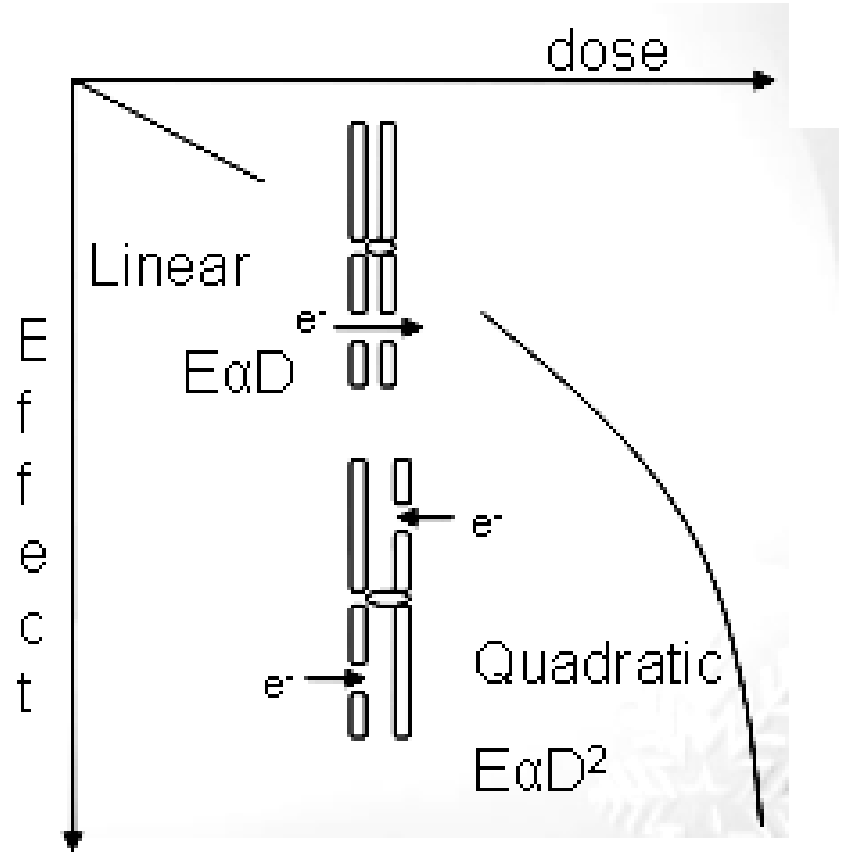
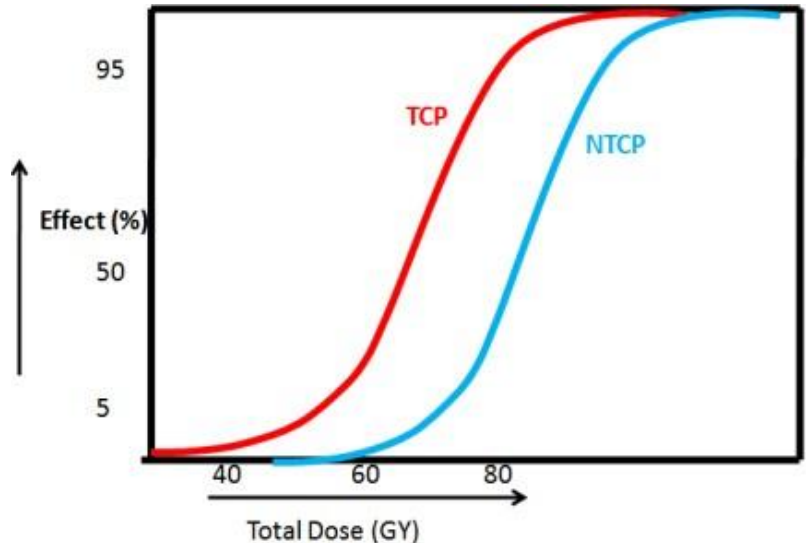
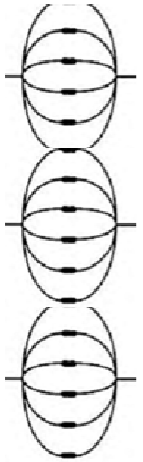
Radiobiology of Normal Tissue Toxicities and its clinical correlation





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.



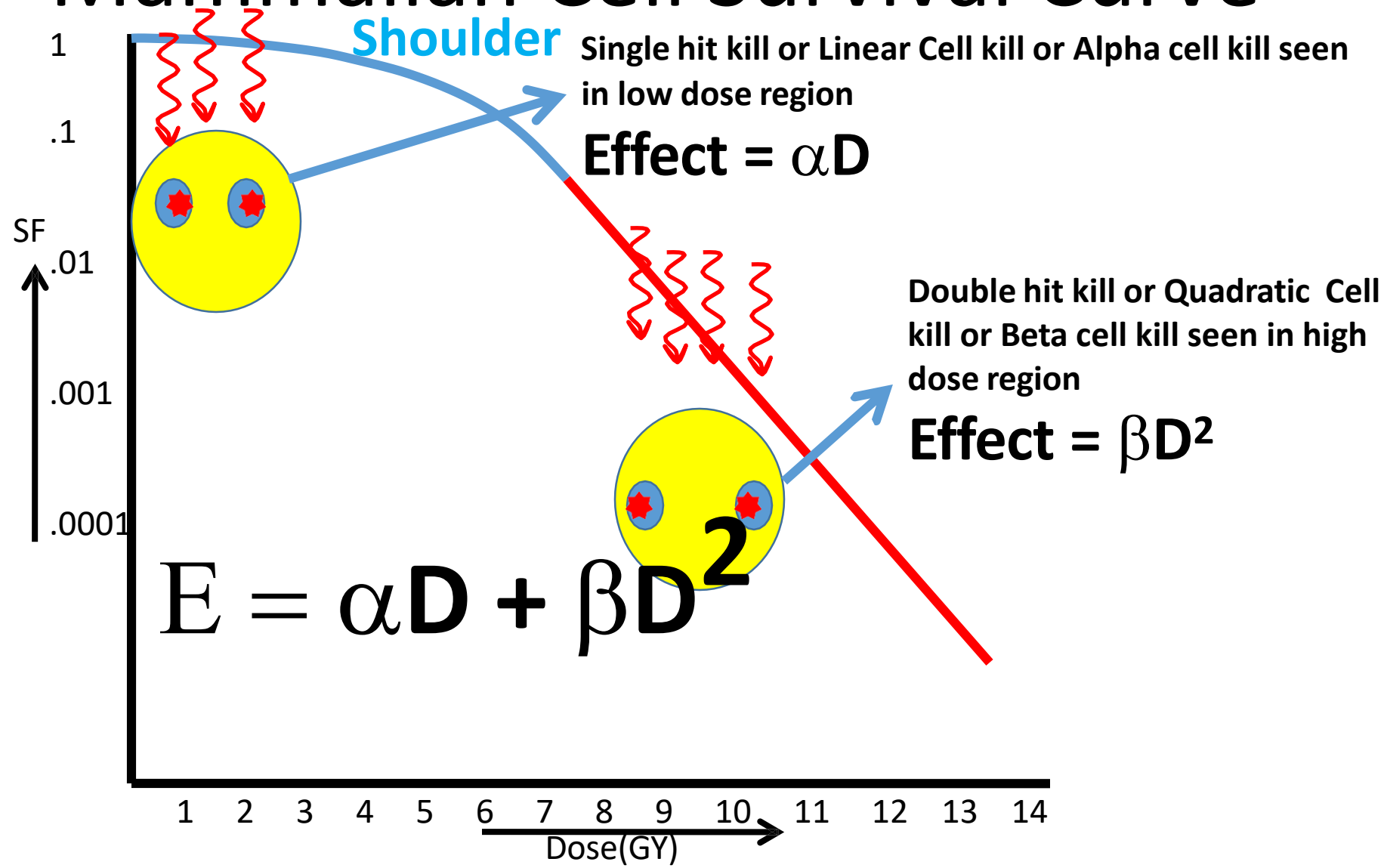
Parallel like kidney

Volume of the organ is important

Prof Manoj Gupta
Head, Radiaiton Oncoloogy
AIIMS Rishikesh

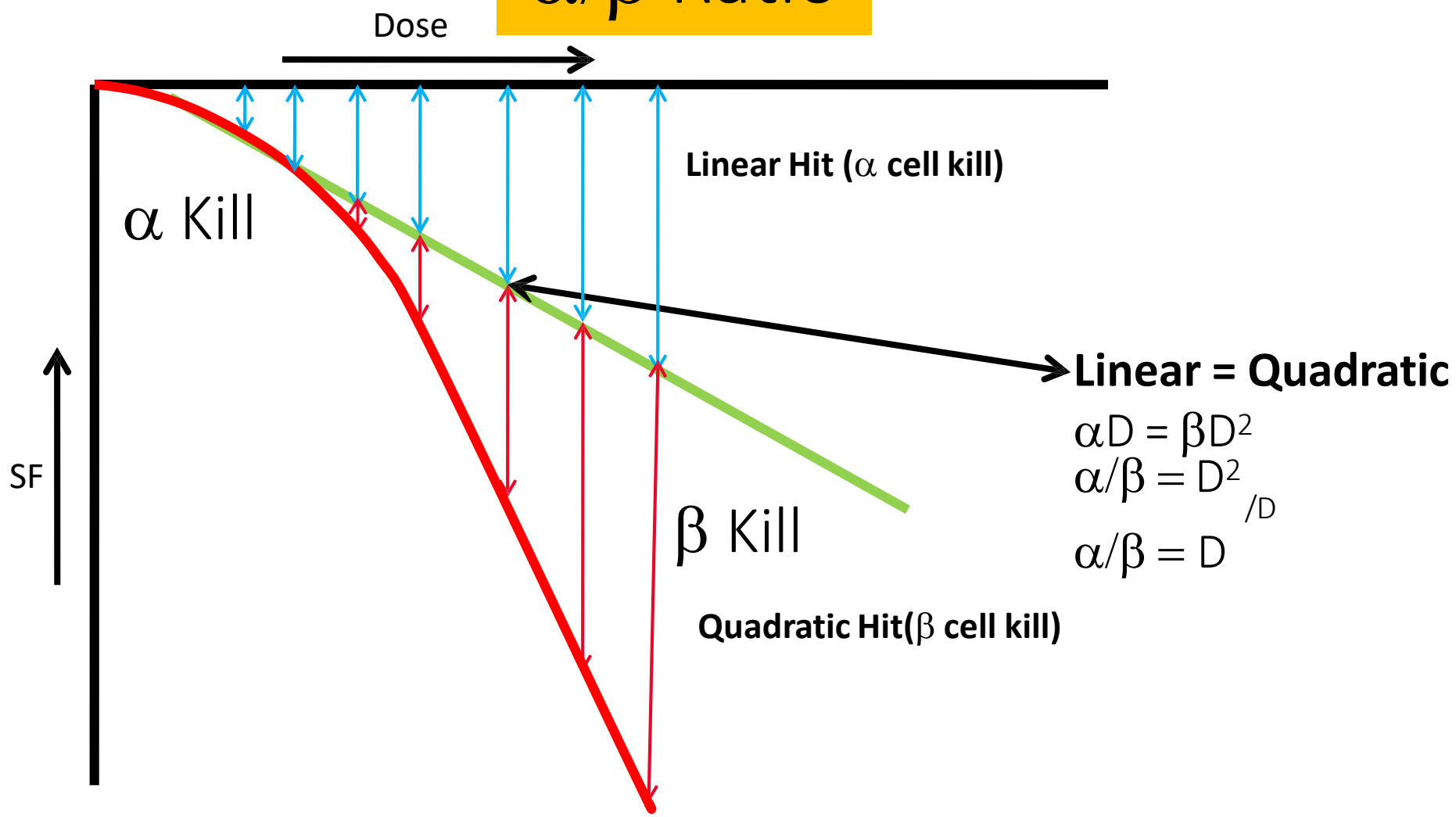
ICRO PG April 2024
Bhopal

Mammalian Cell Survival Curve



Linear-Quadratic Model

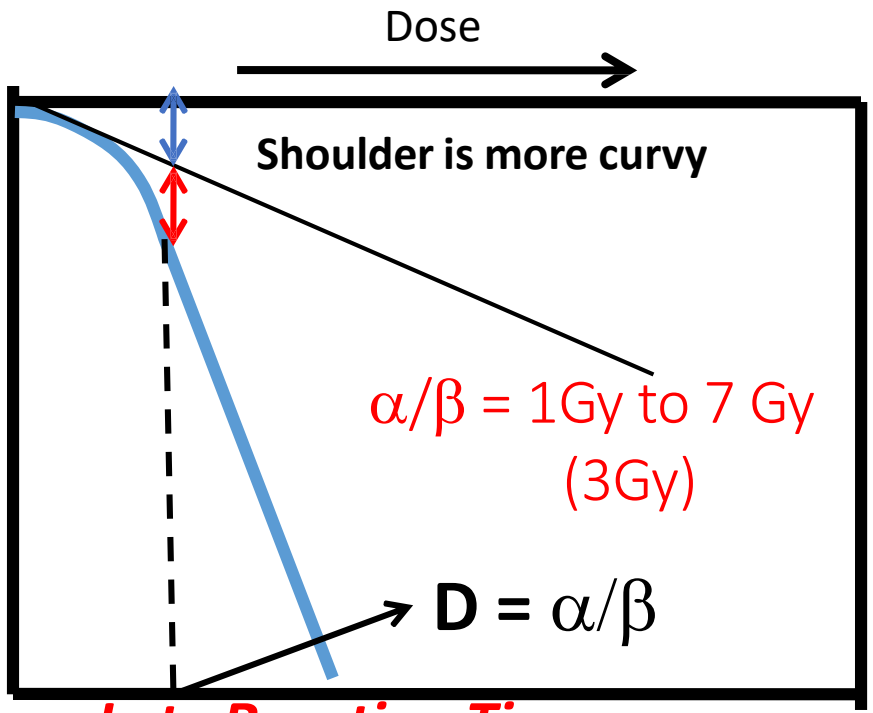
α/β Ratio

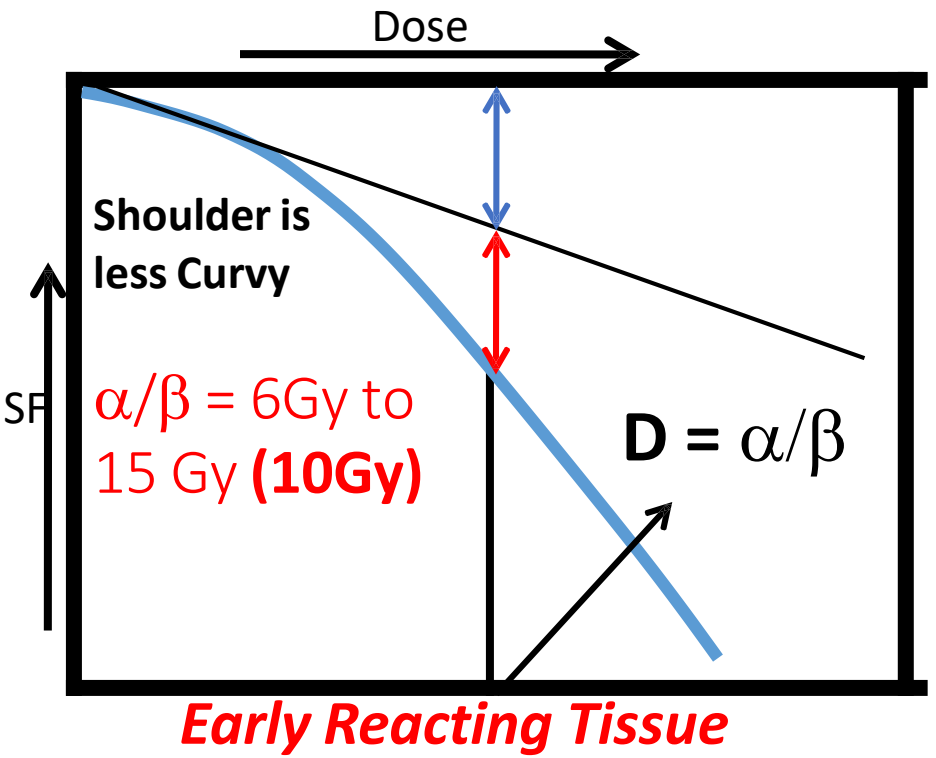


➢So α/β can be defined as the dose at which contribution by single hit (Linear) kill becomes equal to double hit (Quadratic) kill.

α/β Ratio **defines "curviness" of survival curve**

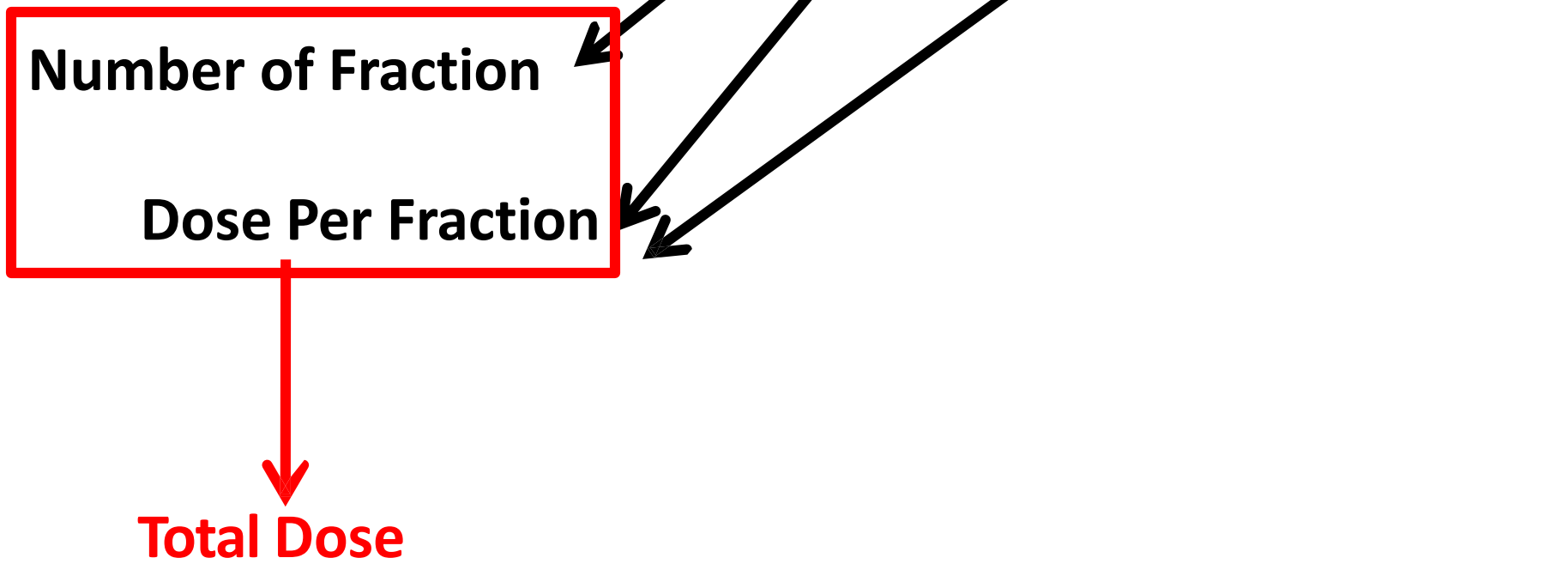
Based on α/β ratio, the body tissues have been divided into two category.





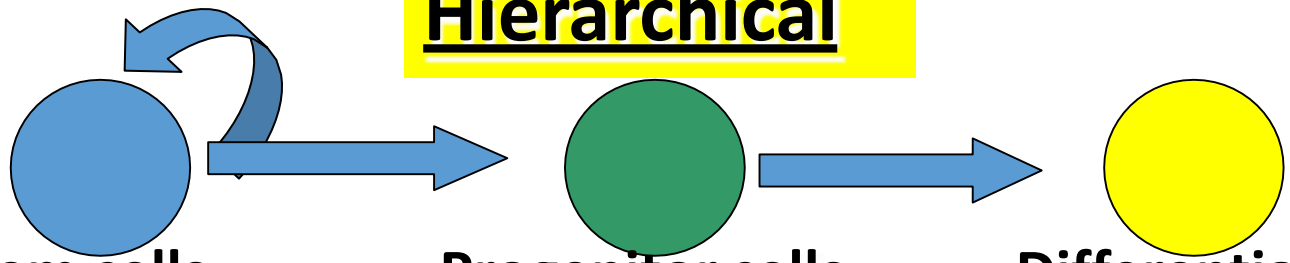
Biological Effective Dose (BED)

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



Types of Normal Tissues

Hierarchical



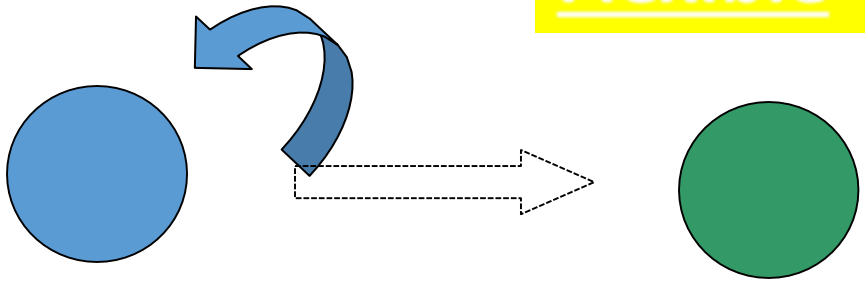
Stem cells
Low proliferation
Non-Functional

Progenitor cells
Rapid proliferation
Non-Functional

Differentiated cells
No proliferation
Functional

- Respond rapidly to irradiation.
- Responsible for early radiation reactions.

Flexible



- Respond slowly to irradiation.
- Responsible for late radiation reactions.

Stem cells
Low proliferation
Non-Functional

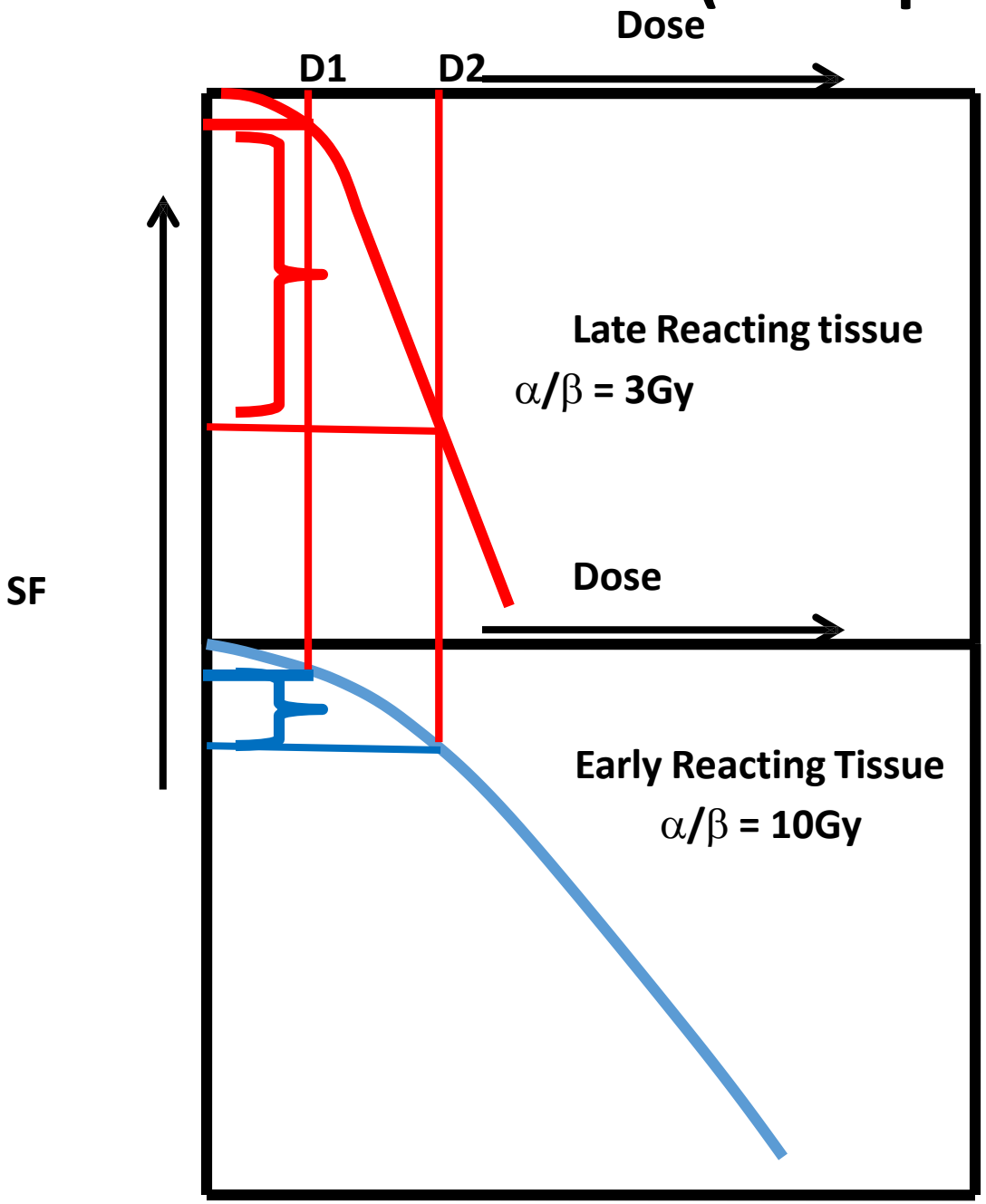
Progenitor/functional cells
Slow proliferation but Functional
Proliferate on Demand

Factors affecting Normal Tissue Injury

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

Fraction size
or
dose per fraction

Fraction size (Dose per fraction)

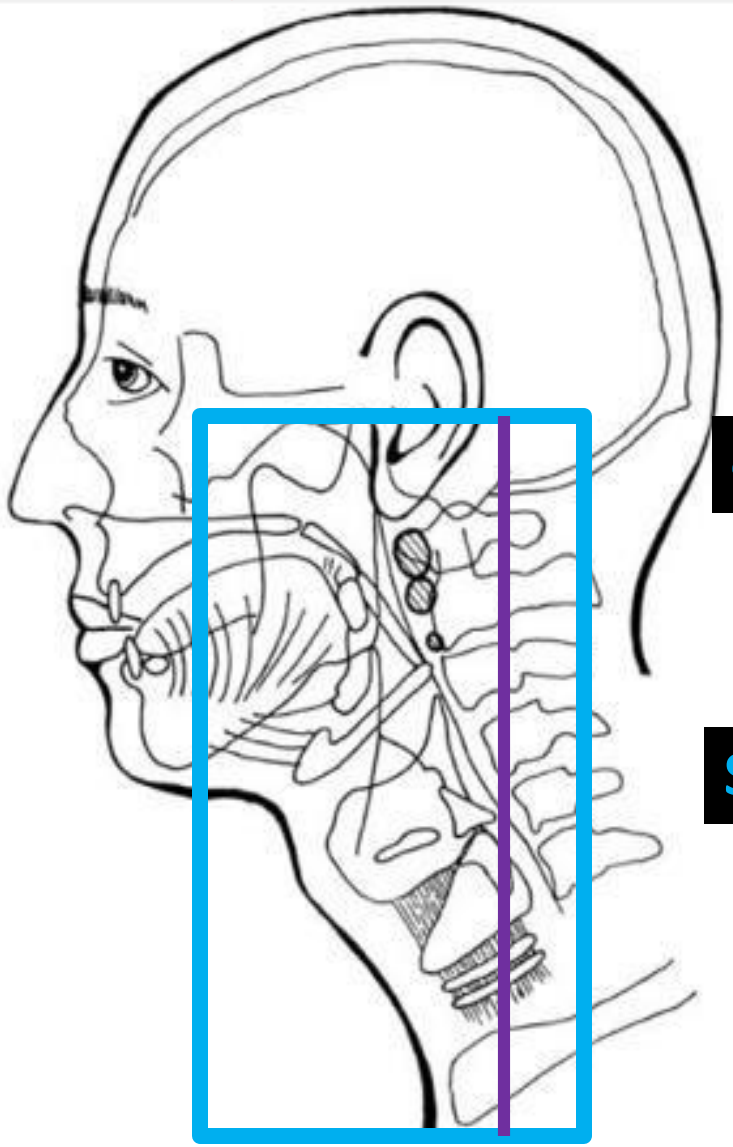


Increase in dose per fraction damages late reacting tissue more than early reacting tissues

Reducing the dose per fraction will spare the late reacting tissue (Spinal Cord)

How it helps in Clinical Setting?

1. Non IMRT Plan by Shrinking field technique.
2. IMRT Plan



Irradiation with IMRT is better than non-IMRT plan

46Gy/23F → 2Gy/F BED = 77 (Tolerance)

IMRT Plan 70 Gy/35

Re-irradiation not possible

Spinal Cord 46/35F → 1.31 Gy/F

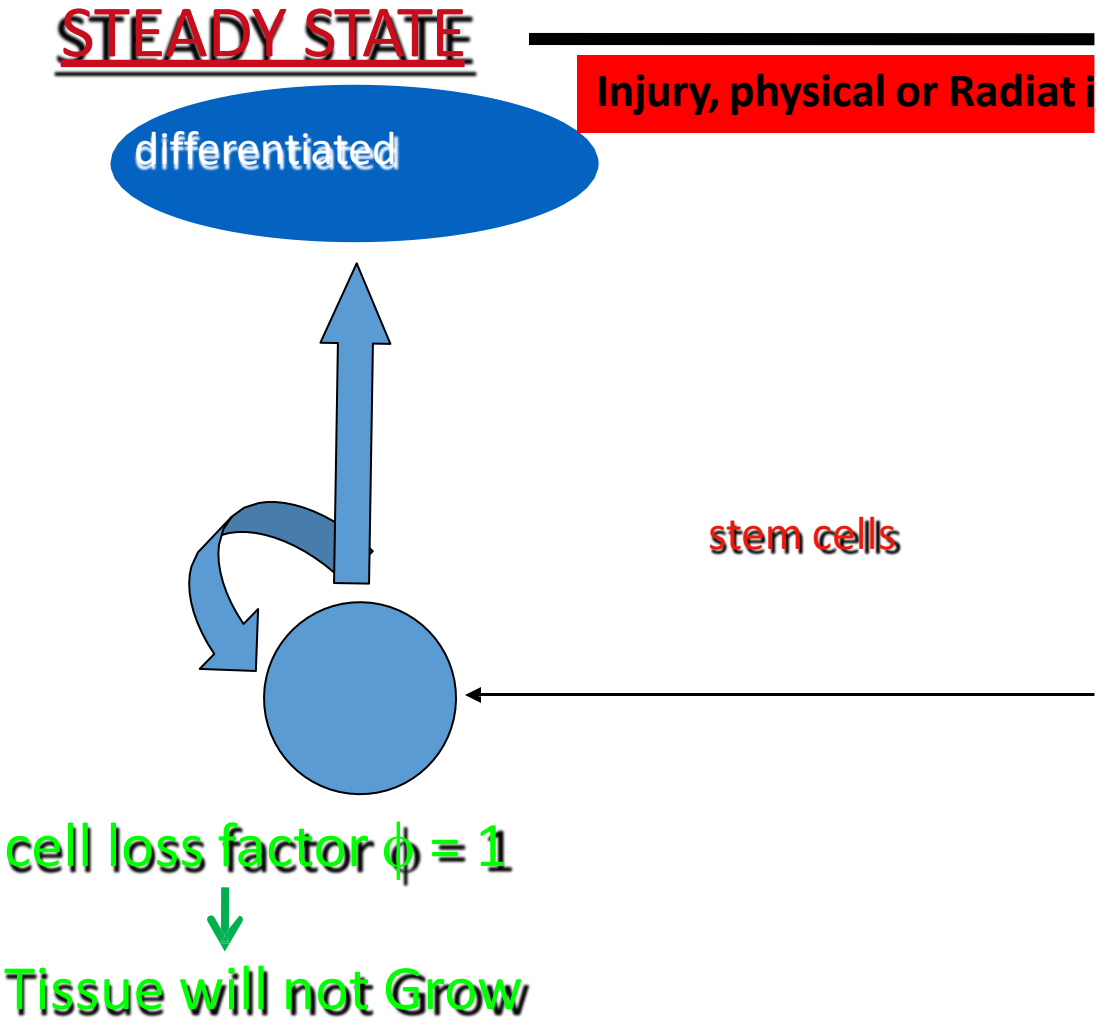
BED = 66 (Less than Tolerance)

Re-irradiation is possible

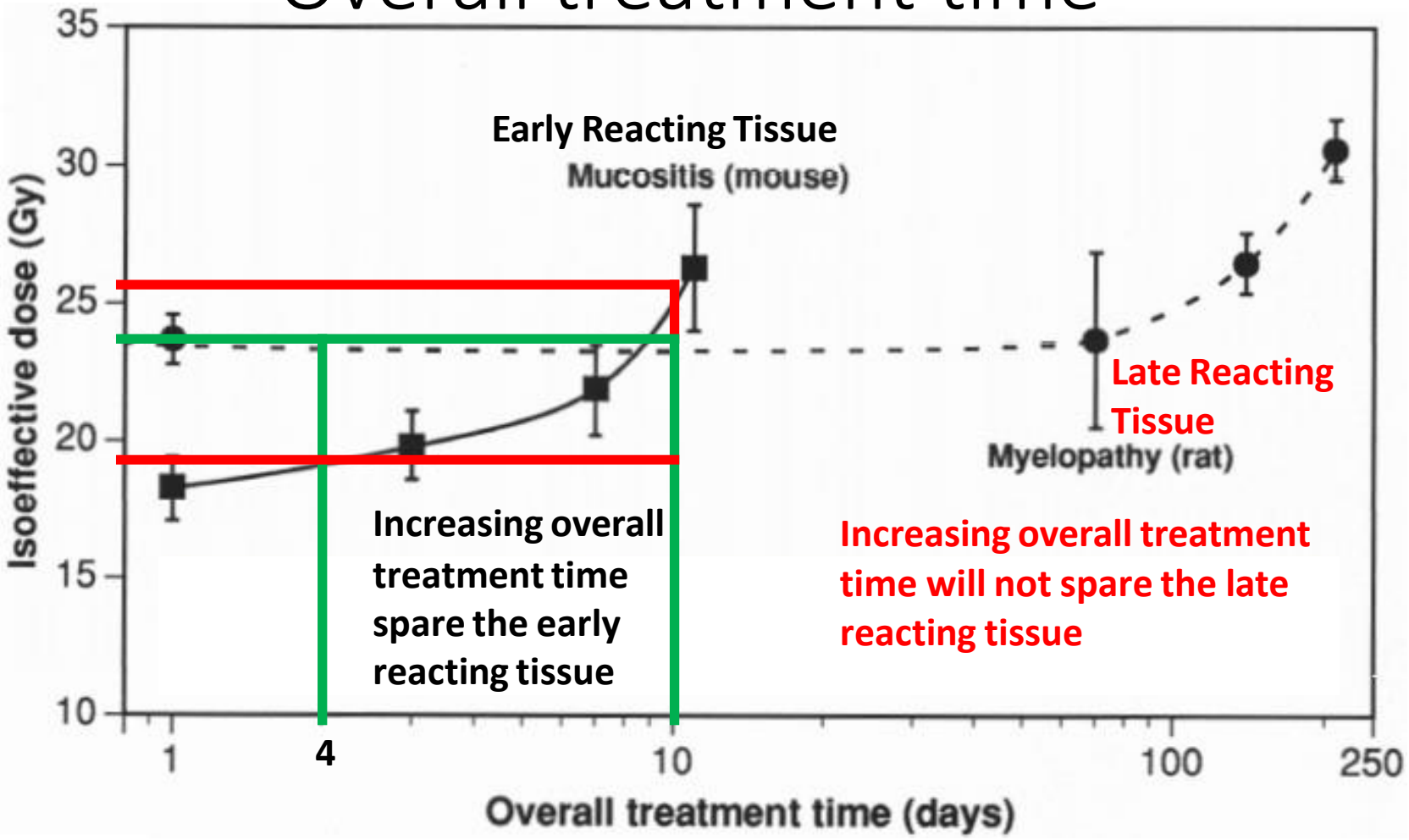
Overall treatment time (Accelerated repopulation)

Overall treatment time

Overall treatment time affects normal tissue injury because of Accelerated repopulation (Regeneration)



Overall treatment time



- During Radiation Treatment, the regeneration only seen in early reacting tissues and not in late reacting tissue.

van der Kogel *et al*, 1982; Dörr & Kummermehr, 1990

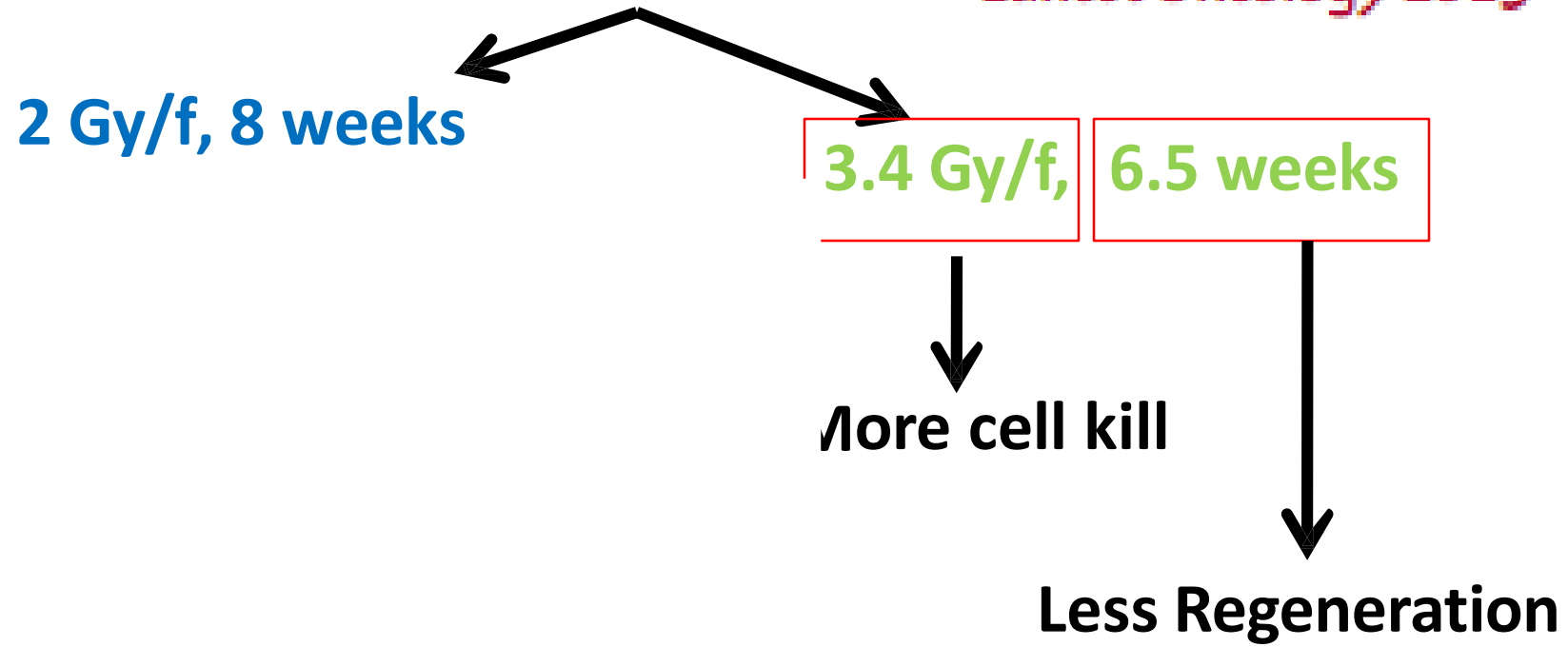
Clinical Relevance

- protracting overall treatment time beyond the conventional 6 weeks may result in sparing of acute reaction(but tumors may also be spared)
    - treatment time do not have any effects on late reactions.
- decreasing overall treatment time to less than the conventional 6 weeks may result in more acute normal tissue reactions

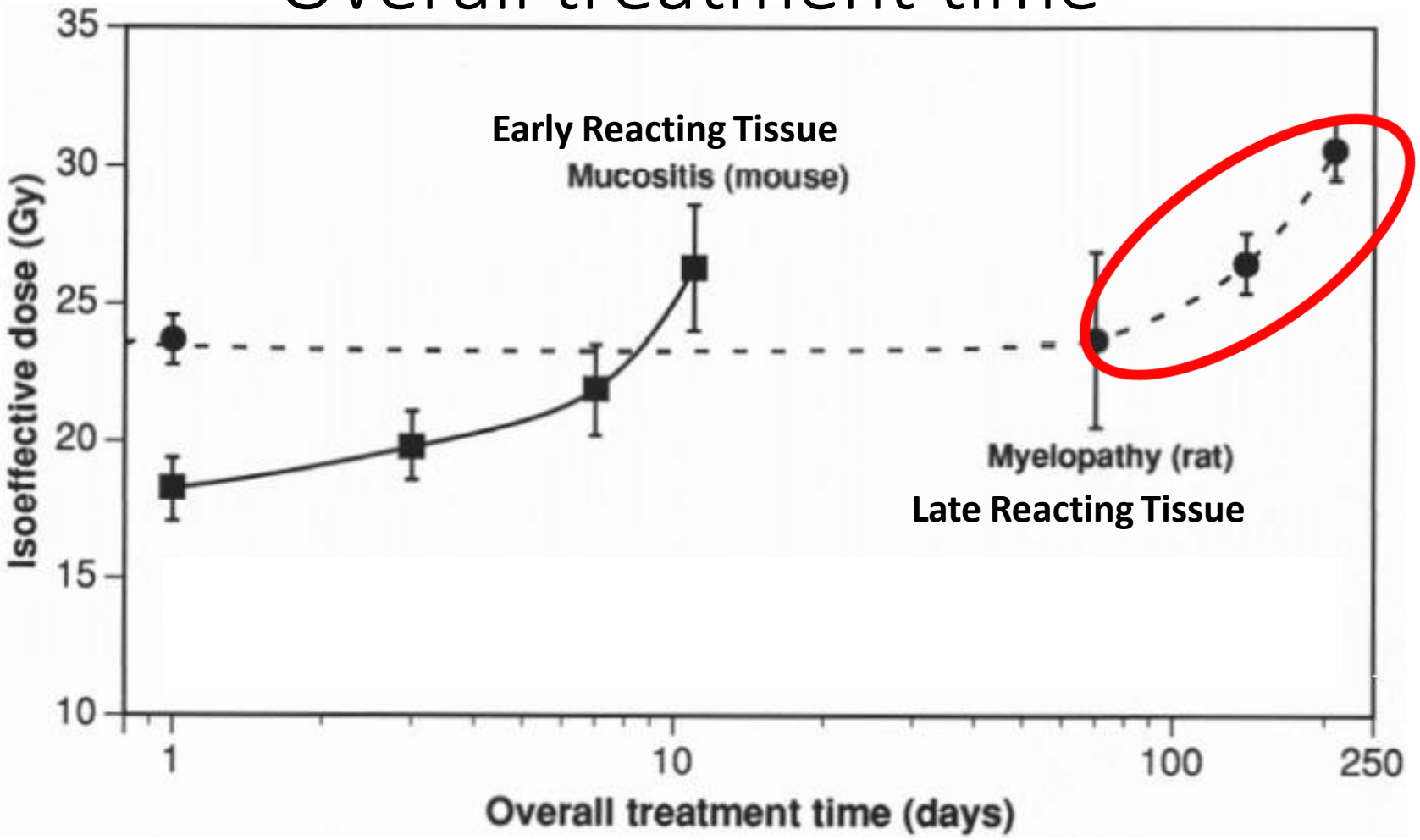
Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial

Shafak Aluwini, Floris Pos, Erik Schimmel, Emile van Lin, Stijn Krol, Peter Paul van der Toorn, Hanja de Jager, Maarten Dirkx, Wendimagegn Ghidey Alemayehu, Ben Heijmen, Luca Incrocci

Lancet Oncology 2015



Overall treatment time



Regeneration/repopulation in late Reacting tissue eg Spinal cord

van der Kogel *et al*, 1982; Dörr & Kummermehr, 1990

Recovery from Radiation Injury in Spinal Cord

- Spinal Cord remember the irradiated dose.

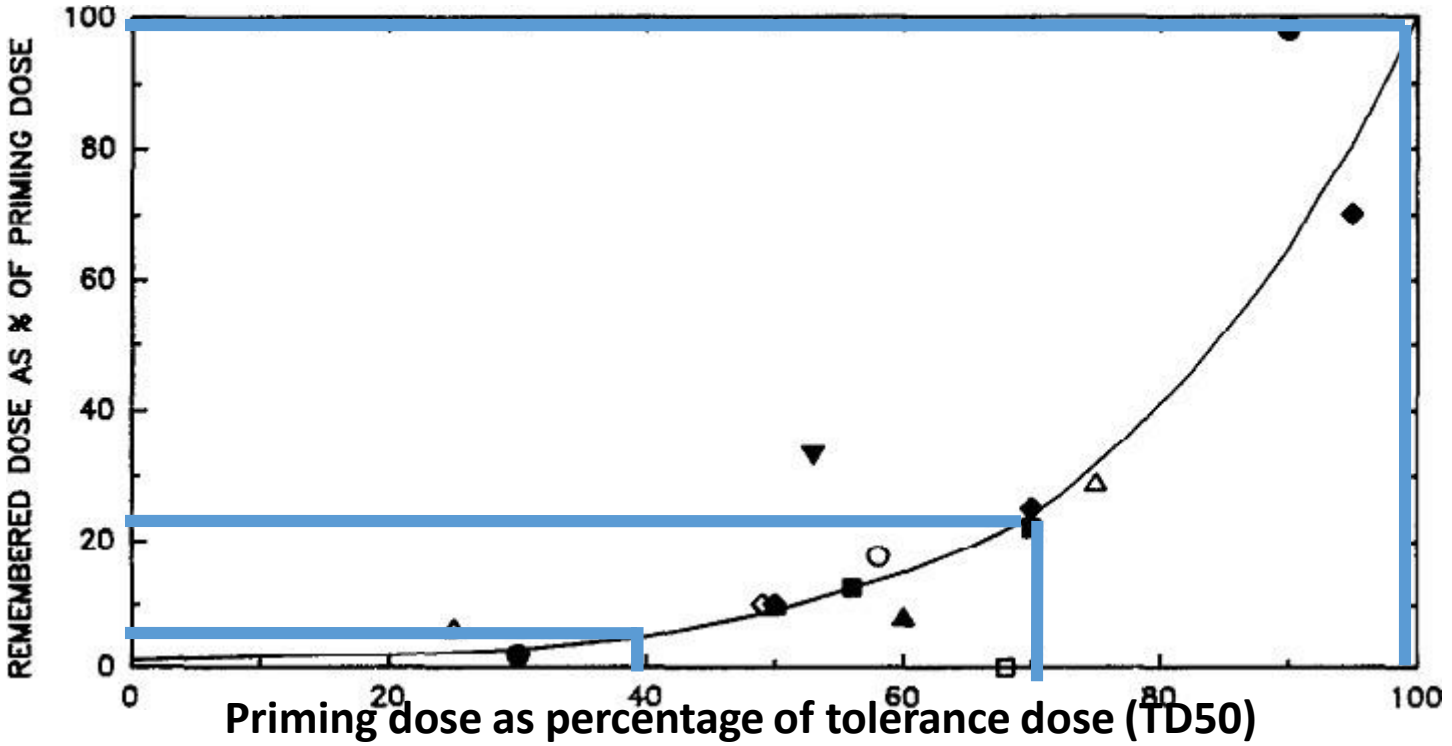
How much dose is remembered

How much dose to the cord is given during 1st irradiation (Priming Dose to Spinal Cord)

- With time cord start forgetting the irradiated dose.

Time of Re-irradiation

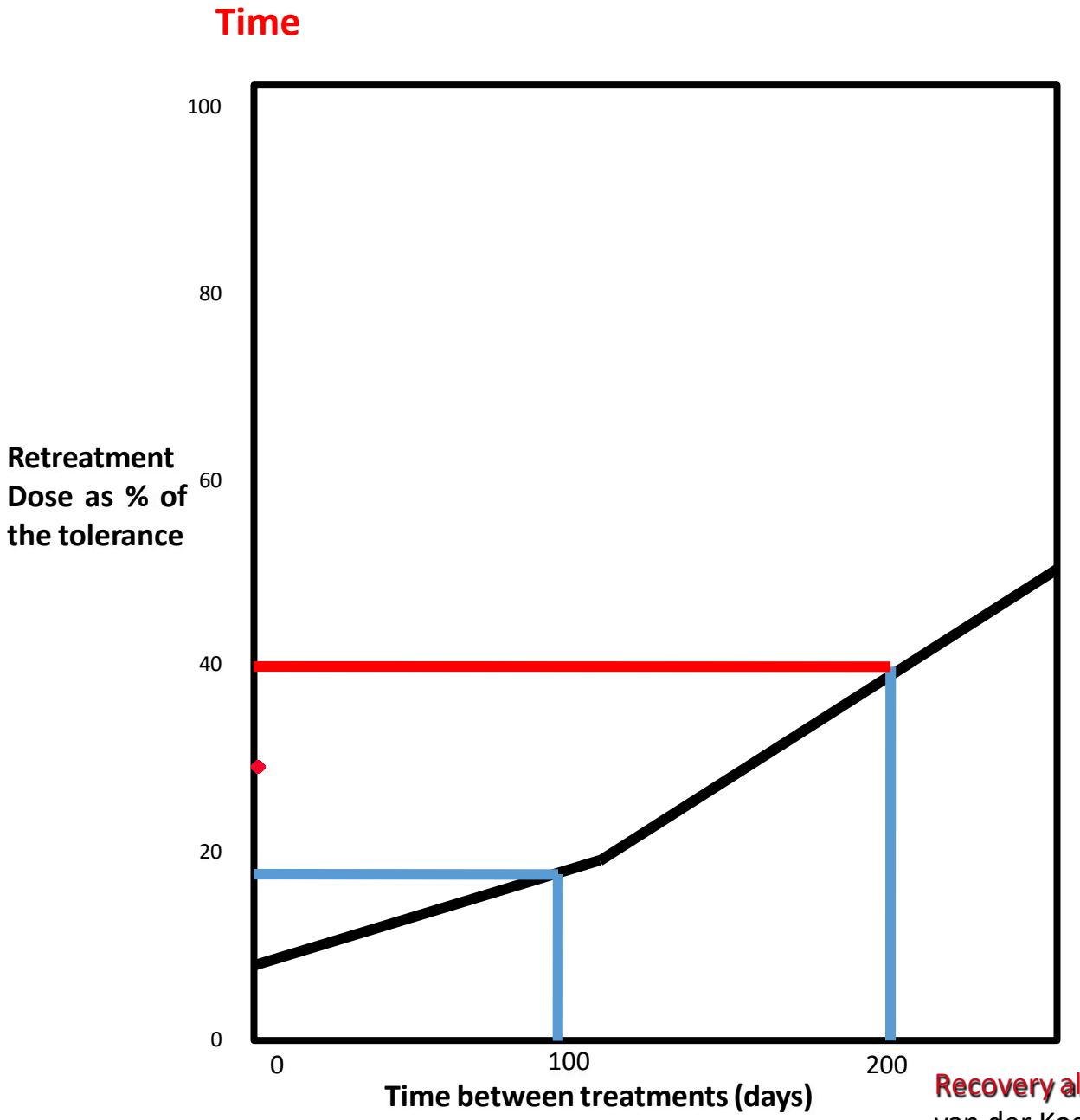
Remembered Dose to Spinal cord



Initial RT Dose as % of Tolerance Dose	Remembered Dose	Re-irradiated Dose
100%	100%	Nil
70%	20%	80%
40%	5%	95%

Mason et al., Int J Radiat Biol Phys 26:643, 1993

Re-irradiation of Spinal Cord → Time of Re-RT



Recovery also depends on time

van der Kogel and Fawcett

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 50, No. 4, pp. 1013–1020, 2001

0360-3016/01/$–see front matter

PII S0360-3016(01)01599-1

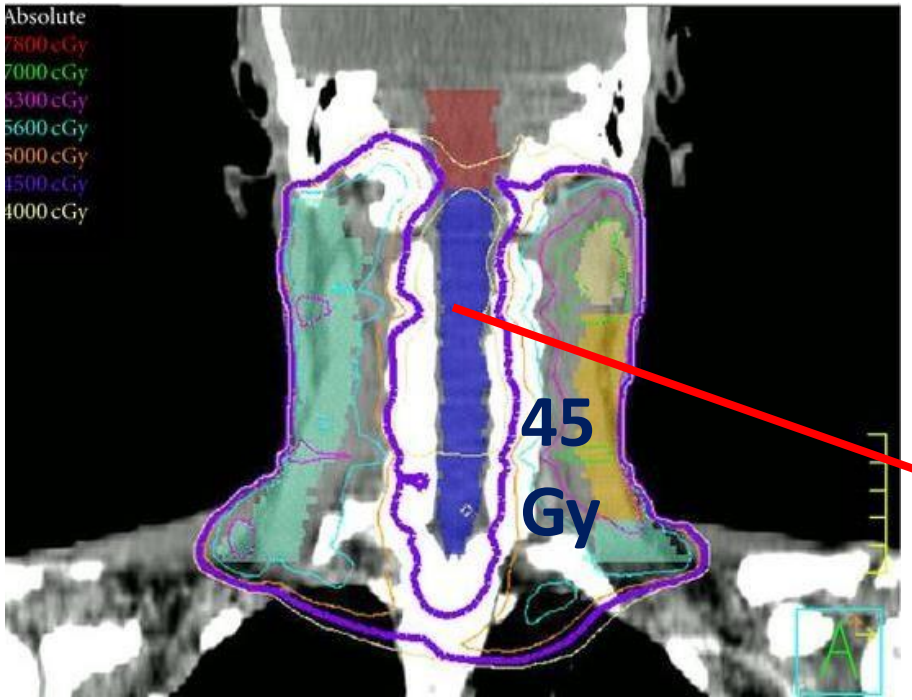
BIOLOGY CONTRIBUTION

EXTENT AND KINETICS OF RECOVERY OF OCCULT SPINAL CORD INJURY

K. KIAN ANG, M.D.,* GUO-LIANG JIANG, M.D.,* YAN FENG, M.D.,* L. CLIFTON STEPHENS, D.V.M.,† SUSAN L. TUCKER, PH.D.,‡ AND ROGER E. PRICE, D.V.M.†

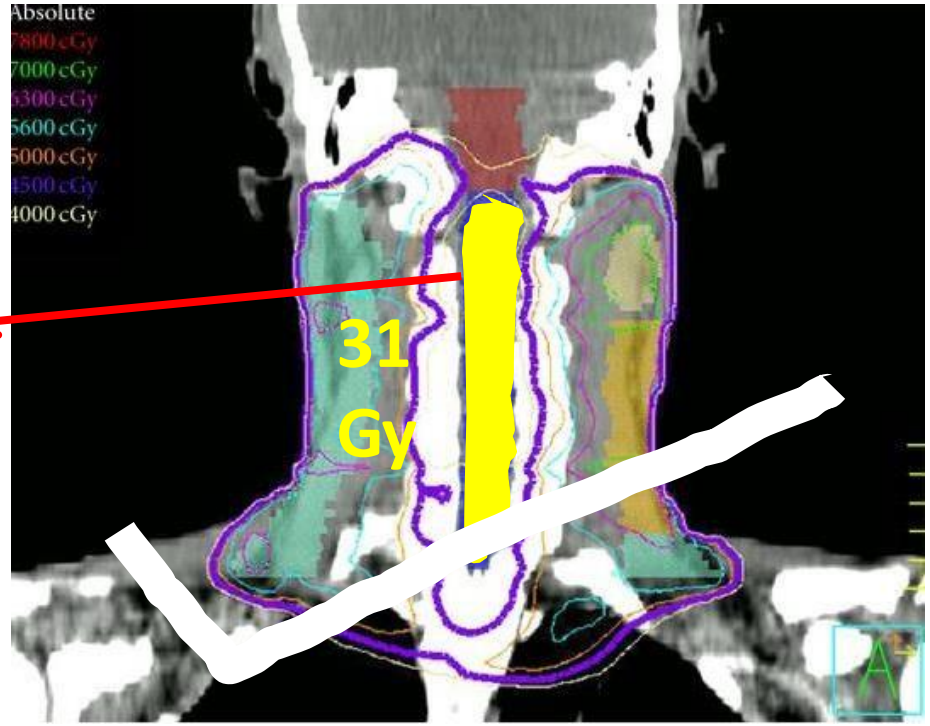
Departments of *Radiation Oncology, †Veterinary Medicine and Surgery, and ‡Biomathematics, the University of Texas M. D. Anderson Cancer Center, Houston, TX

Time Interval	% of Recovery
1 year	50%
2 years	60%
3 years	70%



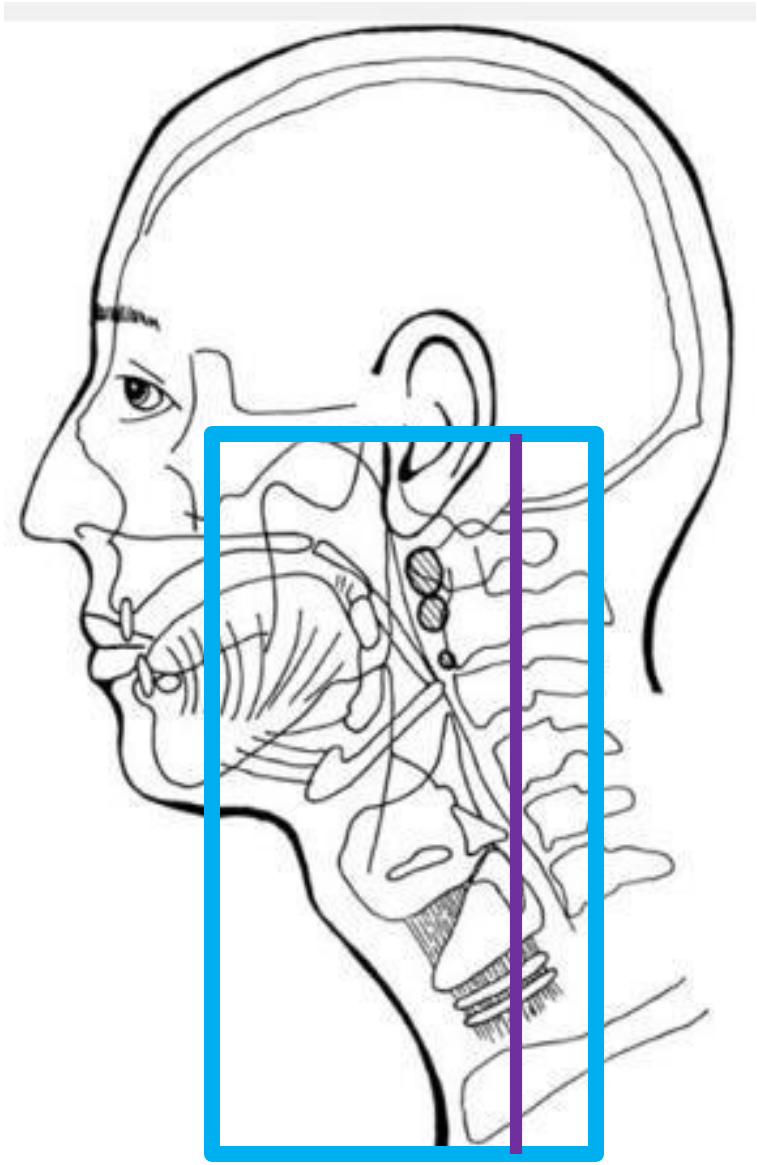
Two IMRT plans. Which one is better??

- 100% tolerance dose.
- Can not be re-irradiated in case of Relapse.



- 70% of the tolerance dose
- 20% will remember after 2 years
- Can be re-irradiated with 80% of tolerance dose after 2 years in case of relapse

Effect of dose per fraction on Spinal Cord



Non-IMRT Plan

46Gy/23F → 2Gy/F BED = 77

IMRT Plan 70 Gy/35

Spinal Cord 46/35F → 1.31 Gy/F BED = 66

14% less BED than the tolerance

Take Home Message

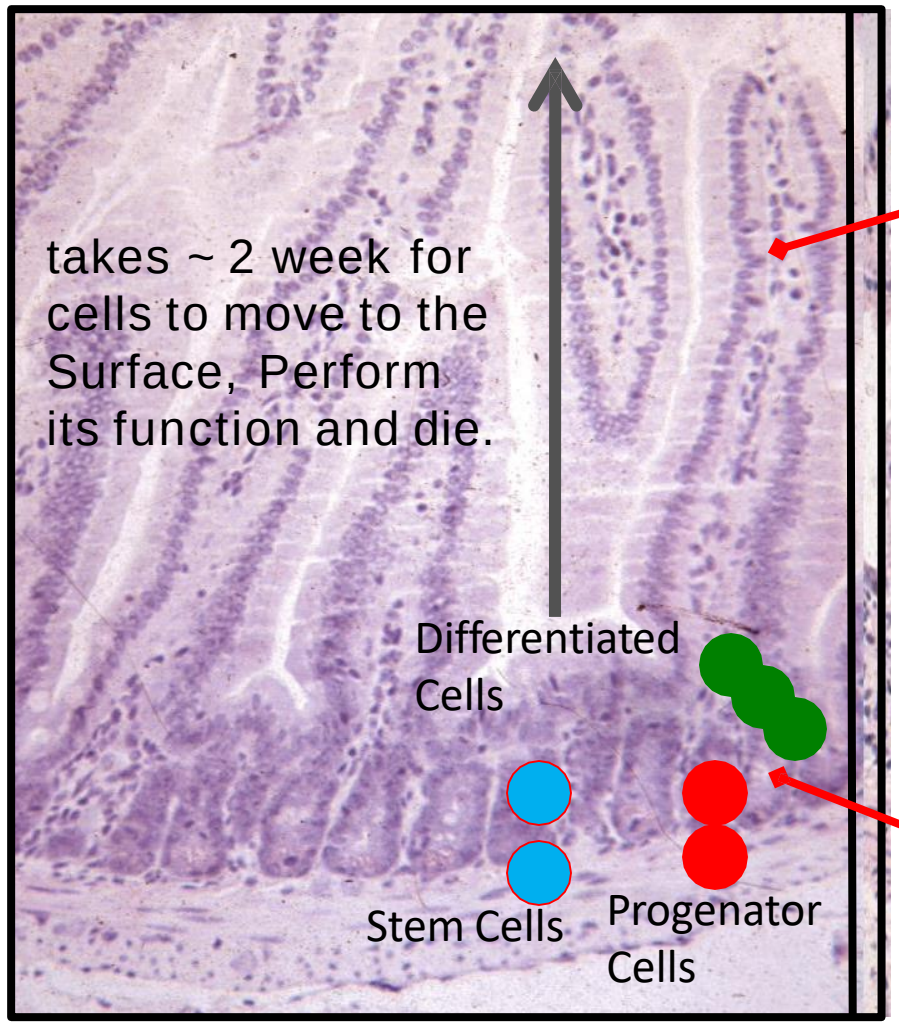
Upfront IMRT treatment is better than Non-IMRT treatment for reducing the toxicity in spinal cord and for safety during Re-Irradiation.

Turnover (proliferative status)

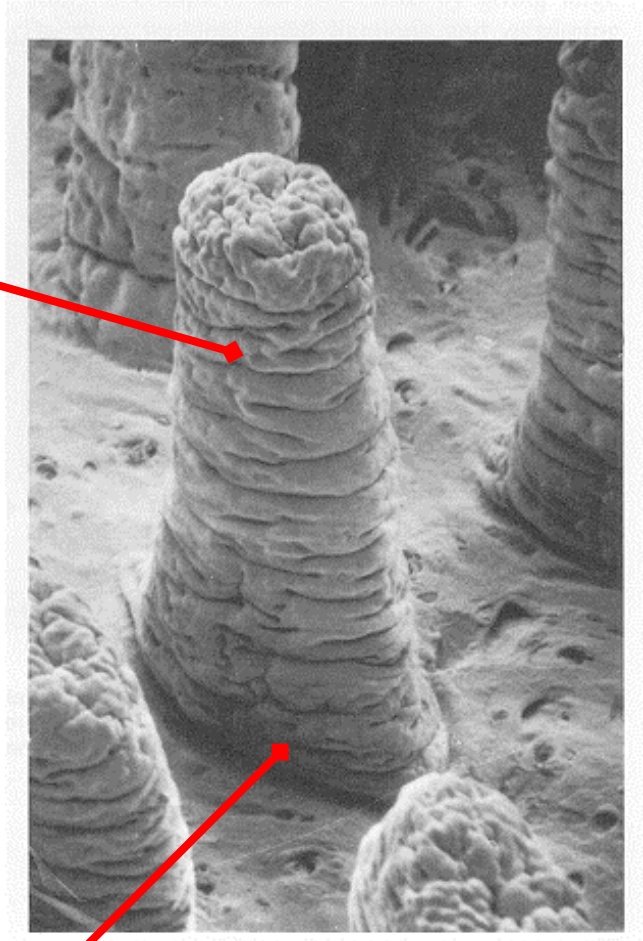
Turnover(Proliferative status)

- Proliferative status mainly determine the timing of manifestation of injury which is known as latency (i.e. time between exposure and manifestation of the effect)
- Different tissues have different latent period before the radiation injury is manifested depending upon the turnover of the cells of that particular tissue.

Jejunum Villi

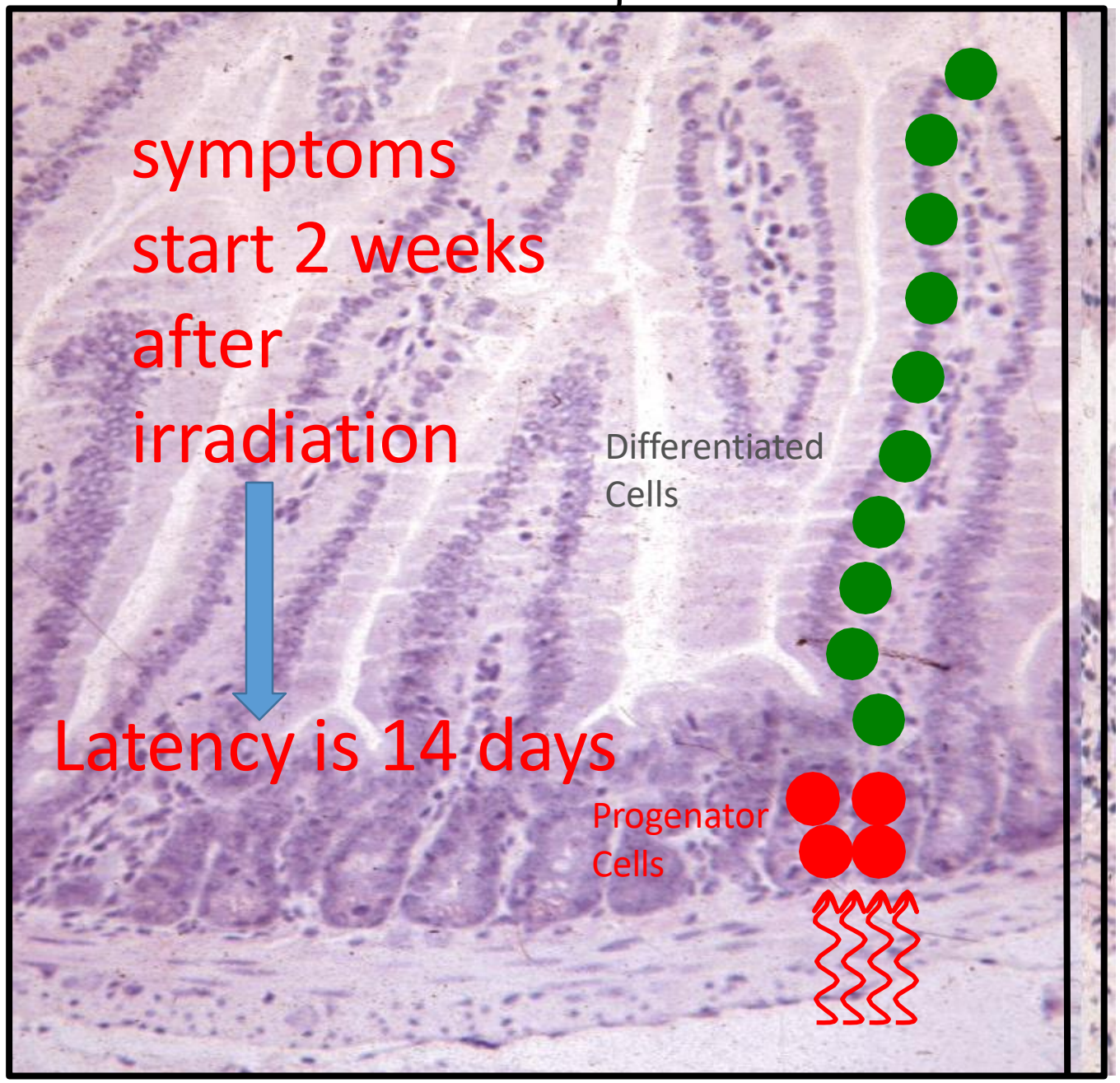


Villi



crypts, ~ 60 at
the base of each villi having stem cells

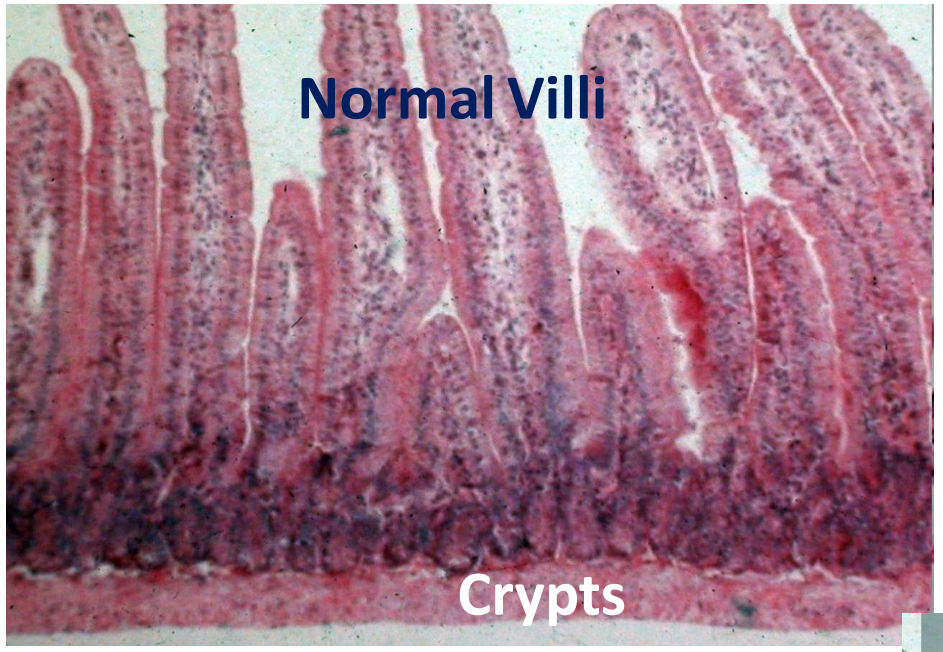
Jejunum Villi



14 days

No Symptoms
for 14 Days

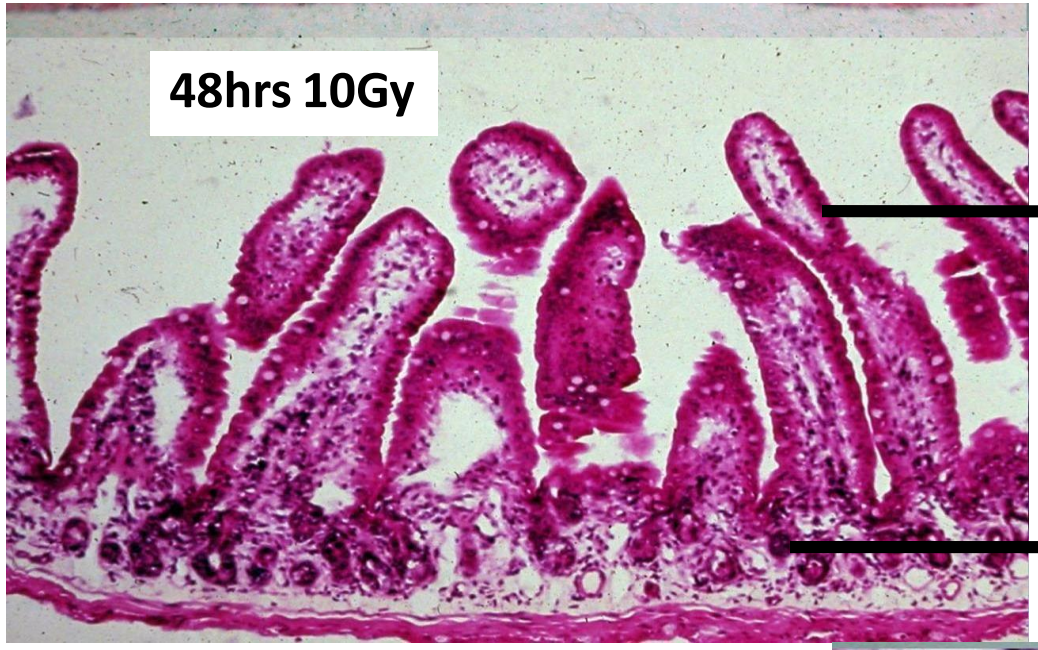
Murine Small Intestine



No change in villi

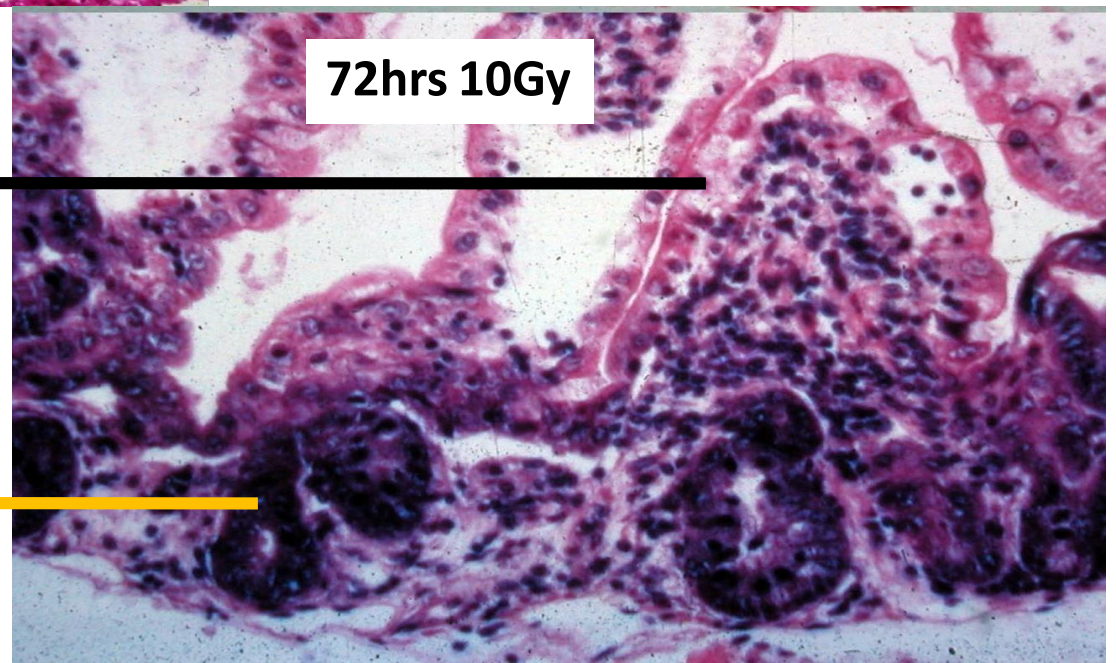
Depopulation of cells at crypts

Murine Small Intestine



Still no change in villi

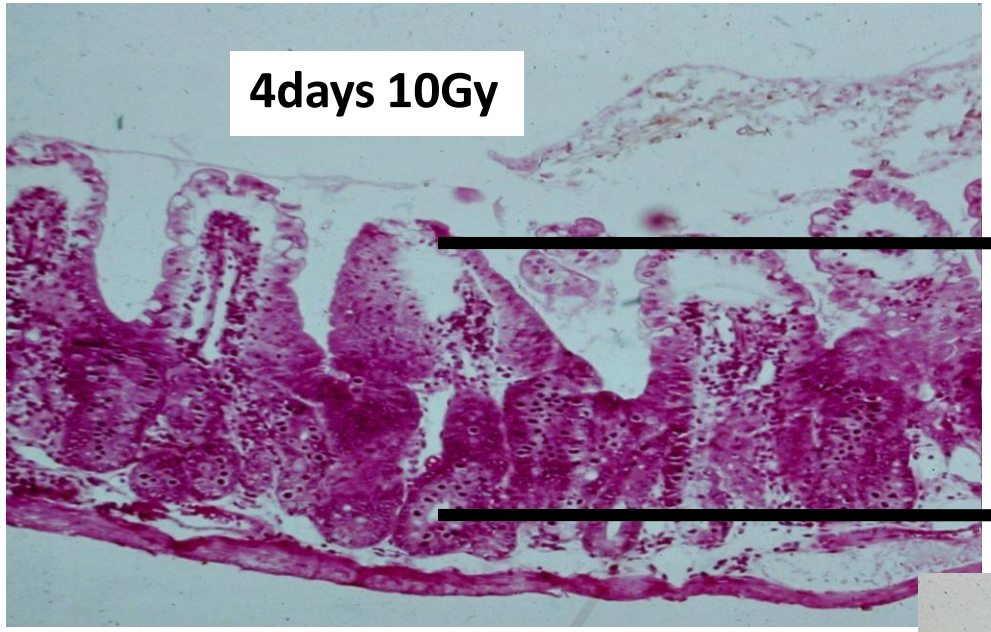
Regeneration Start



Villi Shortened

Marked Regenerations

Murine Small Intestine



Early recovery in Villi

Regenerated Crypts

Good Recovery in villi by day 5th

There is no Relationship between Latency and Tolerance

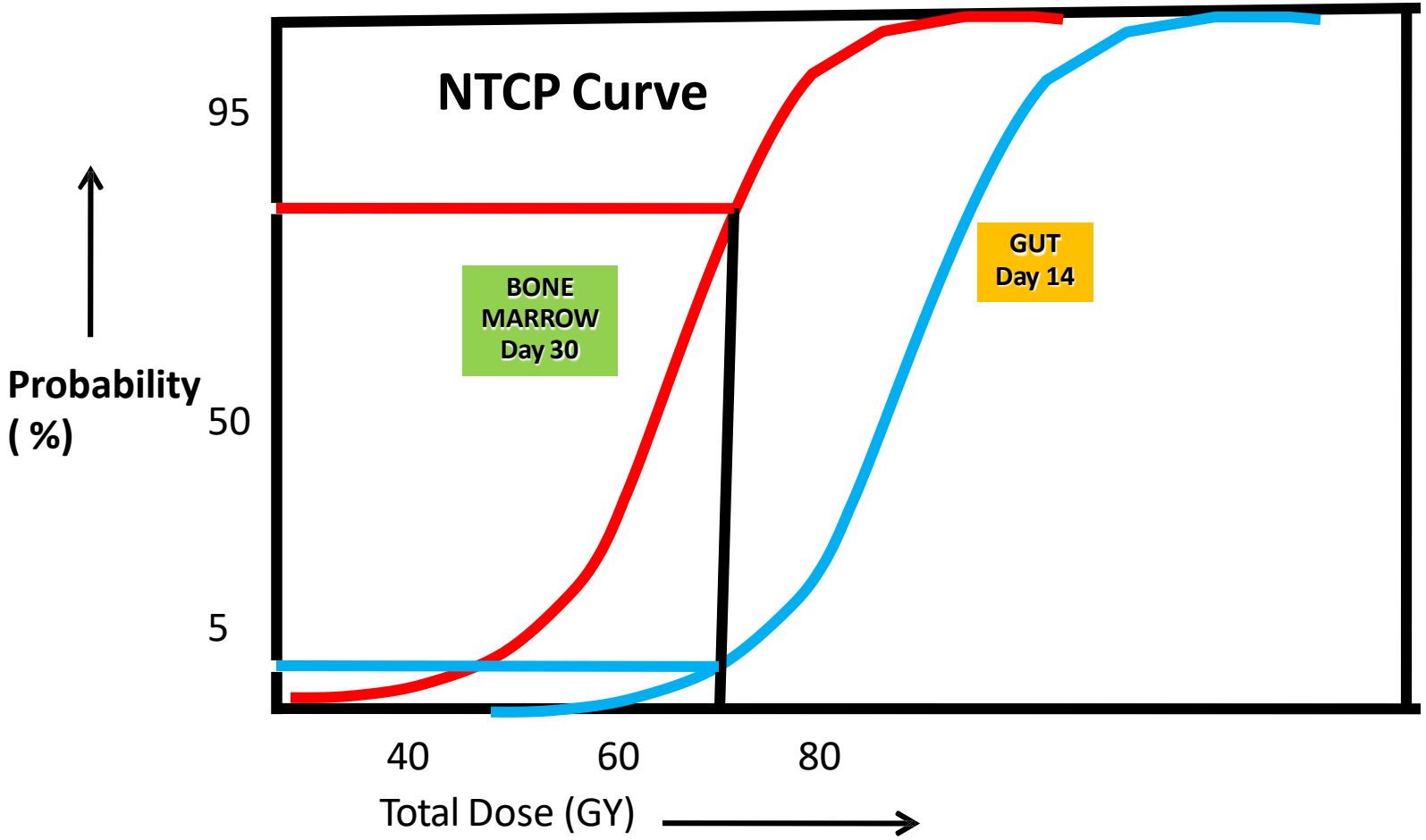
Tolerance ↓

Organ sensitivity to Radiation

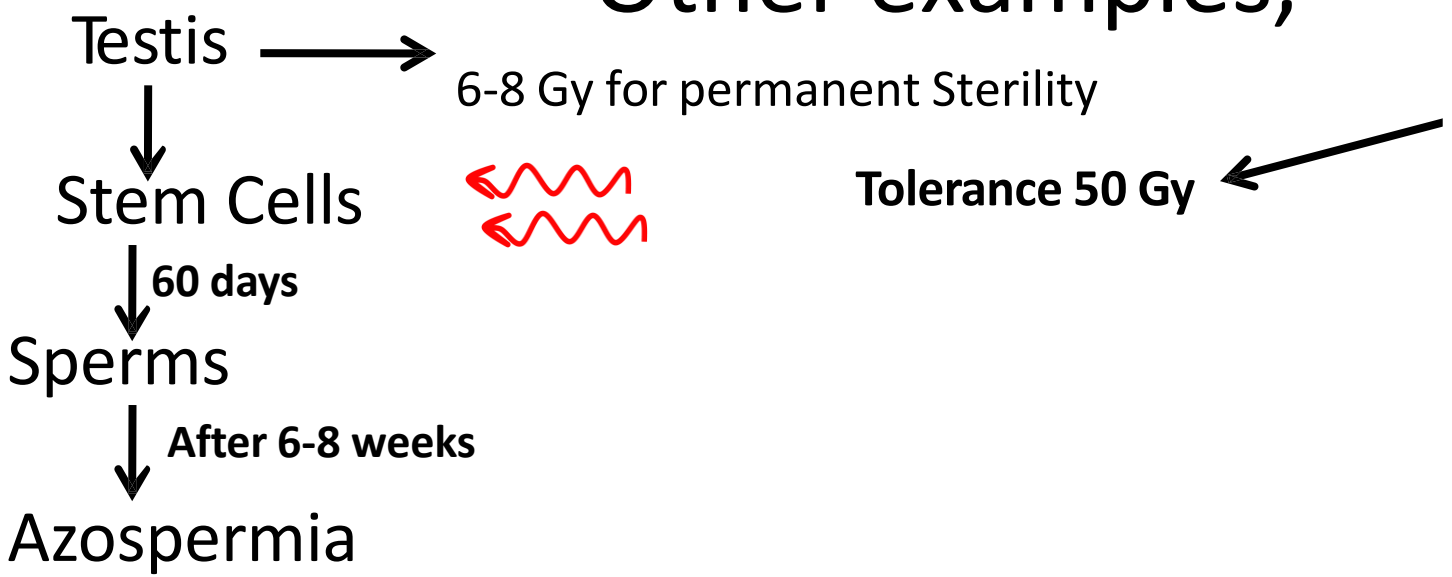
Latency ↓

Time interval between exposure and manifestation

After Whole Body exposure, Diarhhoea appear early and pancytopenia appear later



Other examples,



Though Testis is more sensitive to radiation than Gut but radiation injury manifested much later than gut injury.

Take Home Message

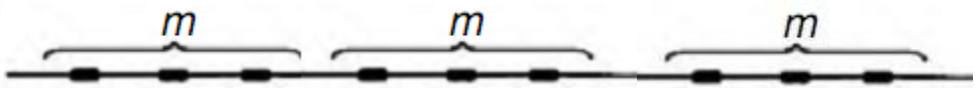
If clinical manifestation of radiation injury appears early, it does not mean that the organ is more sensitive and has less tolerance dose.

Clinical Relevance of turnover.

- Radiation induced acute injury does not start immediately following radiation.
- In Head & Neck irradiation, mucositis appear during 3rd week after start of RT.
- Diarrhea starts 2-3 weeks after pelvic radiation.

Organization of functional subunit in the organ.

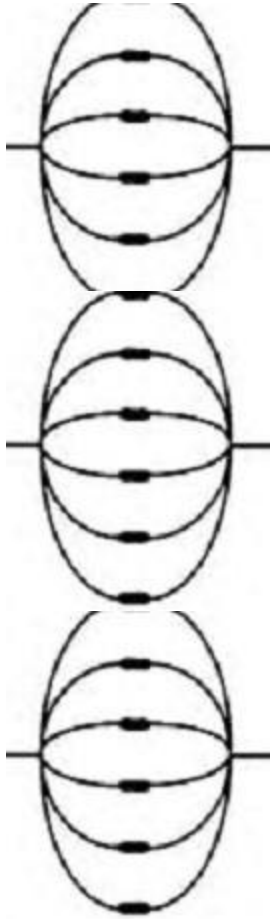
Functional Sub Unit (FSU) of Critical Organ



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.

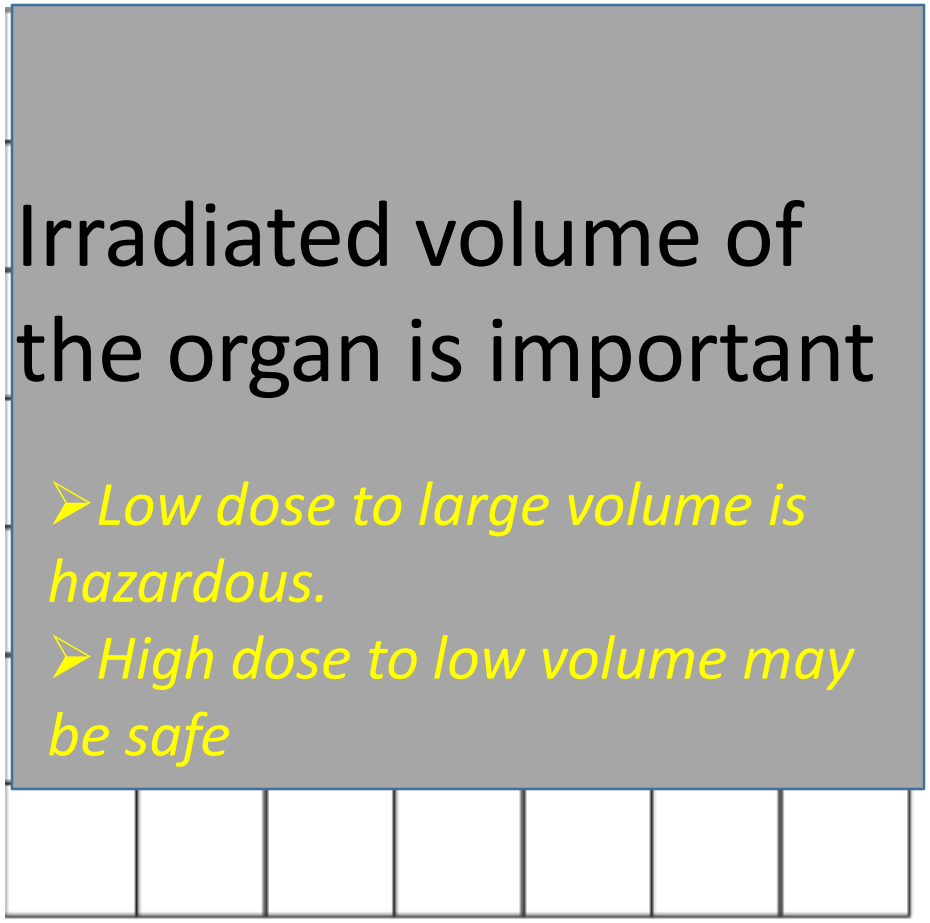


Parallel like Lung

Volume of the organ is important

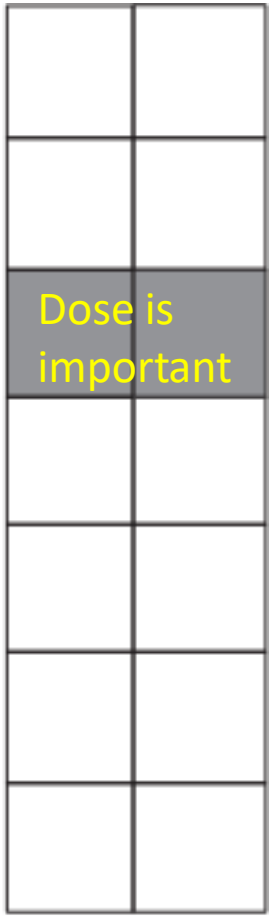
Functional Sub Unit (FSU) of Critical Organ

Parallel



(a)

Serial

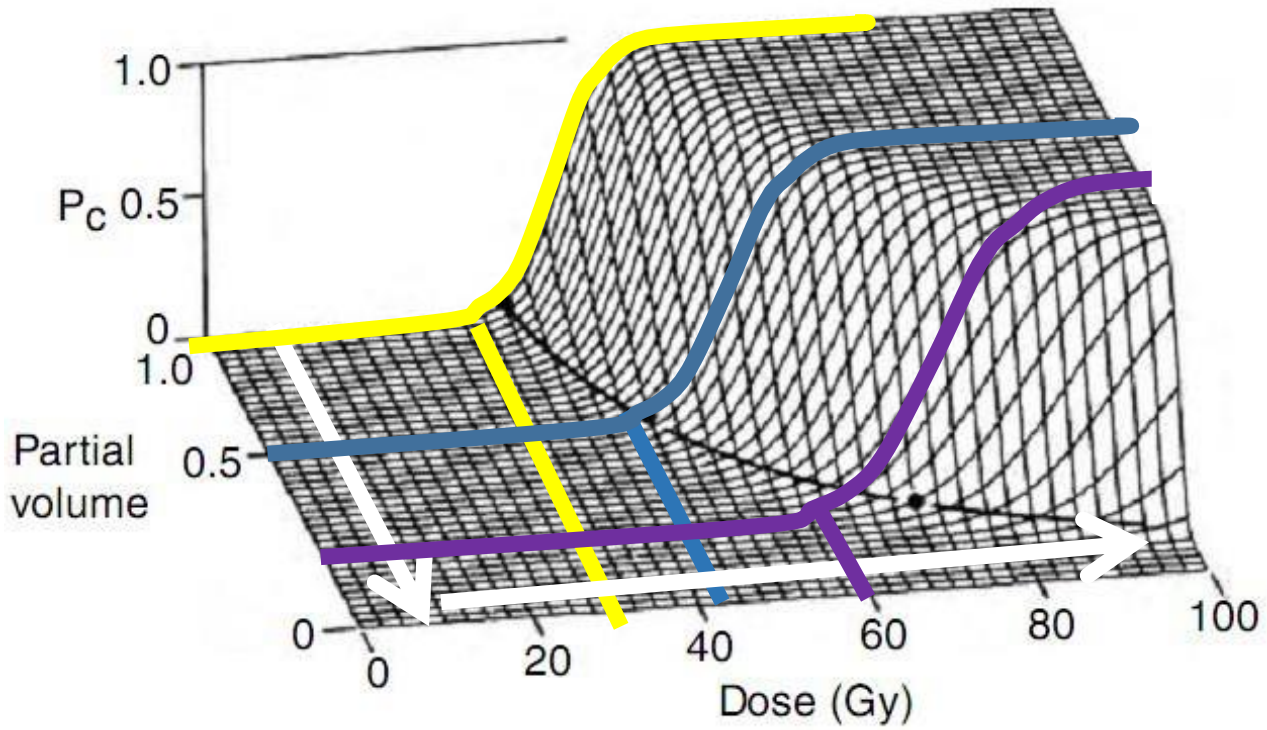


(b)

➢*High dose to small volume is hazardous.*

➢*Low dose to large volume may be safe.*

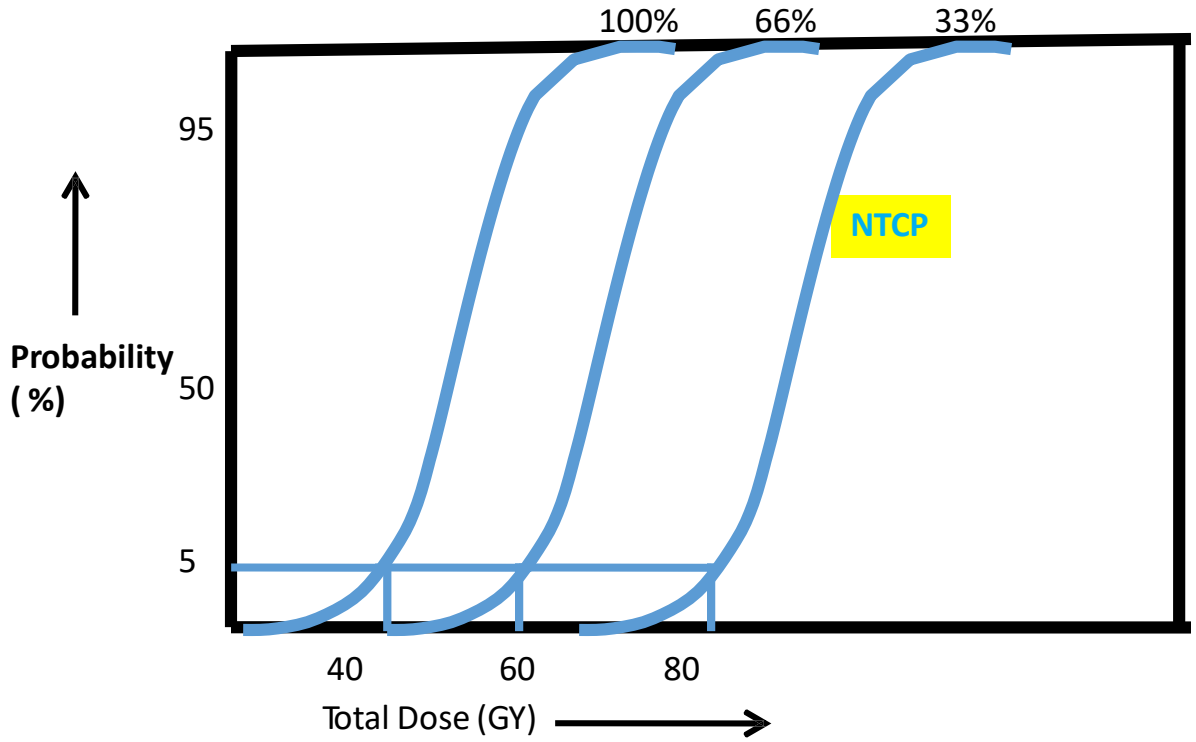
NTCP, Partial Volume and Dose Relationship for Heart



As partial volume decreases, safe dose to heart keeps increasing

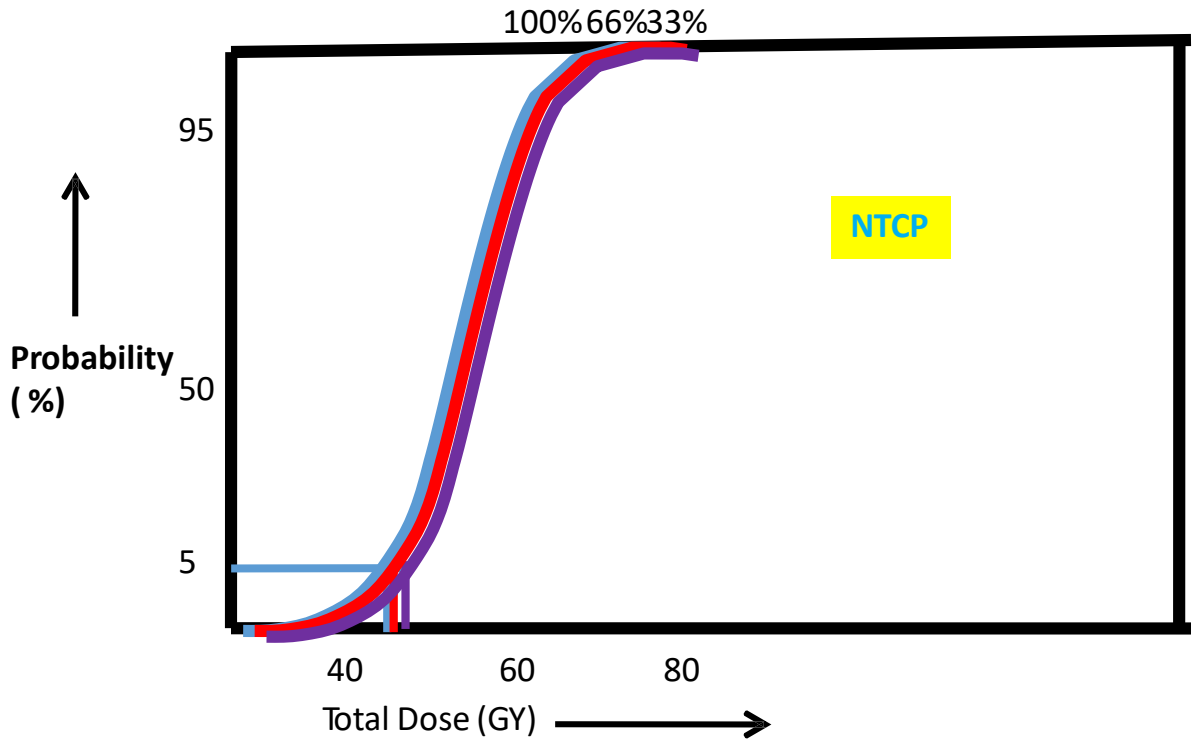
Volume effect for NTCP

This seen in parallel organ. Useful to have less no of fields so that low dose is not distributed to large volume of the organ.



Volume effect for NTCP

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

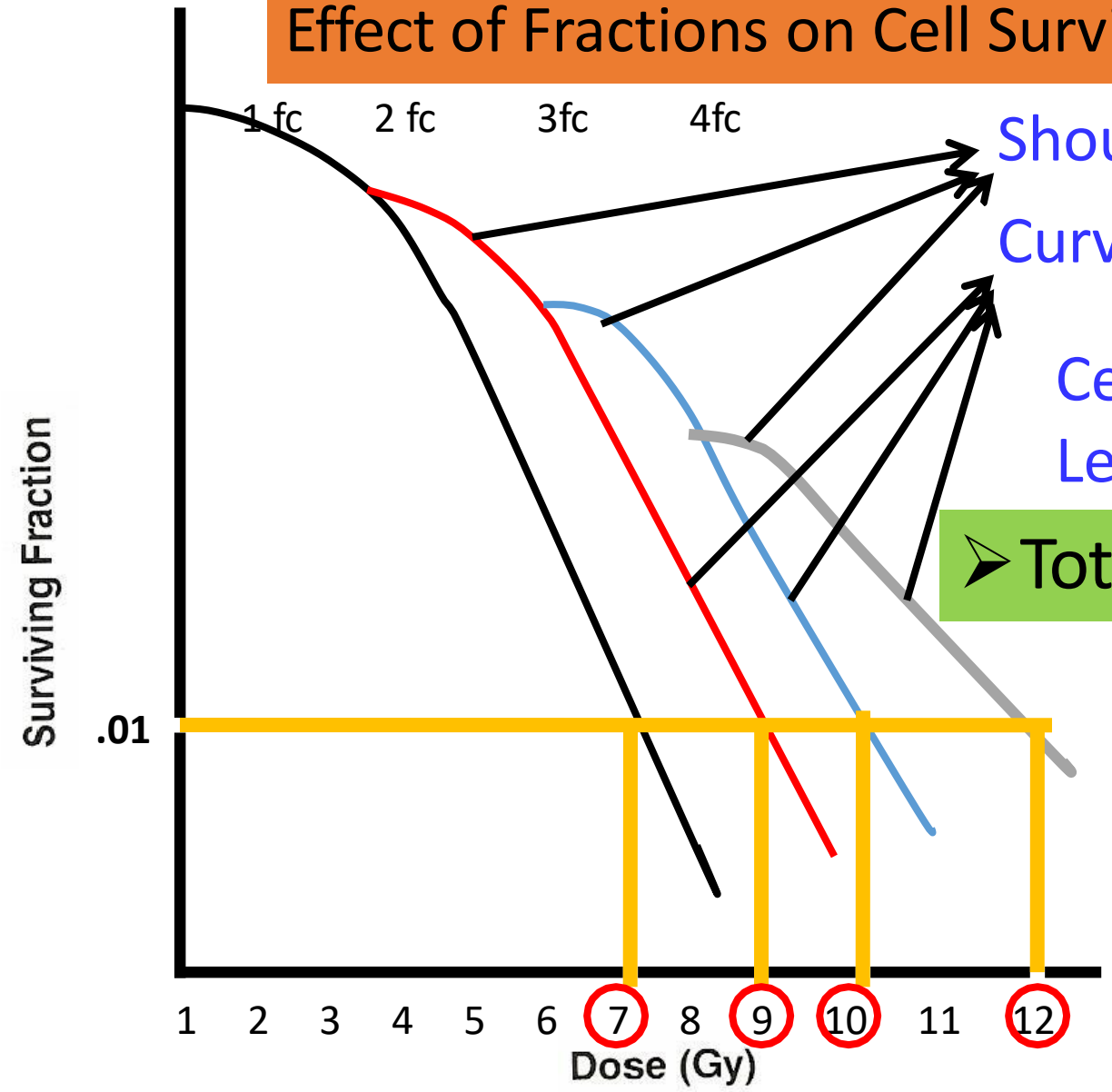


Four Rs of Radiotherapy

1. Repair
2. Repopulation
3. Re-distribution
4. Re-oxygenations

Repair of Sub-lethal Damage

Effect of Fractions on Cell Survival Curve



Shoulder Reappear

Curve gets shallower

↓

Cells become Less Sensitive

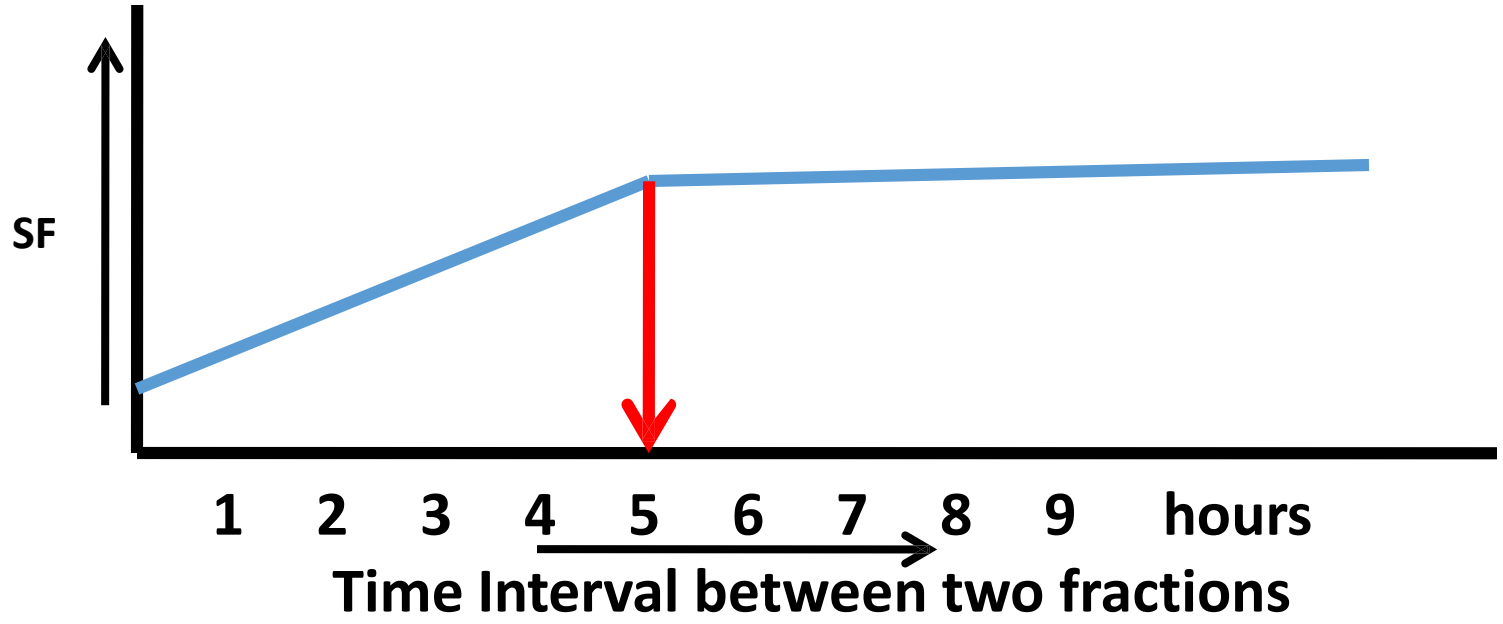
➢ Total dose α no of fractions

In fractionated RT the efficiency to kill the cell decreases.

Repair of Sub-lethal Damage(SLDR)

SLDR is seen in normal and tumor cells both.

Effect of time interval between two fraction on Survival Fraction



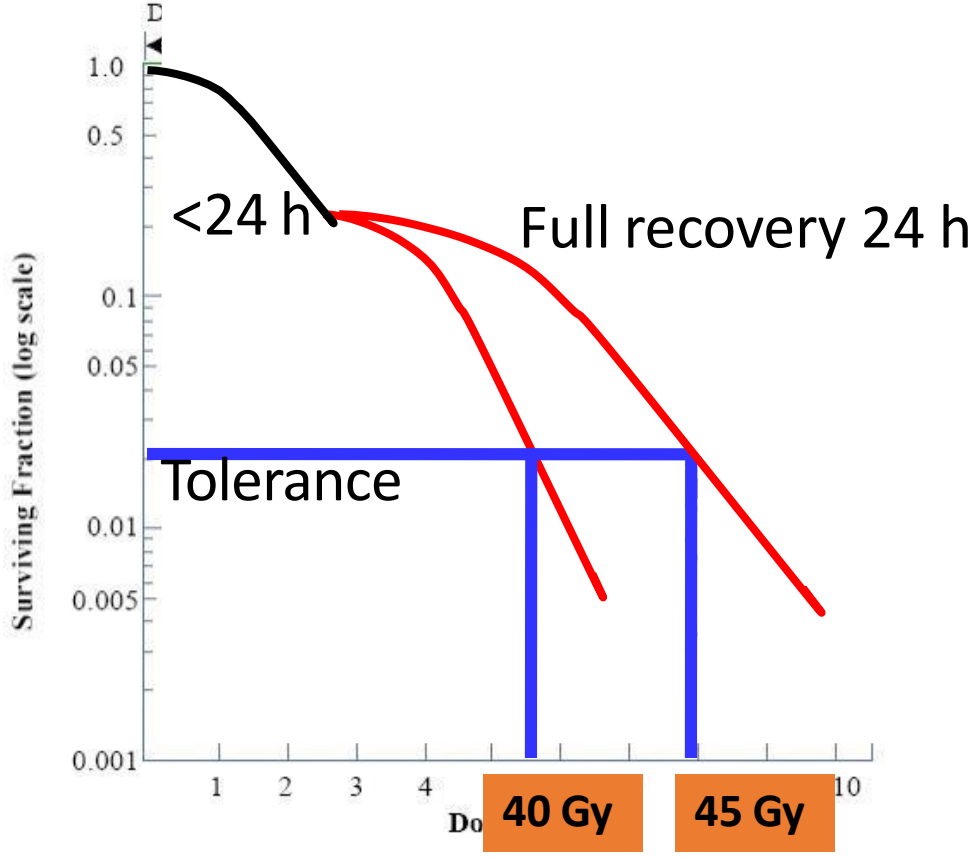
- **Early Reacting Tissues :-** T1/2 is 0.5 to 1 hours i.e. repair is fast with recovery time of 4 to 8 hours
- **Late Reacting Tissues :-** T1/2 is 1.5 hours i. e. repair is slow with recovery time of > 12 hours.

Repair in Spinal Cord

Reduction of interfraction interval from 24 hours to 6-8 hours require a 10 to 15% reduction in spinal cord tolerance dose.

T ½ 3.8 h (2.5; 4.6)

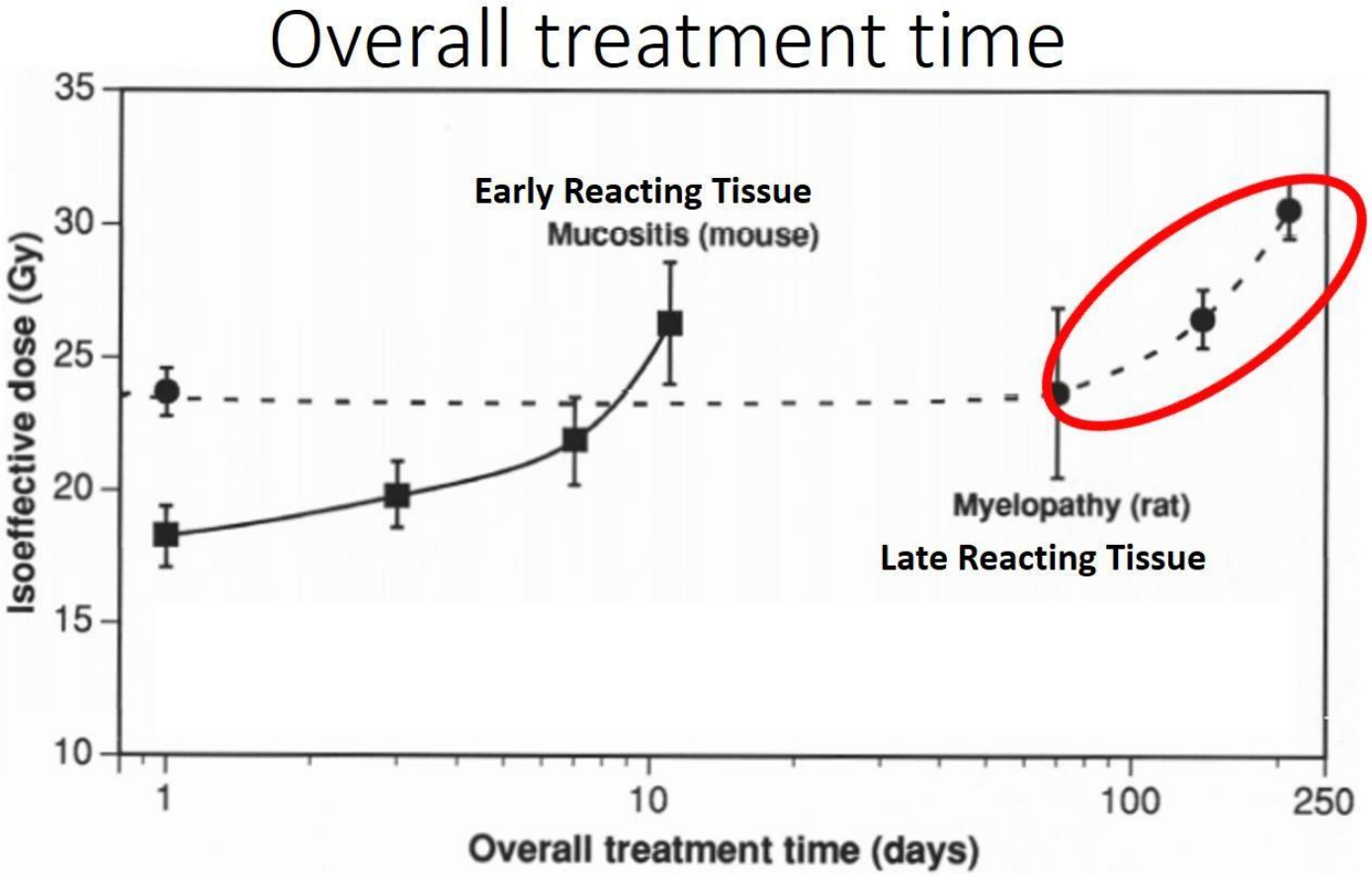
Complete recovery 24 hr



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

Take Home Message

In hyper-fraction radiation treatment, tolerance of spinal cord to be kept 10% less than actual if time interval between two fraction is less than 24 hours.



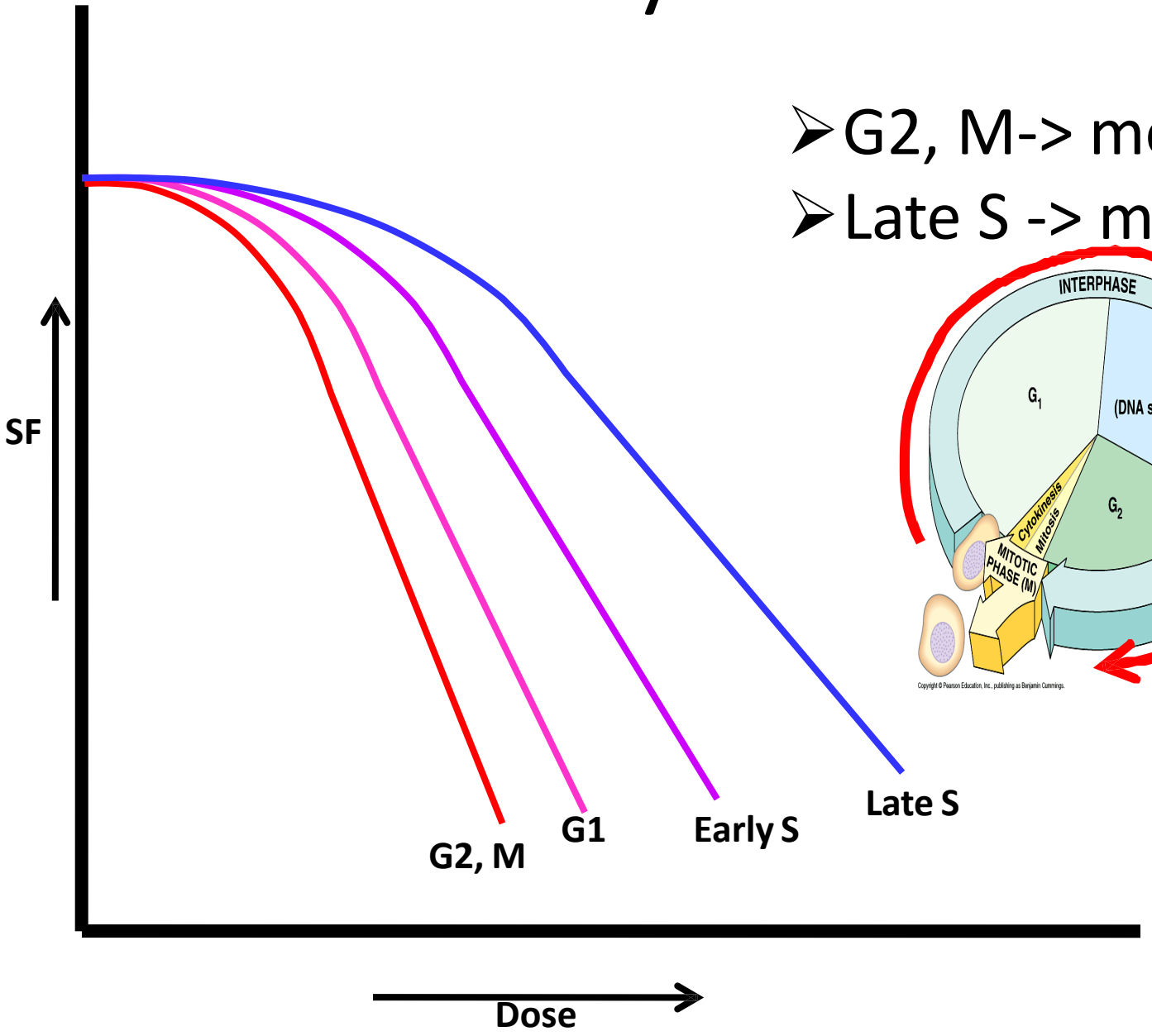
Regeneration/repopulation in late Reacting tissue eg Spinal cord

(Repopulation)

Already Discussed

Re-distribution

Effect of cell cycle on cell survival curve

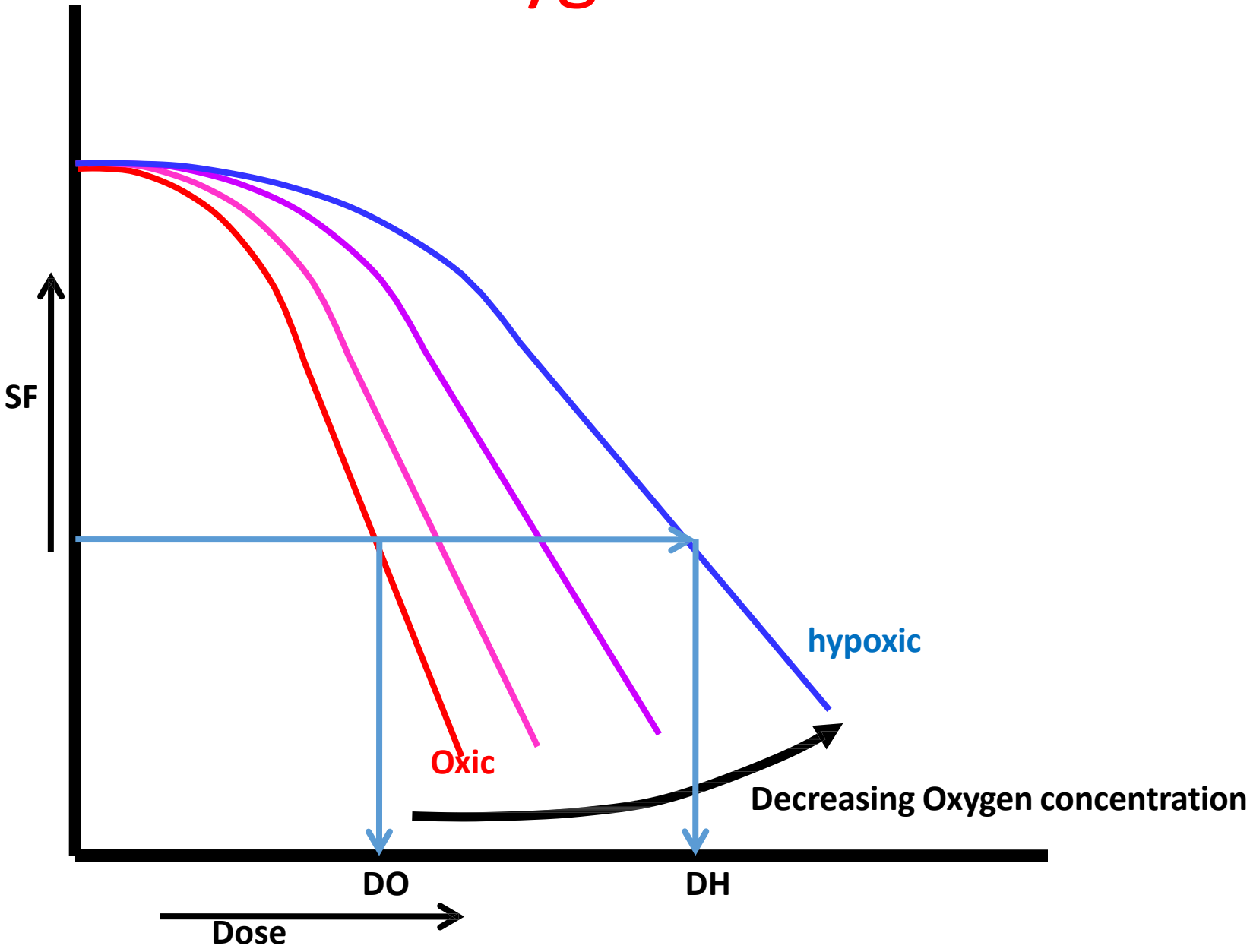


- G2, M-> most sensitive
- Late S -> most resistant

Late reacting tissues are Not dividing so no radio sensitization

Re-oxygenation

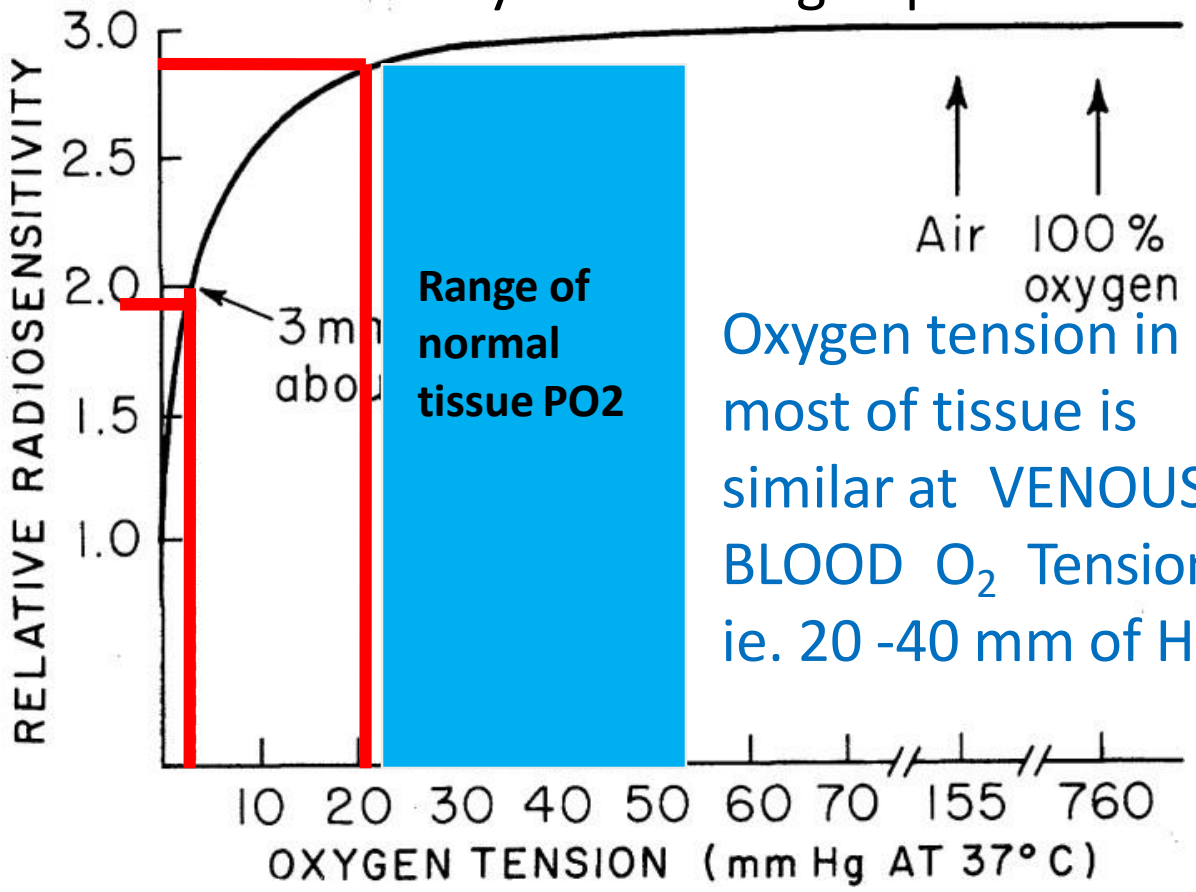
Effect of Oxygen on cell survival curve



Radio sensitivity and Oxygen Pressure

Sharp fall in sensitivity and reduces to half at around 3mm of Hg.

Very Little change up to 20mm of Hg.



Oxygen tension in most of tissue is similar at VENOUS BLOOD O_2 Tension ie. 20 -40 mm of Hg.

So most of the normal tissues have good sensitivity to radiation.

Thank you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