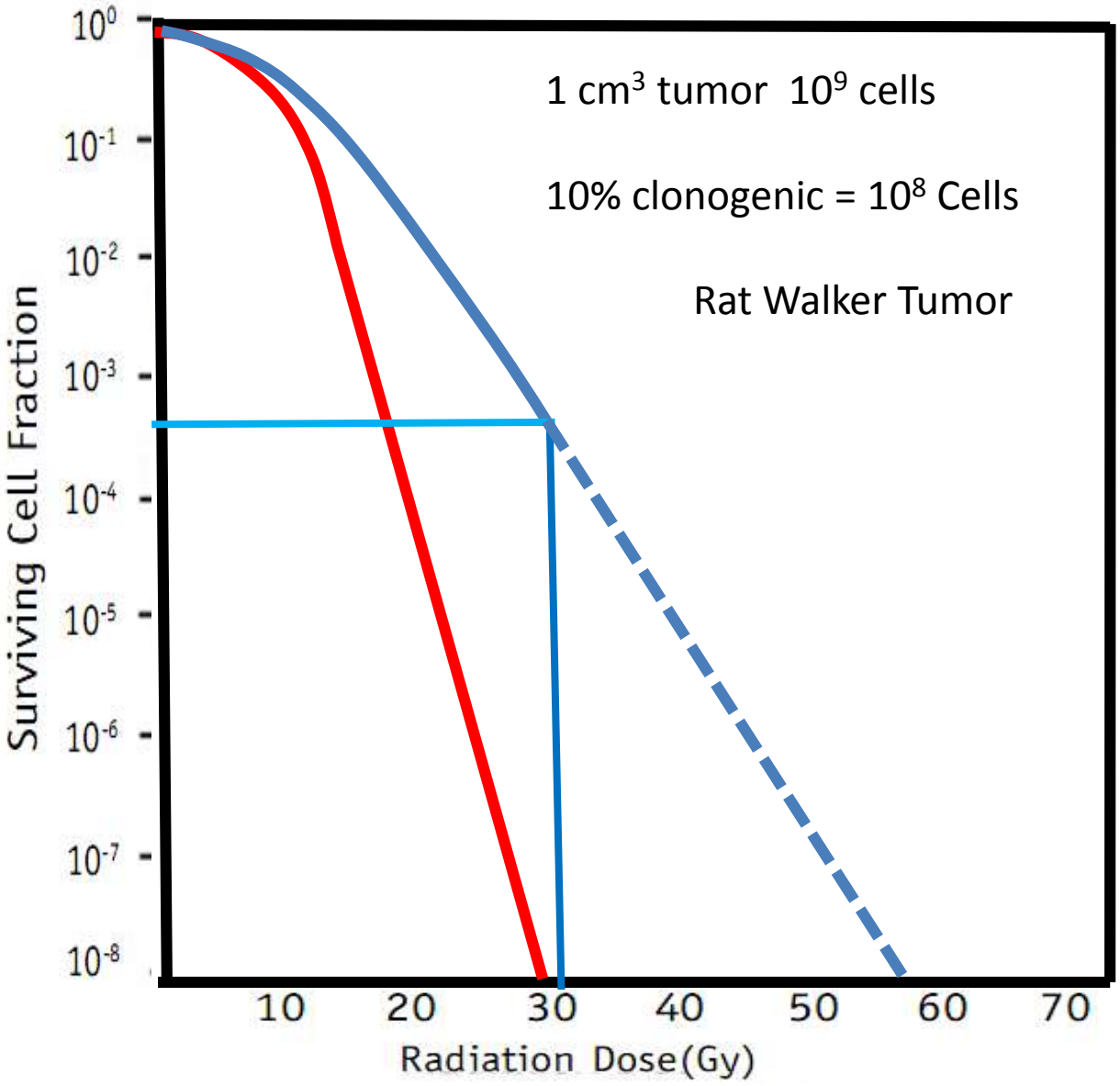
- There is 5 fold difference in survival after 200 rad

D_0 is 2 Gy

D_0 is 10 Gy

SRS/SRT Dose is > 12 Gy

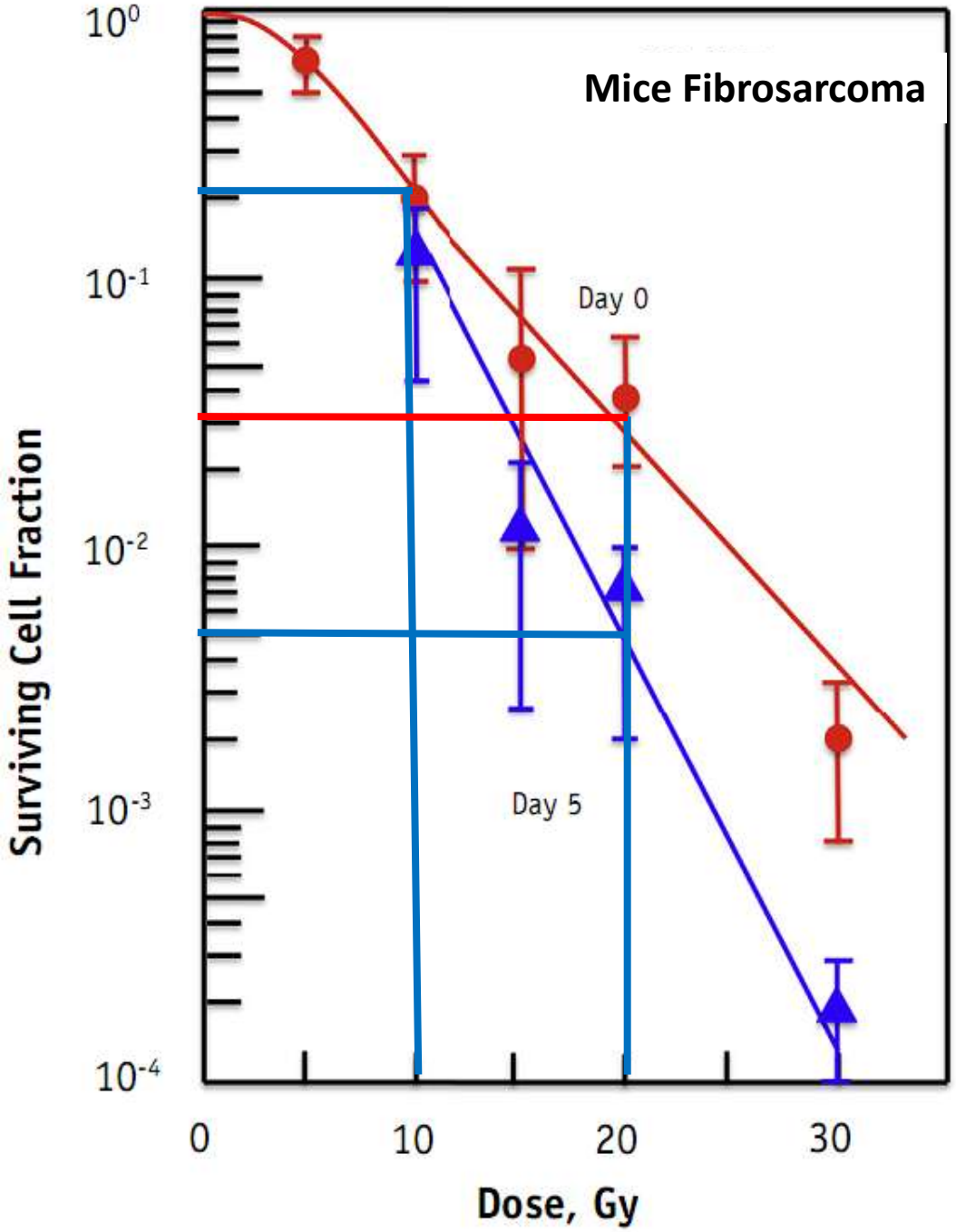
New Biology of High dose RT



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**

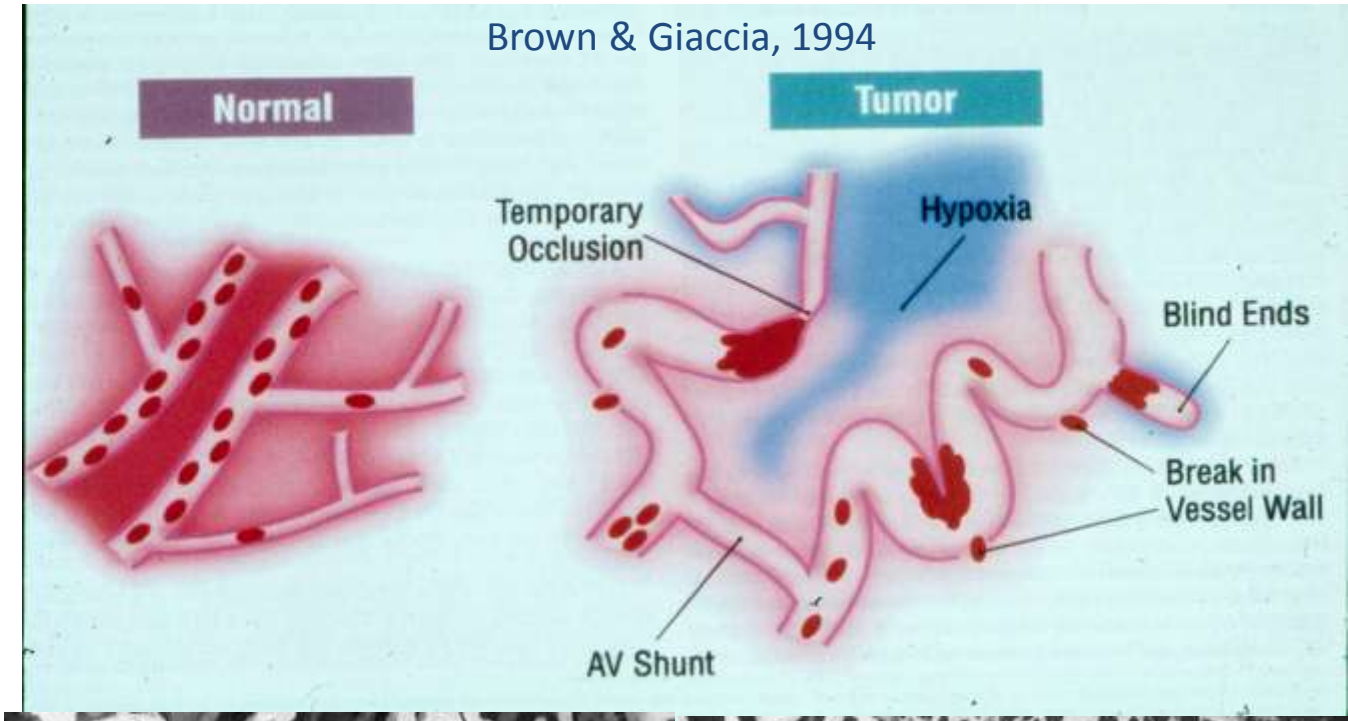
International Journal of Radiation Oncology, Biology, Physics Vol. 110Issue 1p21–34Published online: March 2, 2019

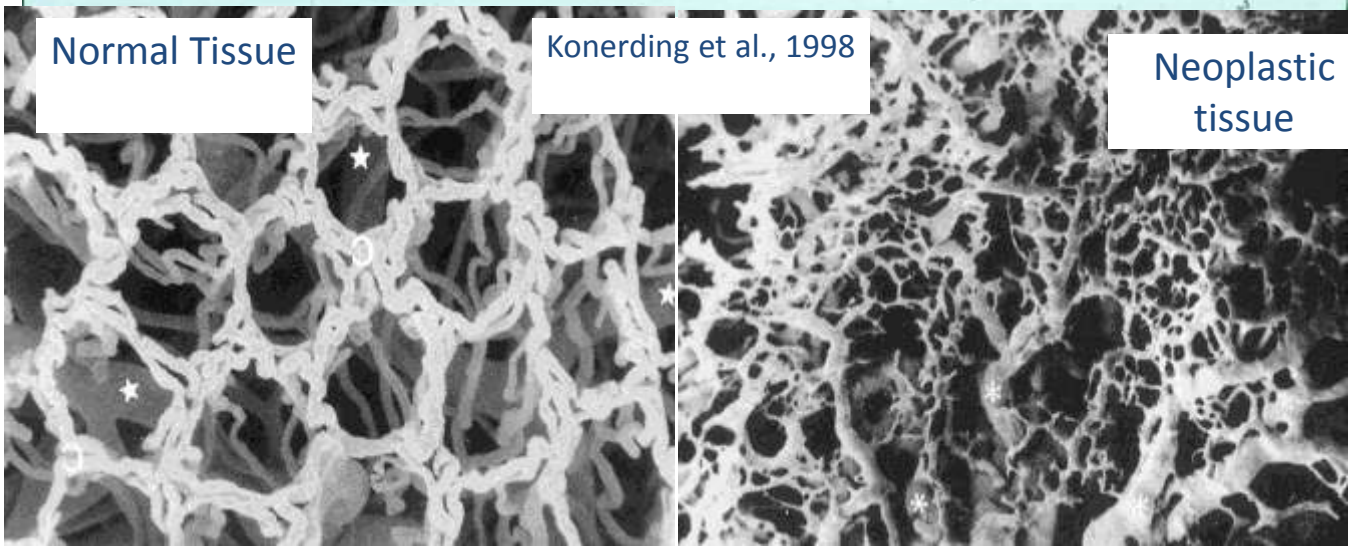
New Biology of High dose RT

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

Tumor Vasculature

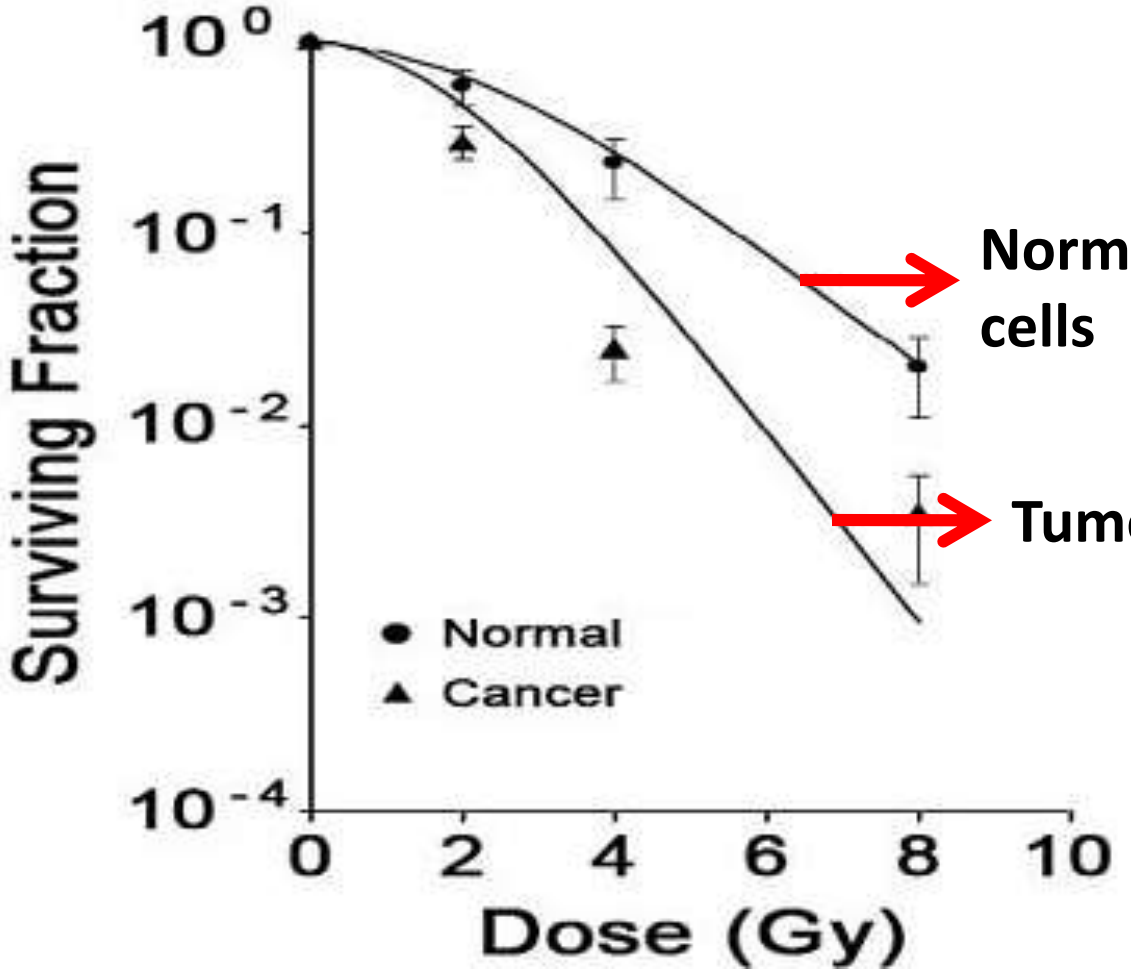
- The vascular network that develops in tumors is structurally abnormal
- Vessels are dilated, tortuous, elongated, with A-V shunts and blind ends
- The basement membrane is thin





Pre clinical Evidence

Tumor vasculature is more sensitive

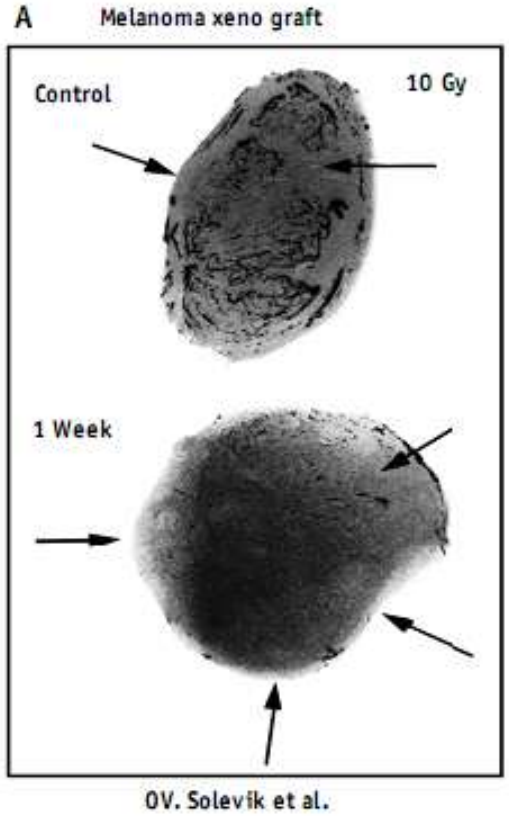


Normal tissue endothelial cells

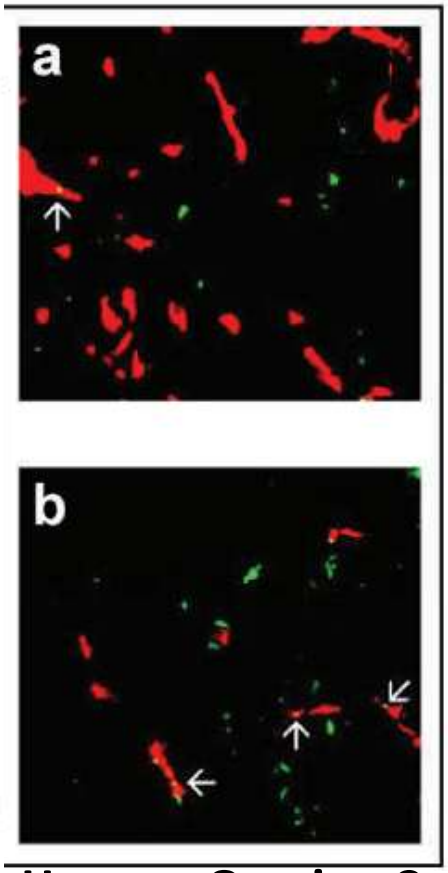
Tumor endothelial cells

Heon Joo Park,[a,b] Robert J. Griffin,[1] RADIATION RESEARCH 177, 311–327 (2012)

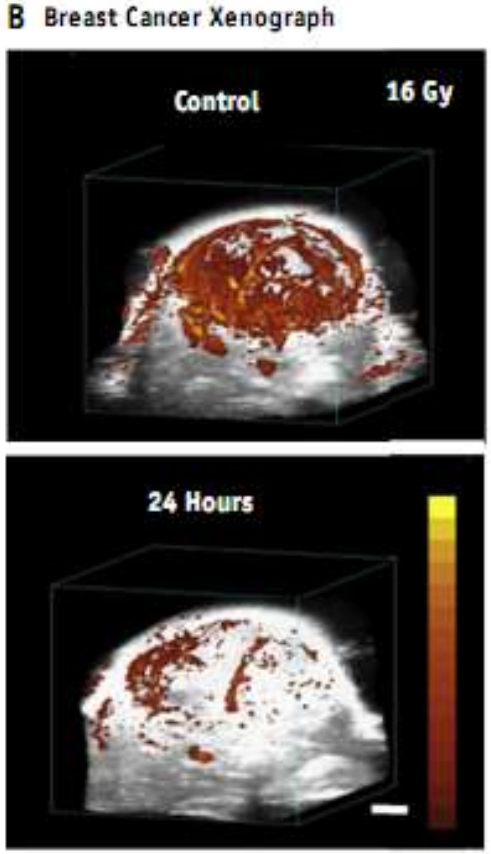
Vascular density in experimental tumor irradiated with high dose per fraction



OV. Solevik et al.



Human Ovarian Ca



A. Kaffas et al.

Pre RT

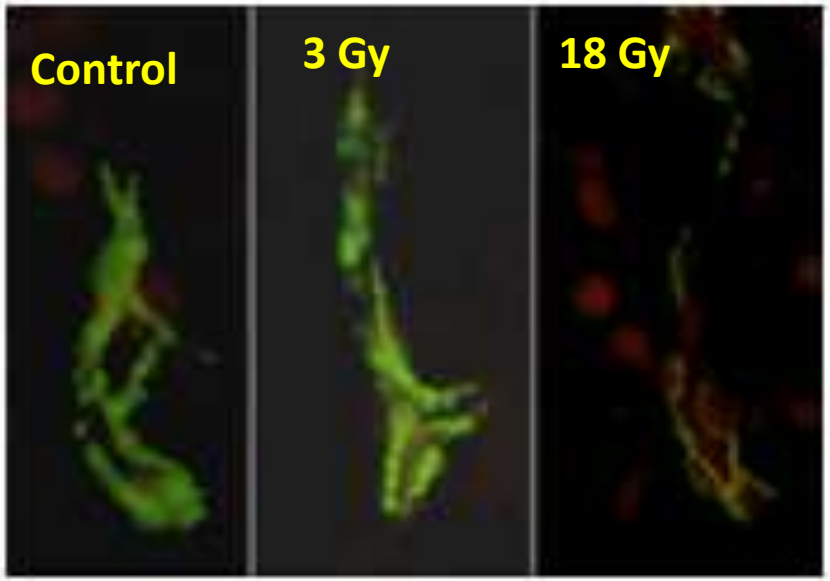
High dose RT

Post RT

Pre clinical Evidence

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

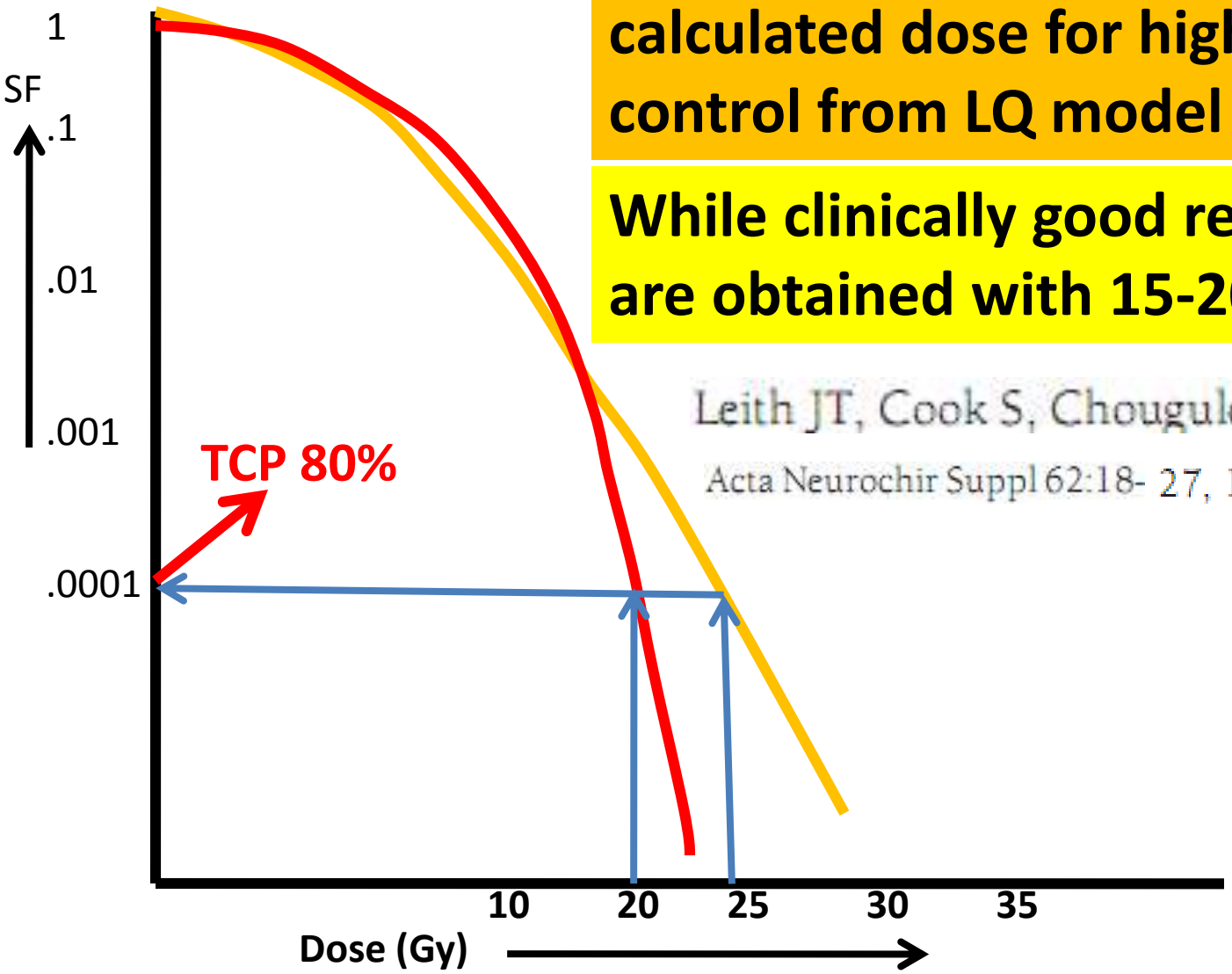
Tumor endothelial apoptosis after 3 Gy or 18 Gy dingle fraction. Larue et al, Rad Res Mtg, 2008 (abst)



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

Clinical Evidence

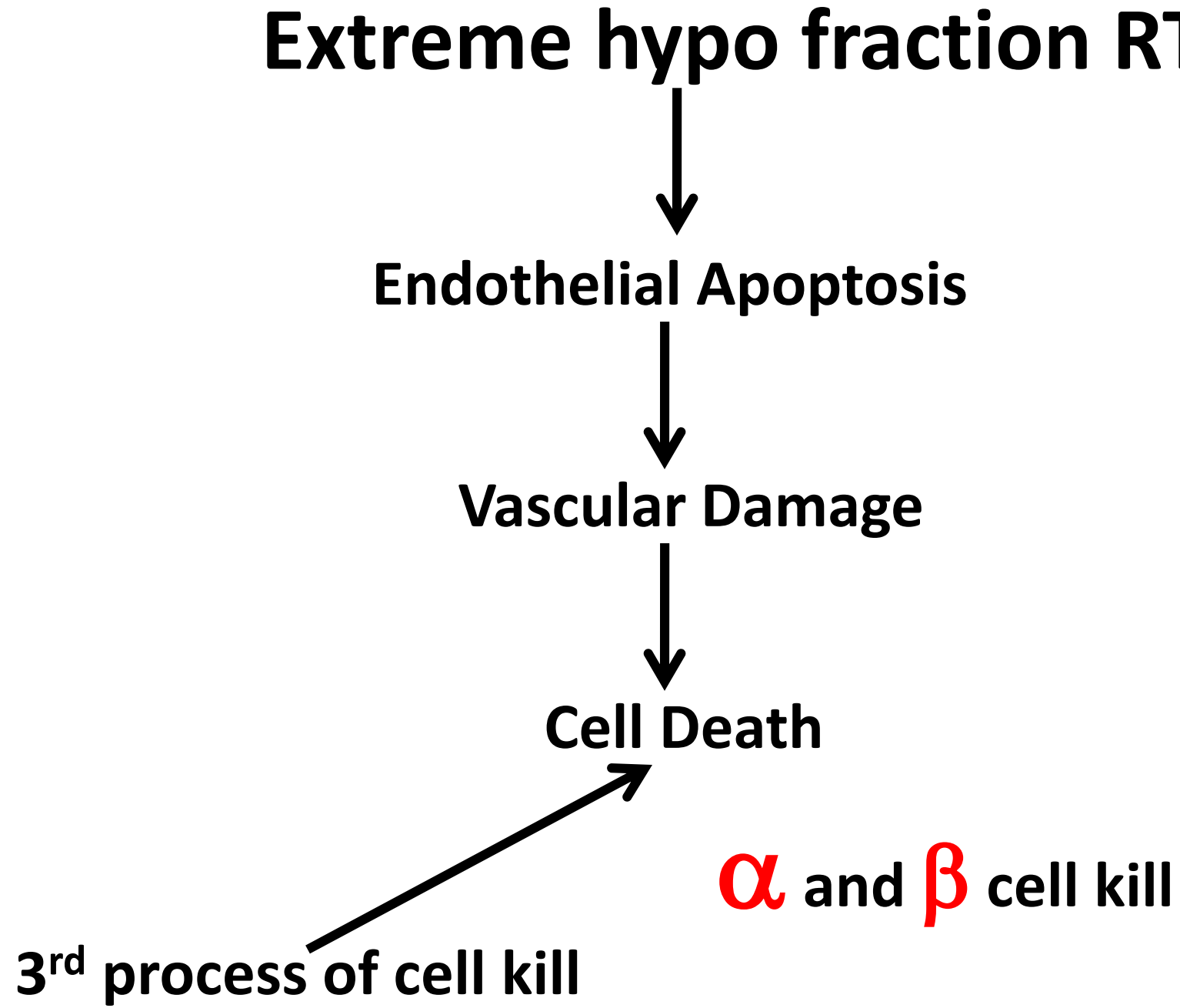
SRS Metastatic Brain Lesions



calculated dose for high tumor control from LQ model is 25-35 Gy.

While clinically good results are obtained with 15-20 Gy.

Leith JT, Cook S, Chougule P, et al:
Acta Neurochir Suppl 62:18- 27, 1994


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

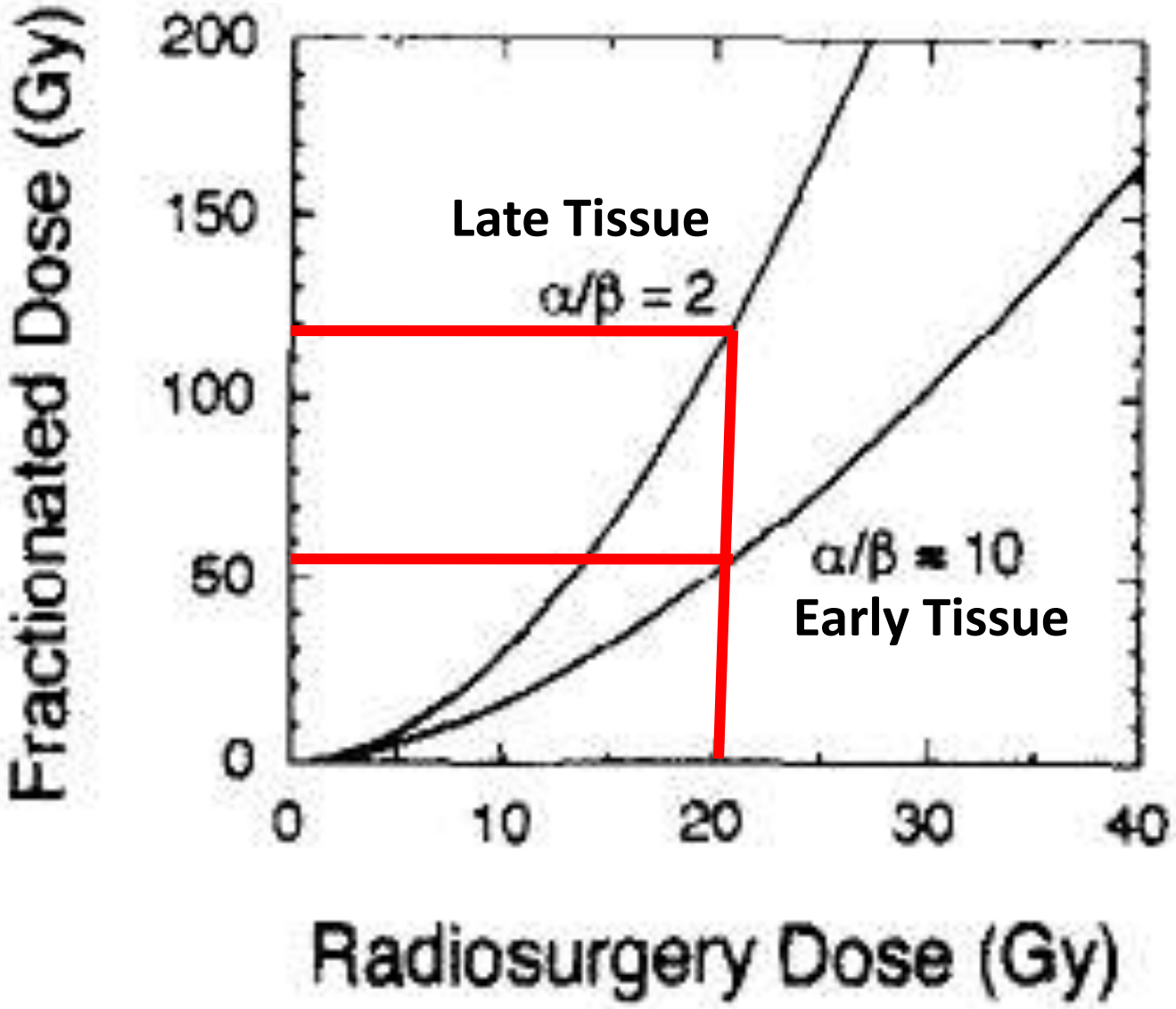
Cell death at High Dose RT

- **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.**

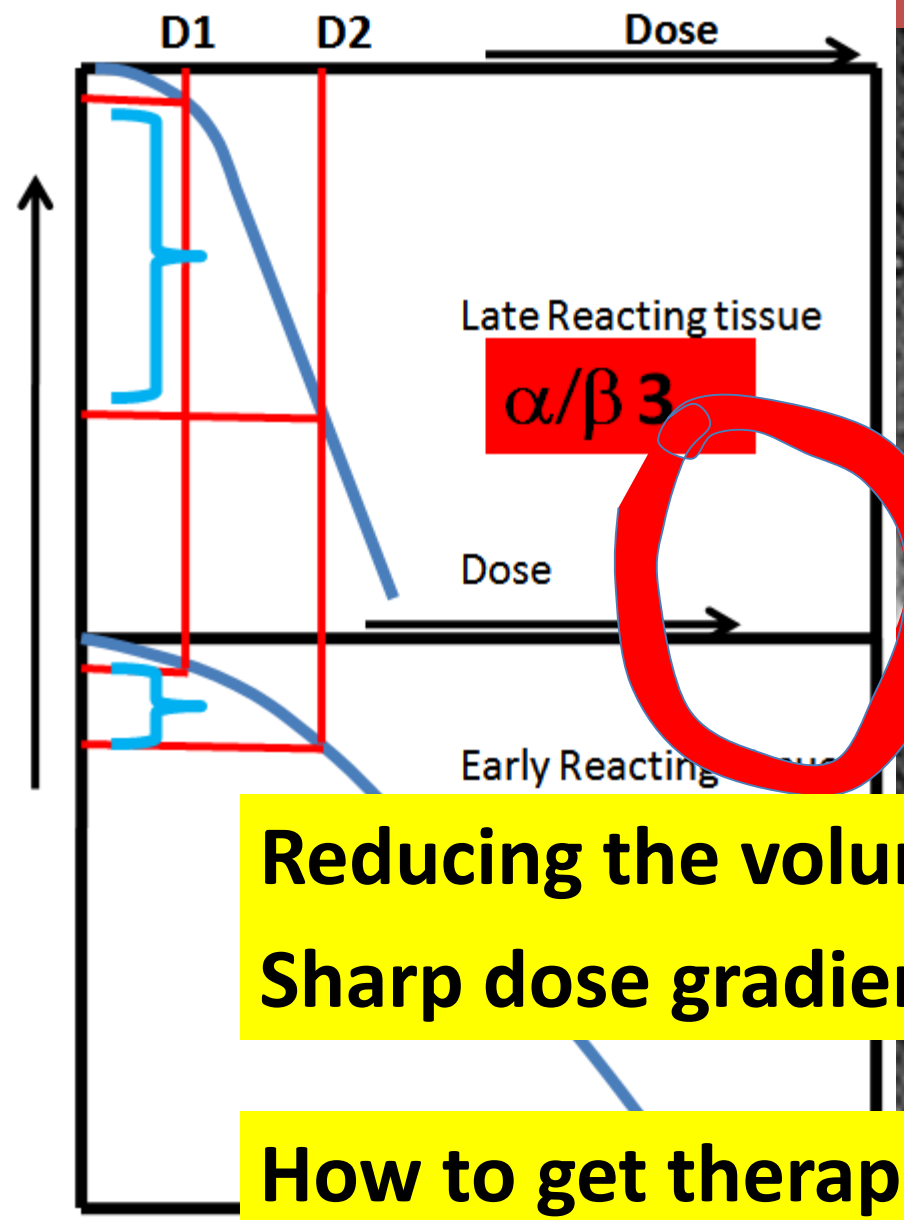
Intracranial SRS

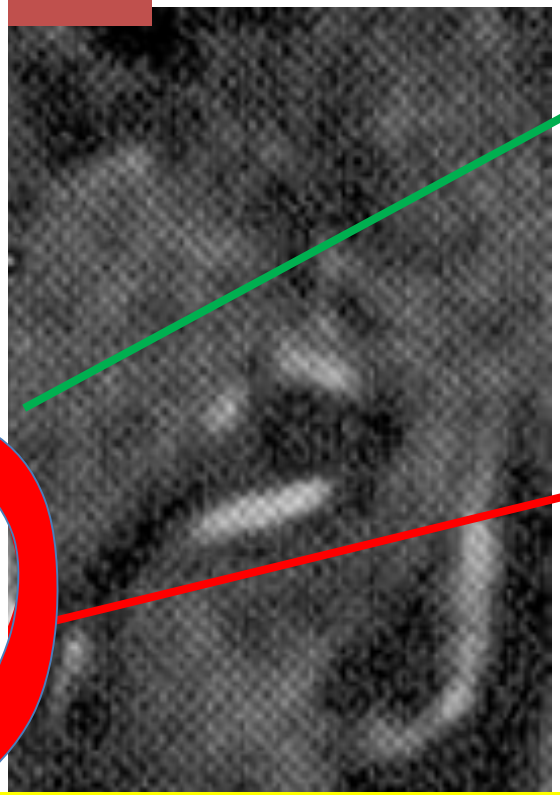
Radio surgery dose vs. fractionated total dose at 2 Gy per Fx

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



Meningioma





Late Reacting
Normal cells

α/β 3

Late Reacting
abnormal cells

α/β 3

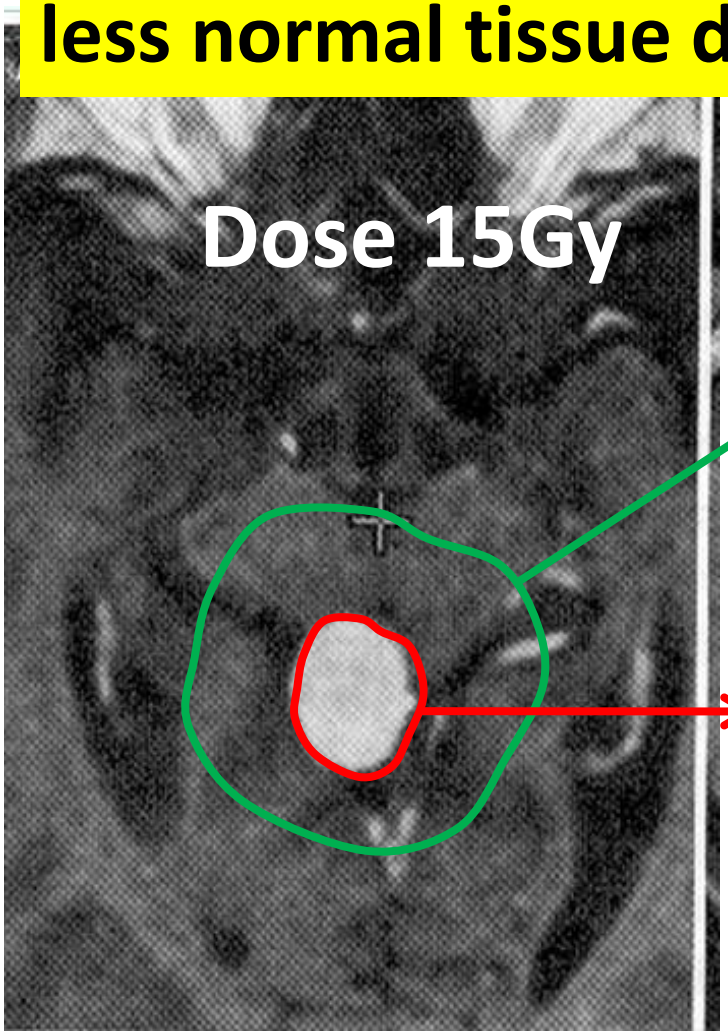
Reducing the volume of Red Shell

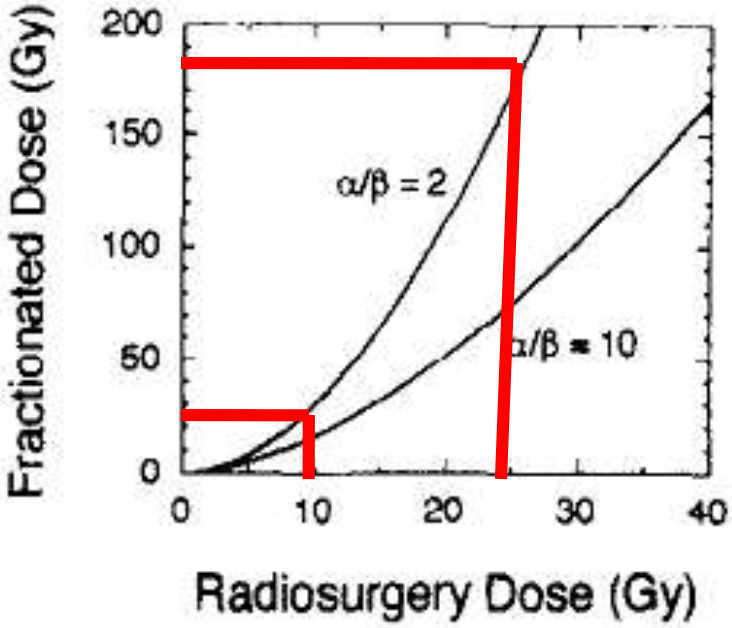
Sharp dose gradient

How to get therapeutic advangae?

Meningioma

Therapeutic Advantage with high tumor dose and less normal tissue doses





Late Reacting Normal cells

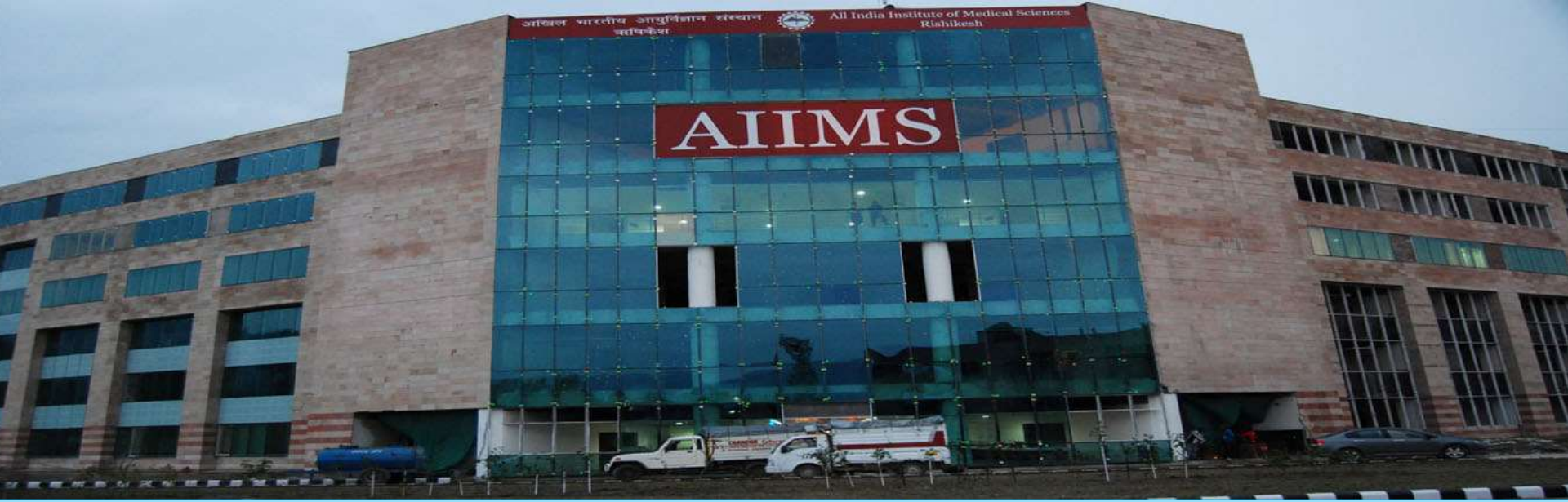
Late Reacting abnormal cells

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

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.


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

Thanks


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