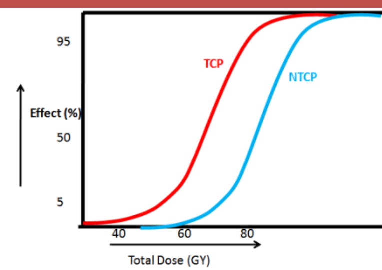
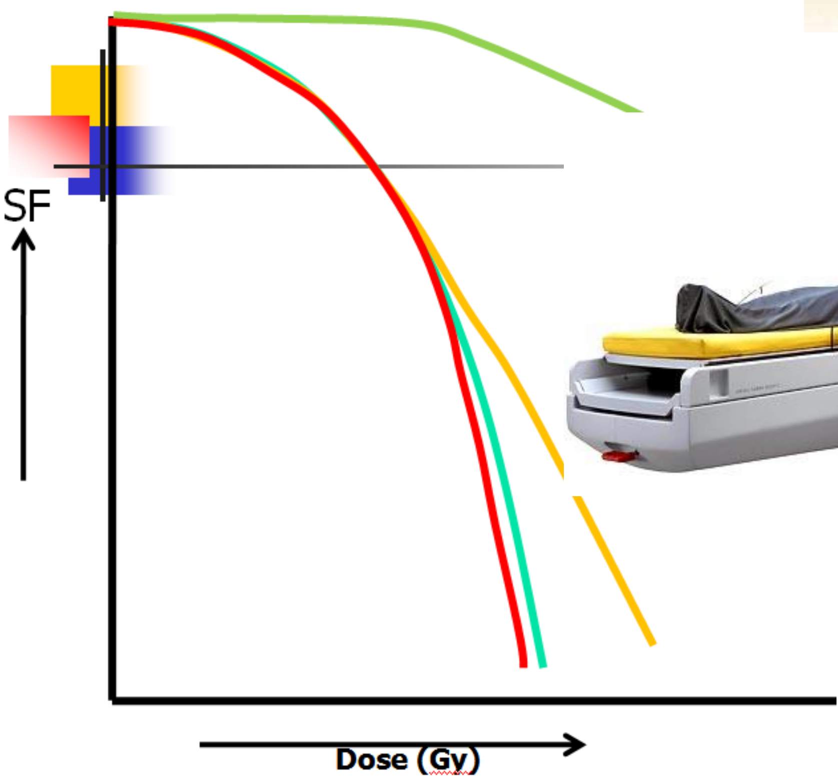
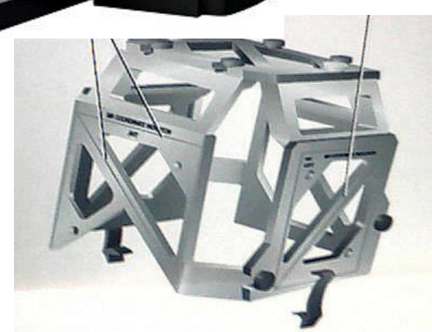
Hypofractionation:The Radiobiological Foundation







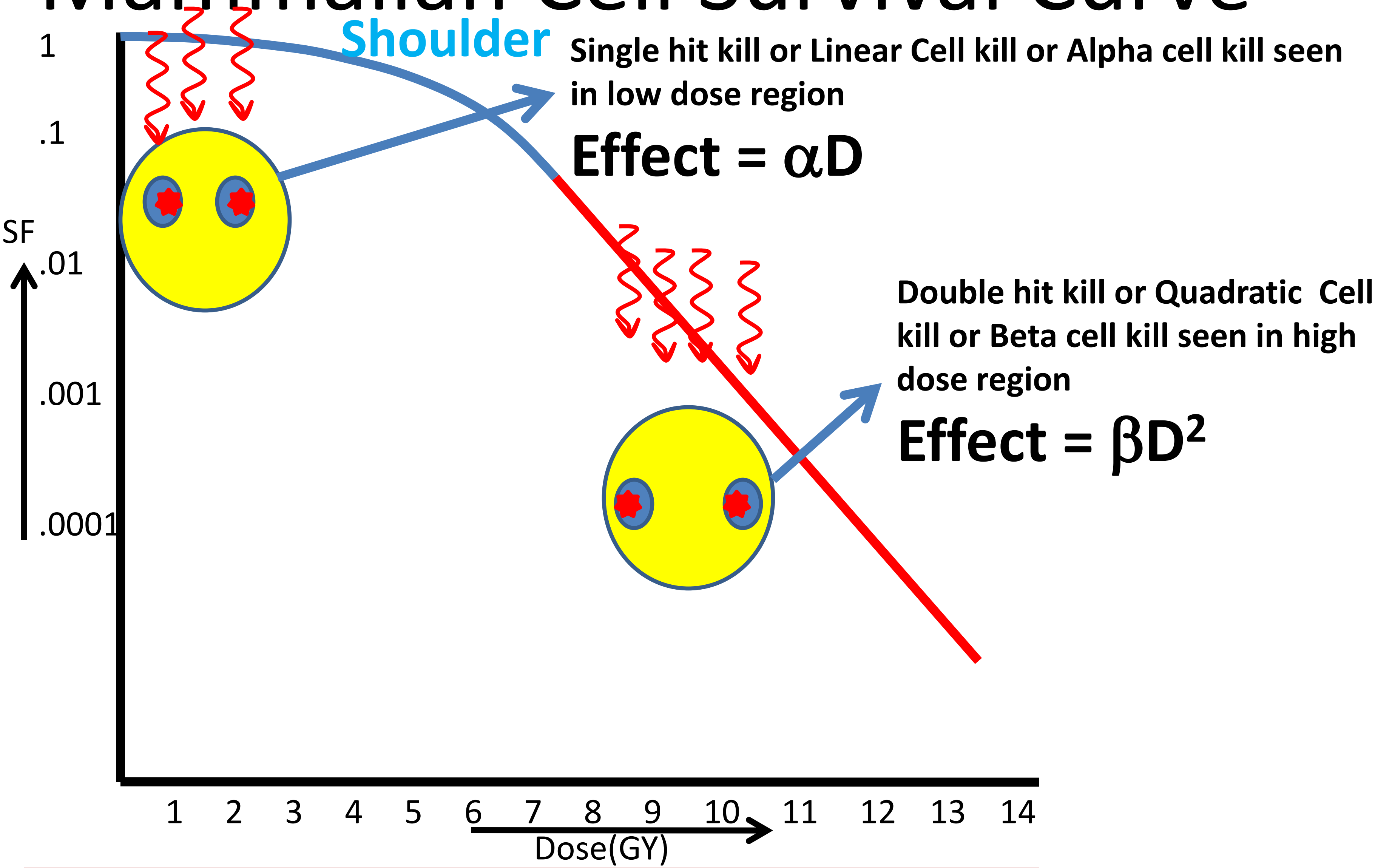
Prof Manoj Gupta
AIIMS, Rishikesh

25th Nov., 2017

Road Map

- Cell Survival Curve
- L-Q Model & Biological Effective Dose (BED)
- How cell survival curve explain the logic behind hypo fraction RT in
    - Breast
    - Prostate
- Rationale for extreme hypo fraction like SRS & SBRT
- How classical 4 Rs of Radiobiology of fractionated RT affect extreme hypofraction RT.
- New Radiobiology triggered at high dose per fraction?

Mammalian Cell Survival Curve

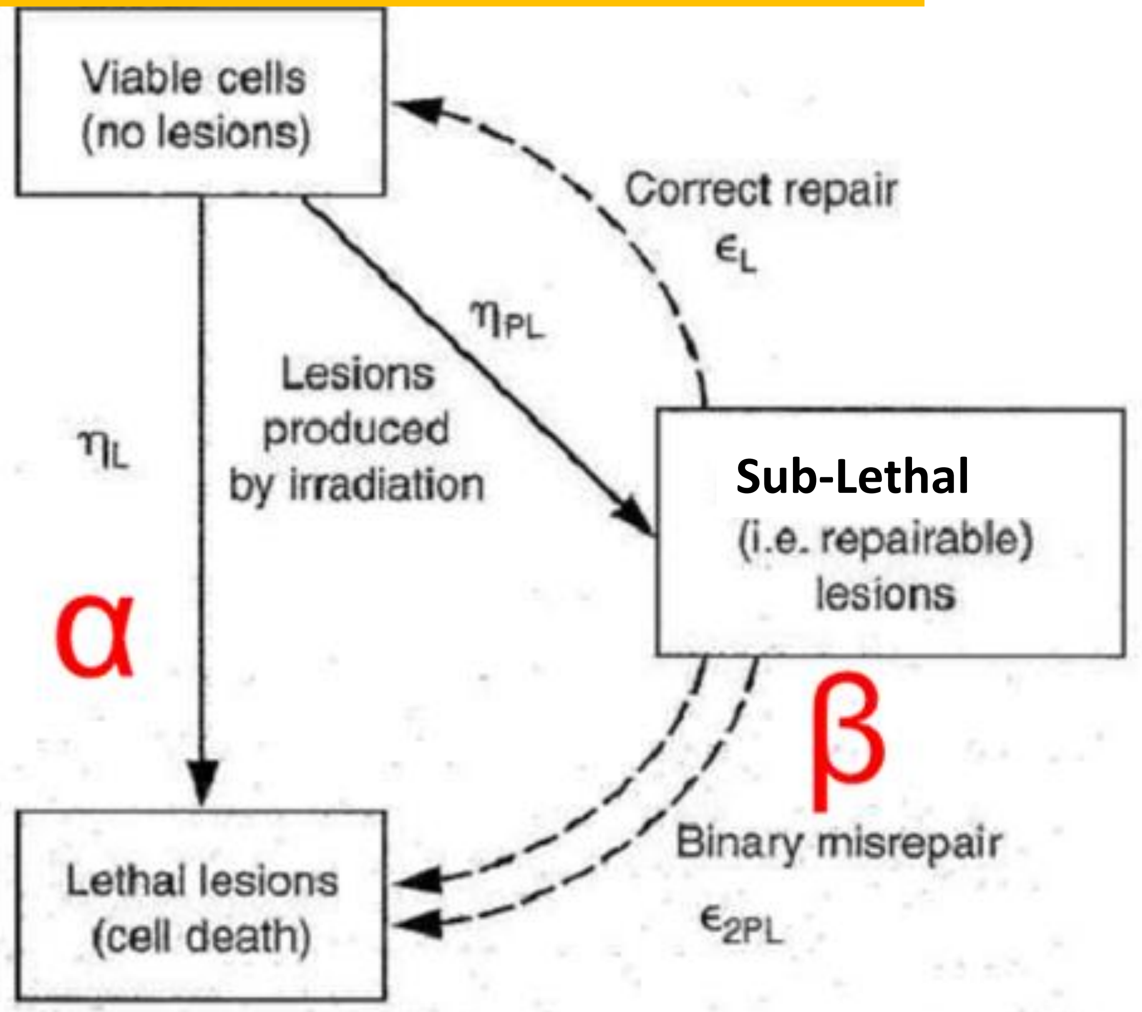


Linear-Quadratic Model

Linear Quadratic model (LQ Model)

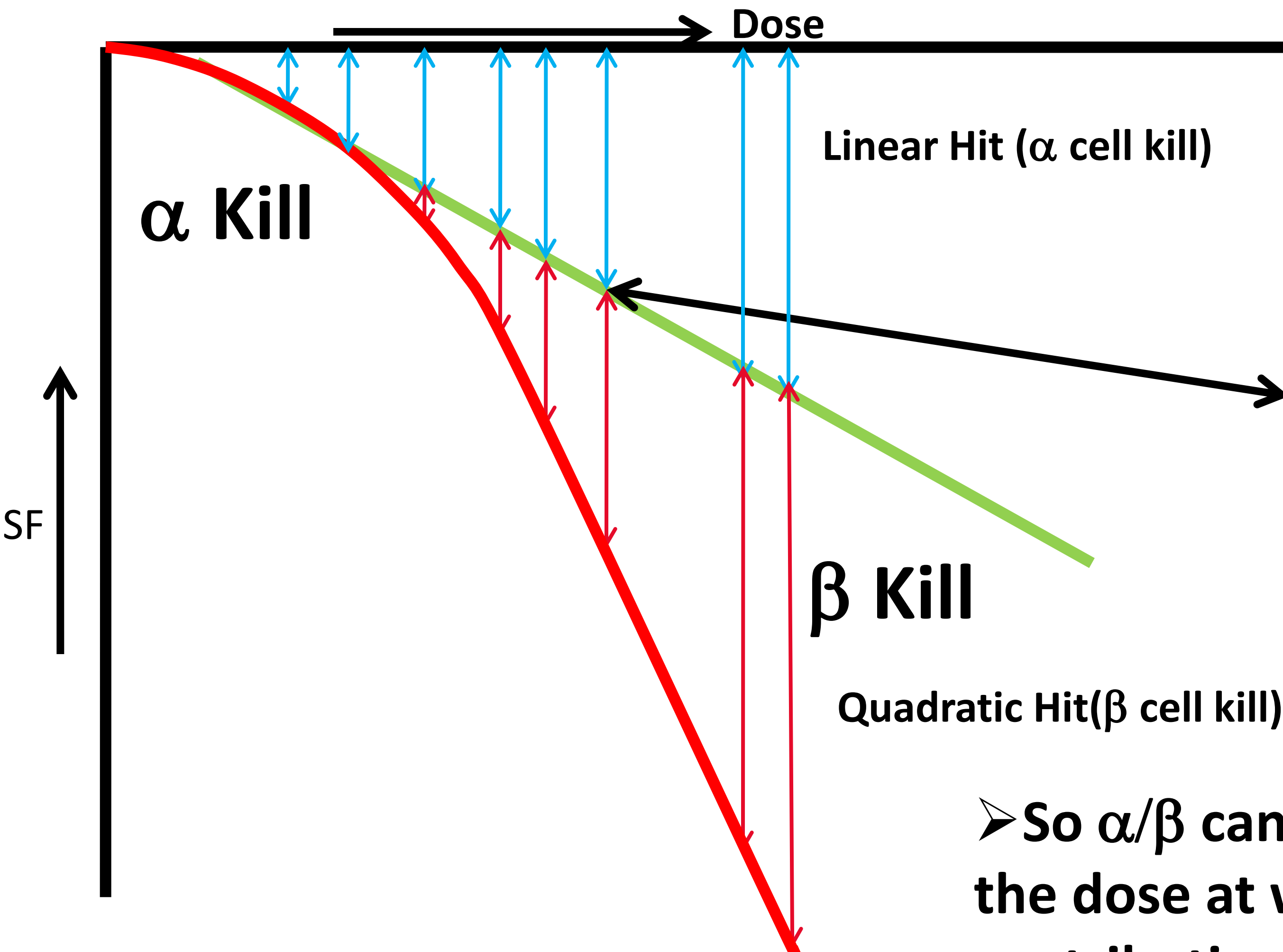
S.F.

$$e^{-\alpha D + \beta D^2}$$



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

$\alpha D = \beta D^2$

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

$\alpha/\beta = D$

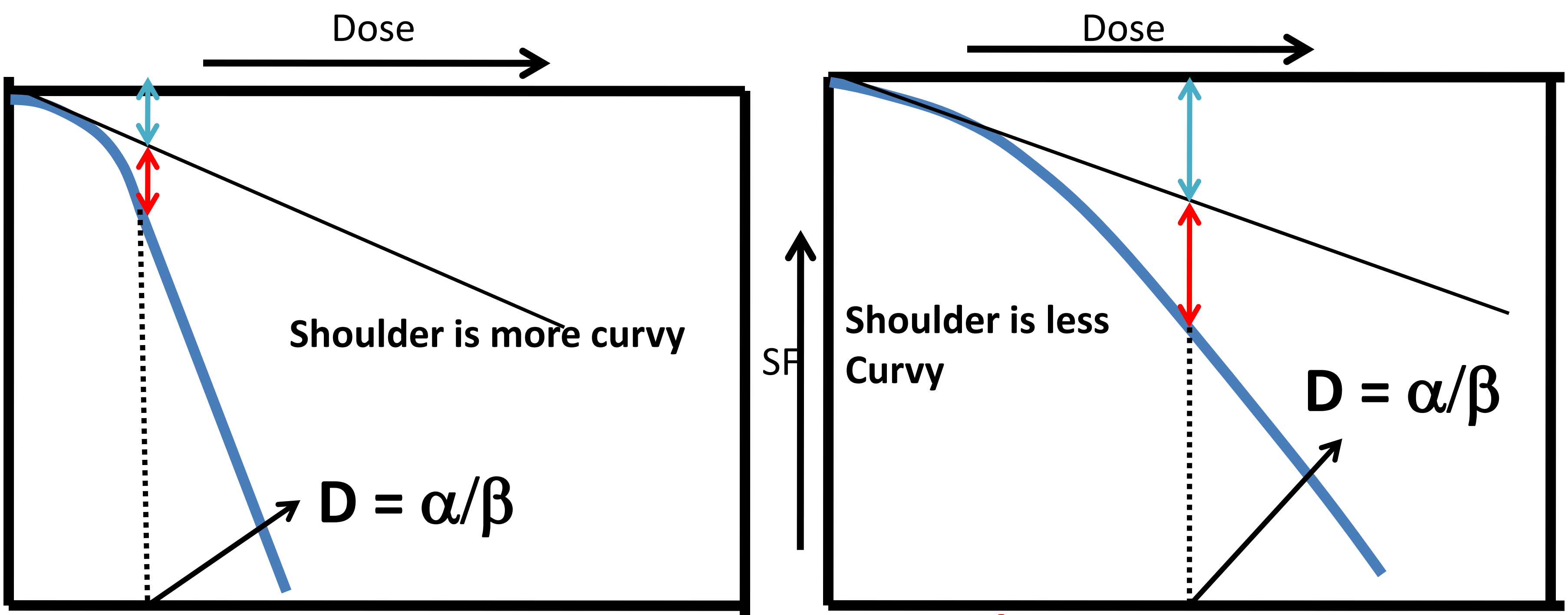
- **So α/β can be defined as the dose at which contribution by single hit kill becomes equal to double hit kill.**

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

Most of the malignant tumors have an average α/β 10



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.

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 (early reactions)

Average 3 (late reactions)

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.

Biological Effective Dose(BED)

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

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

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

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

As suggested by Barendsen, this equation may be rewritten as

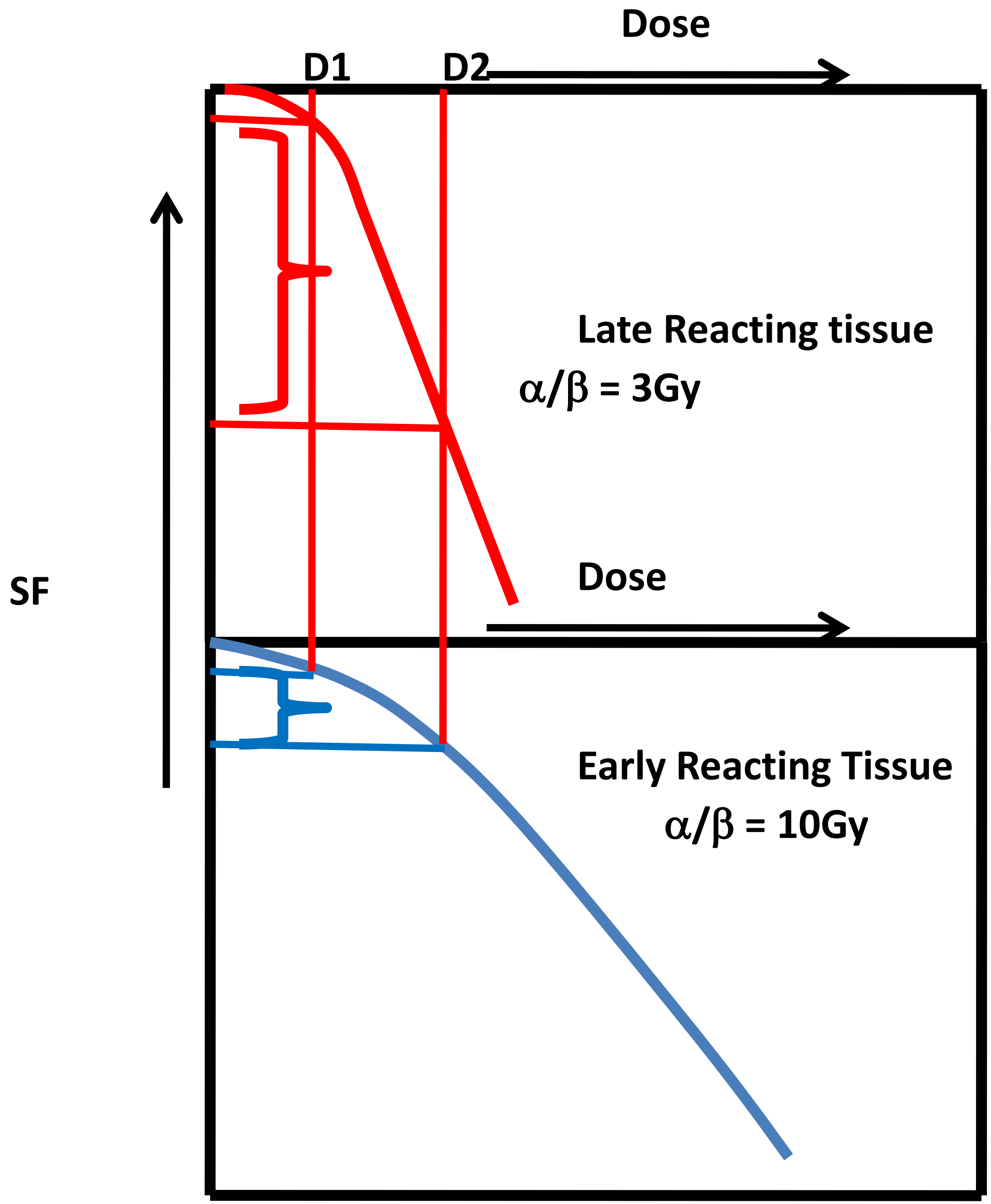
E = (nd)(α + βd)

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

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

Biologically Effective Dose (BED) =

Effect of Fraction size (Dose per fraction)

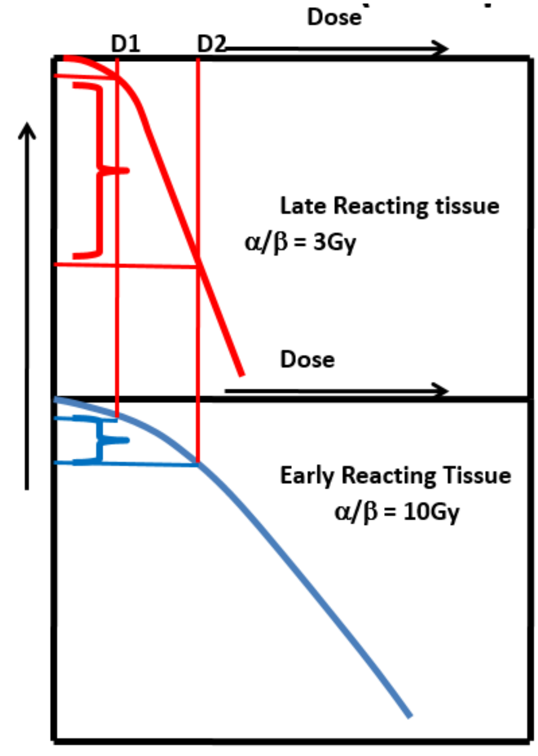


- Depends upon shape of cell survival curve (α/β Ratio)

- Increase in dose per fraction damages tissue with low α/β Ratio more than with high α/β Ratio.

Ca Breast

- The principle is that α/β value for subclinical disease in ca breast is around 4 Gy and for late changes in the breast it is 3.5 Gy.
- So higher dose per F will result into more damages in sub clinical disease.



Ca Breast

Start B Trial

The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

www.thelancet.com Vol 371 March 29, 2008

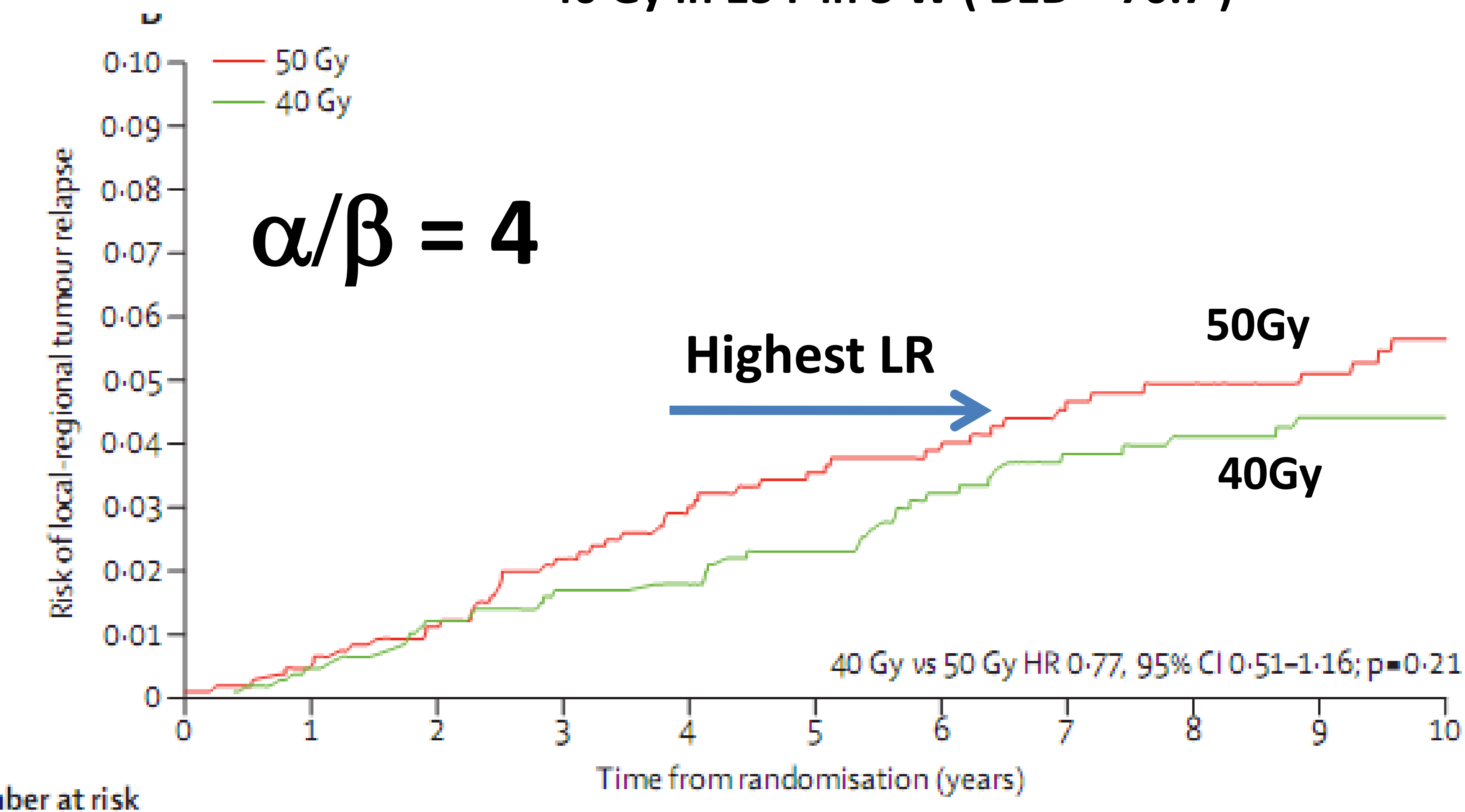
Post BCS → **50 Gy in 25 F in 33days** → **BED = 75**

Post BCS → **42.5 Gy in 16 F in 22 days** → **BED = 70**

Ca Breast

START B Trial

50 Gy in 25 F in 5 W (BED = 75)
40 Gy in 15 F in 3 W (BED = 70.7)



Radiotherapy and Oncology 121 (2016) 420–423

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Phase III randomised trial

Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation

Joanne S. Haviland [a,c], Søren M. Bentzen [b], Judith M. Bliss [c], John R. Yarnold [d,*],
On behalf of the START Trial Management Group

[a] *Faculty of Health Sciences, University of Southampton, UK;* [b] *Department of Epidemiology and Public Health and Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, USA;* [c] *ICR-CTSU, Division of Clinical Studies; and* [d] *Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK*

Accelerated proliferation after 3 weeks

D(prolf) = 0.6Gy per day

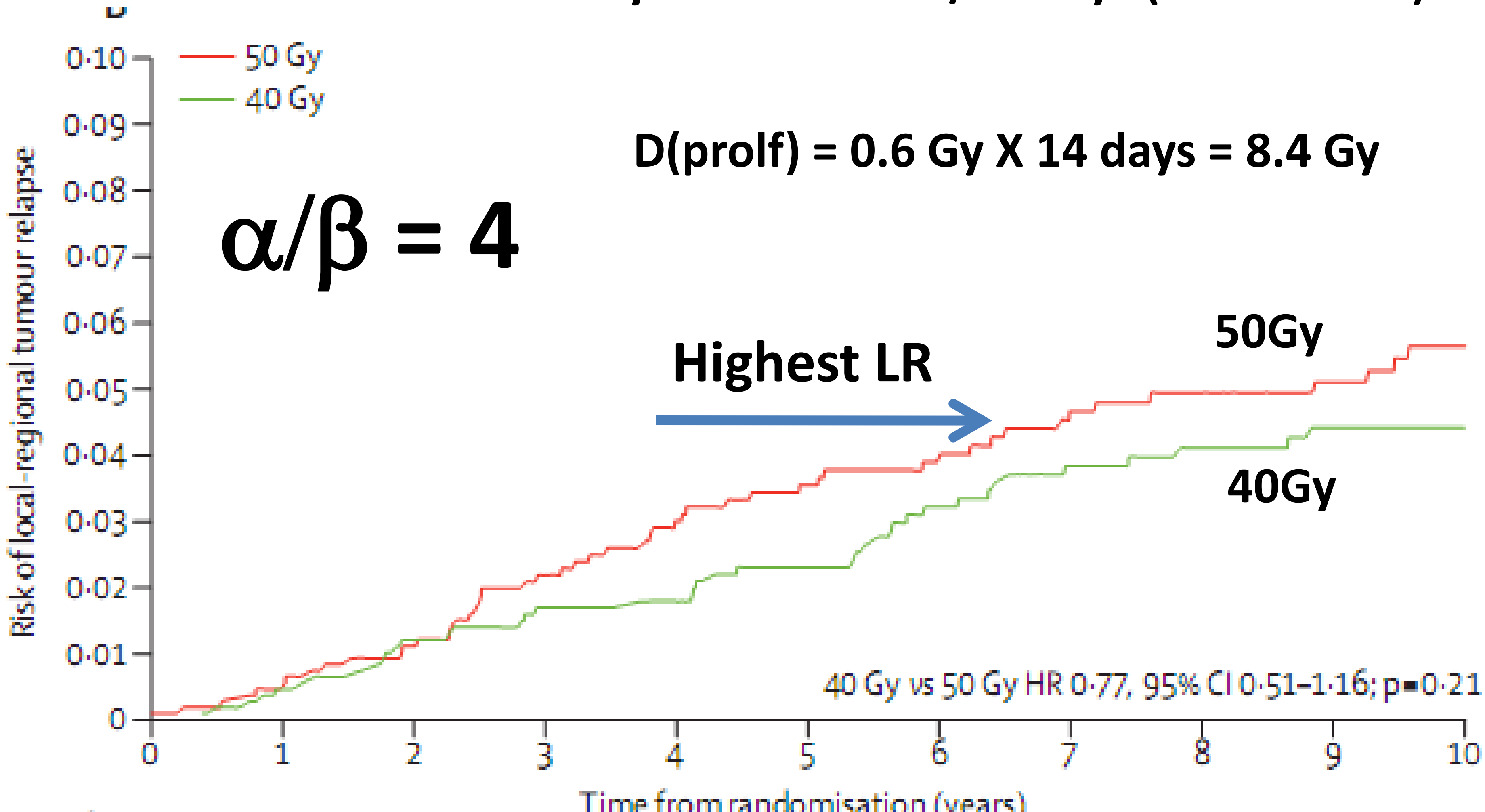
Ca Breast

START B Trial

50 Gy in 25 F in 5 W/33 days (BED = 66.6)
40 Gy in 15 F in 3 W/19 days (BED = 70.7)

D(prolf) = 0.6 Gy X 14 days = 8.4 Gy

α/β = 4



ber at risk

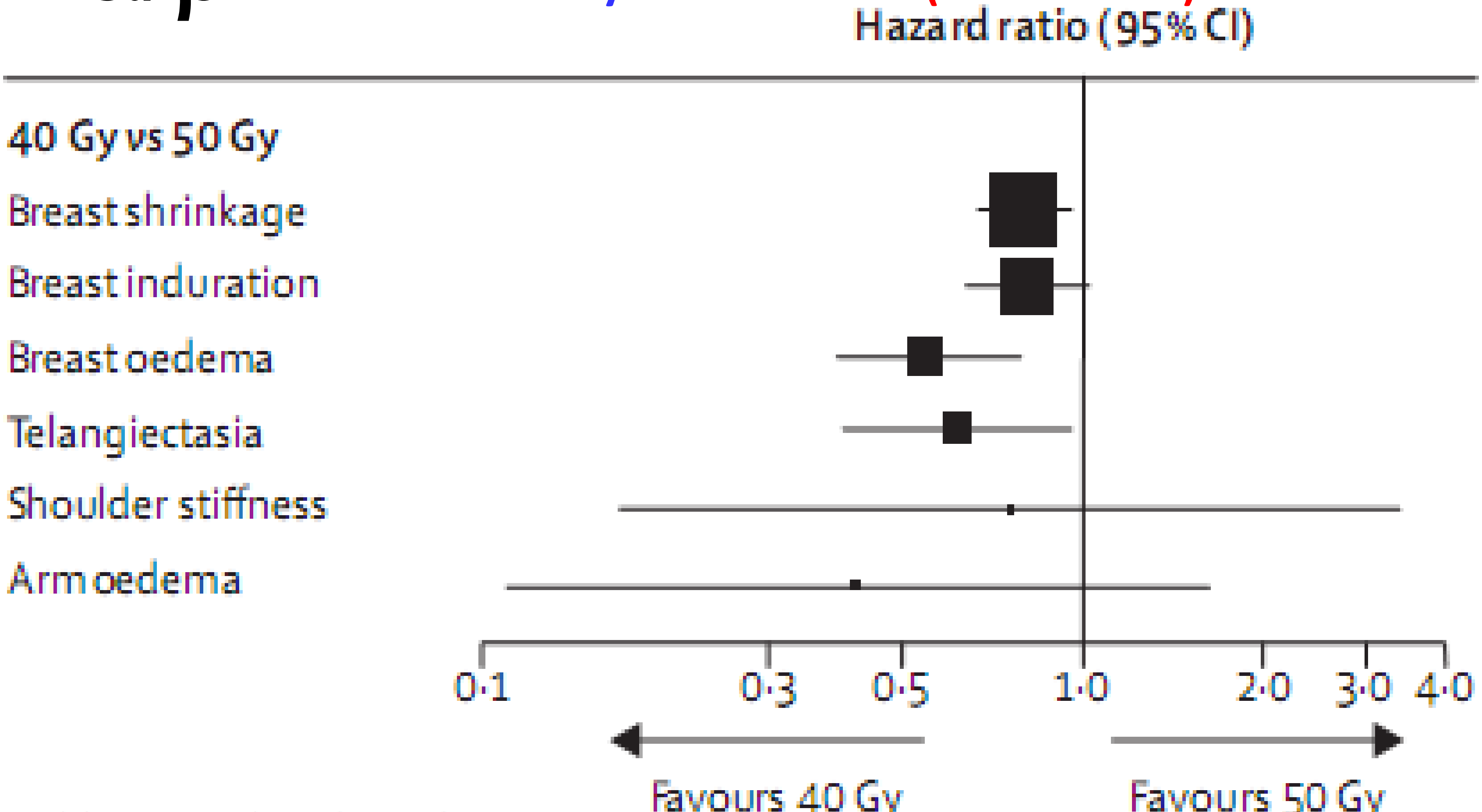
START B Trial

Late side effects in term of cosmesis was better in hypo arm

B $\alpha/\beta = 3.5$

50 Gy in 25 F in 5 W (BED = 78.6)

40 Gy in 15 F in 3 W (BED = 70.5)



www.thelancet.com/oncology Vol 14 October 2013

ORIGINAL ARTICLE

Ca Breast

Canadian Trial

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D., Jim A. Julian, Ph.D., Robert MacKenzie, M.D., Sameer Parpia, M.Sc., Wendy Shelley, M.D., Laval Grimard, M.D., Julie Bowen, M.D., Himu Lukka, M.D., Francisco Perera, M.D., Anthony Fyles, M.D., Ken Schneider, M.D., Sunil Gulavita, M.D., and Carolyn Freeman, M.D.

N ENGL J MED 362;6 NEJM.ORG FEBRUARY 11, 2010

Post BCS → **50 Gy in 25 F in 33days** → **BED = 75**

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ORIGINAL ARTICLE

Ca Breast **Canadian Trial**

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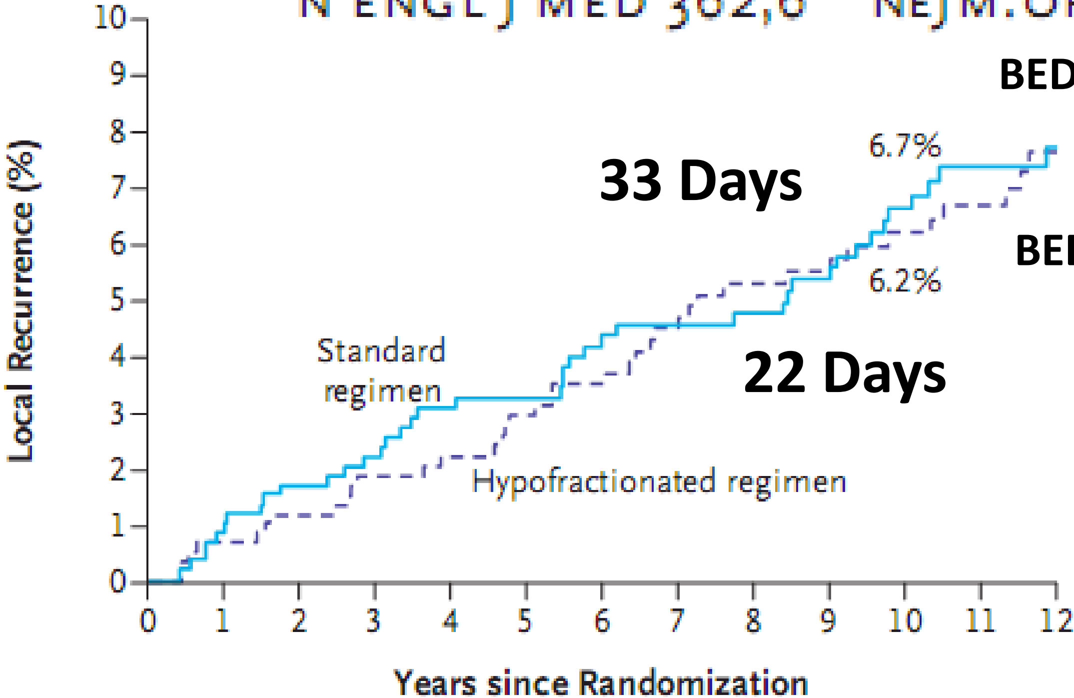


BED 68.4

BED = 70

5 Gy

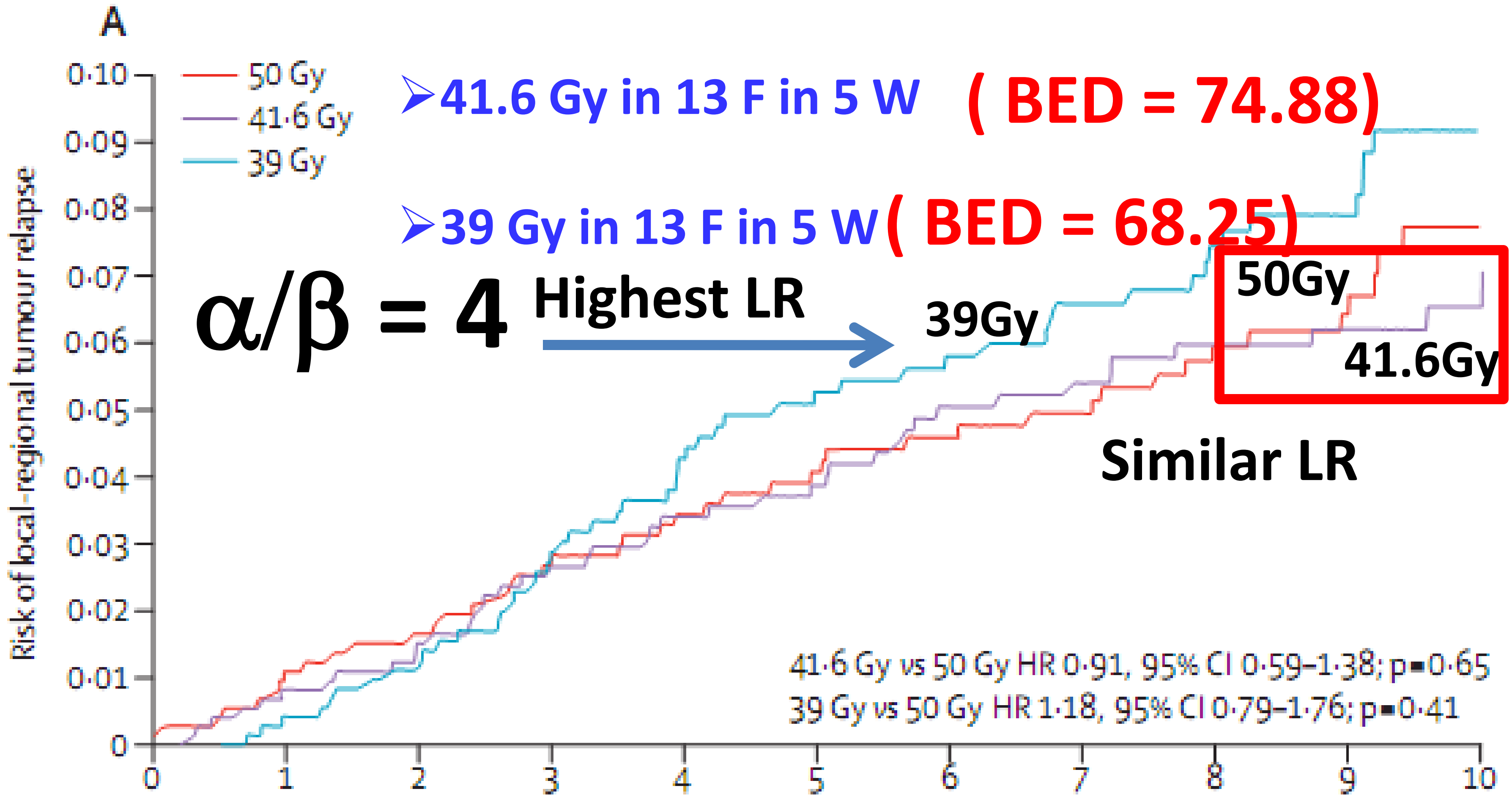
0.6 X 11 = 6.6 Gy

Ca Breast

START A Trial

- 50 Gy in 25 F in 5 W **(BED = 75)**
- 41.6 Gy in 13 F in 5 W **(BED = 74.88)**
- 39 Gy in 13 F in 5 W **(BED = 68.25)**

$\alpha/\beta = 4$



www.thelancet.com/oncology Vol 14 October 2013

Ca Prostate

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

Phase III Trial of Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHIP)

- Hypothesis: alpha/beta ratio in ca prostate may be low (1.5)

NAD / 3m

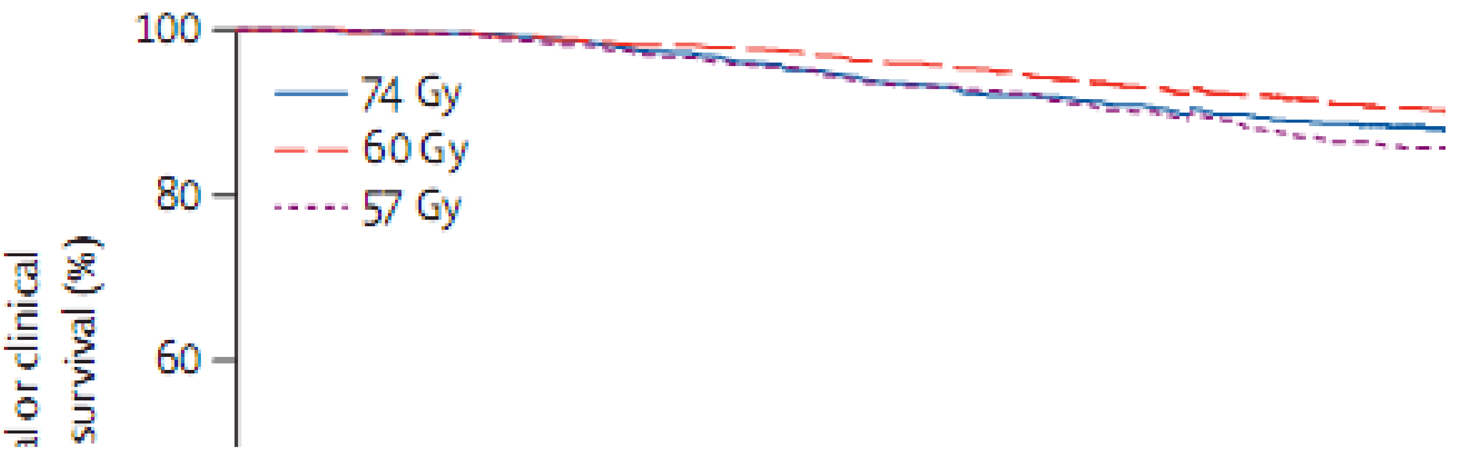
Conventional	74Gy	37F	7.4w
Hypofractionated	60Gy	20F	4w
Hypofractionated	57Gy	19F	3.8w

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

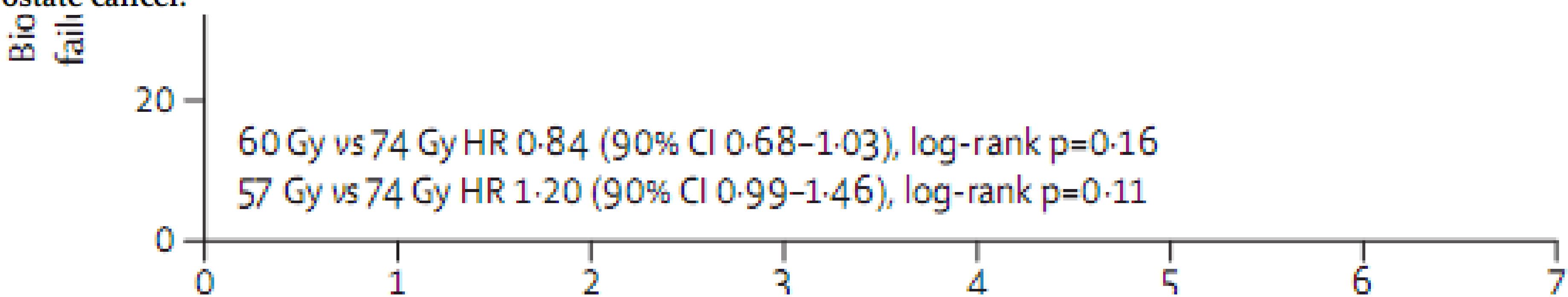
Lancet Oncol 2016; 17: 1047–60

60 Gy in 20F **74 Gy in 37F** **57 Gy in 19F**

BED = 180 ***BED = 173*** ***BED = 171***



Interpretation Hypofractionated radiotherapy using 60 Gy in 20 fractions is non-inferior to conventional fractionation using 74 Gy in 37 fractions and is recommended as a new standard of care for external-beam radiotherapy of localised prostate cancer.



Lancet Oncol 2016; 17: 1047–60

Hypofractionation

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 77–82, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2005.06.014

CLINICAL INVESTIGATION **Head and Neck**

RADIOTHERAPY FOR EARLY GLOTTIC CARCINOMA (T1N0M0): RESULTS OF PROSPECTIVE RANDOMIZED STUDY OF RADIATION FRACTION SIZE AND OVERALL TREATMENT TIME

Hideya Yamazaki, M.D.,* Kinji Nishiyama, M.D.,* Eiichi Tanaka, M.D.,*
Masahiko Koizumi, M.D.,† and Masashi Chatani, M.D.‡

*Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease, Higashinari, Osaka-city, Osaka, Japan; †Department of Radiology, Kyoto Prefecture University, Shimogamo Hangi-Cho, Kyoto, Japan; ‡Department of Radiation Oncology, Osaka Rosai Hospital, Sakai City, Osaka, Japan

T1 Glottic Cancers

60-66 Gy with 2 Gy/fx in 40 to 45 days

56.25-63 Gy with 2.25Gy/fx in 33 to 38 days

Dose per fraction increased and total time decreased in experimental arm

Hypofractionation

BED for late reacting tissue was matched in both arm which was 100 Gy_3

BED for tumor was almost same in both arms which was around 64 Gy_{10}

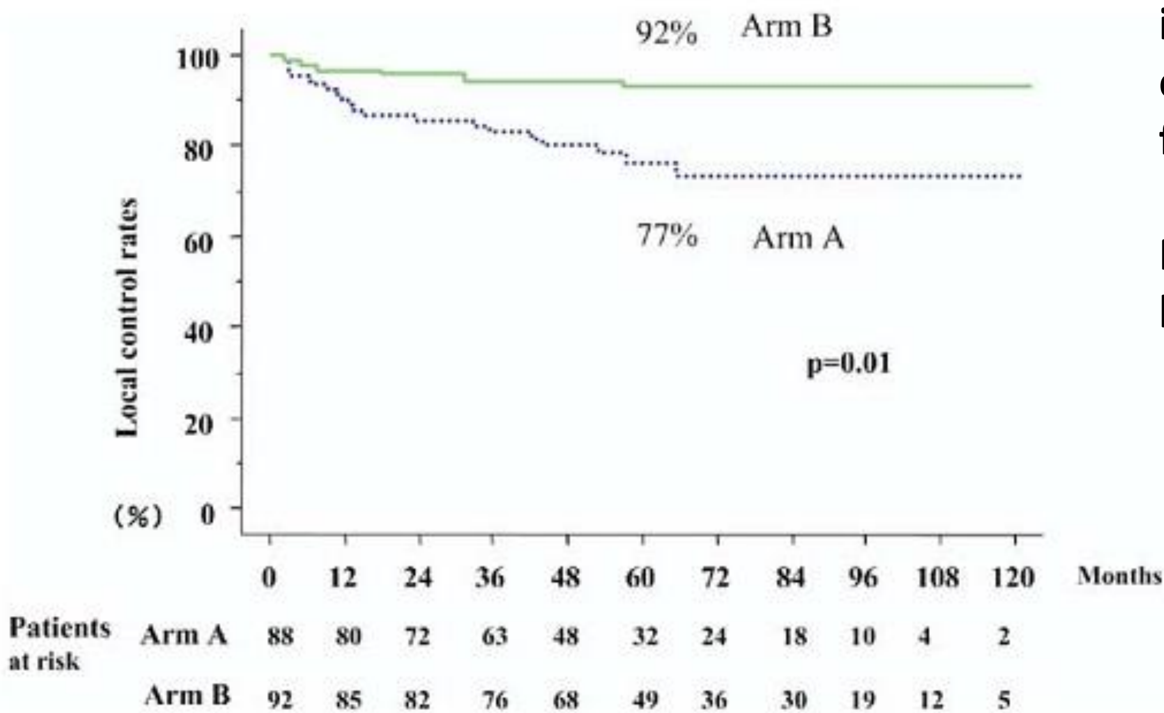


Fig. 1. Local control rates between Arms A and B.

Fraction size and overall treatment time for early glottic carcinoma ● H. Yamazaki *et al.*

Local control was much higher in hypo fraction arm as compare to conventional fractions.

Reason can not be explained by available models

T1 Glottic Cancers

60-66 Gy with 2 Gy/fx in 40 to 45 days

56.25-63 Gy with 2.25Gy/fx in 33 to 38 days

Overall treatment time is reduced

Will counter the repopulation

Mainly seen in well and moderately differentiated ca

Majority of the glottic cancers are well and moderately differentiated

Reduce the effect of repopulation

High dose per fraction will kill more cell than conventional fraction RT

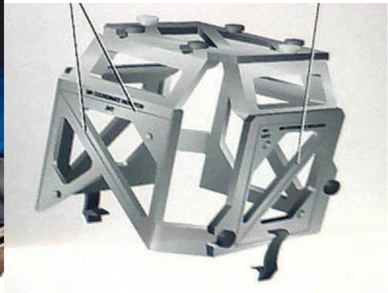
Well differentiated ca are least sensitive

Cellular radiosensitivity

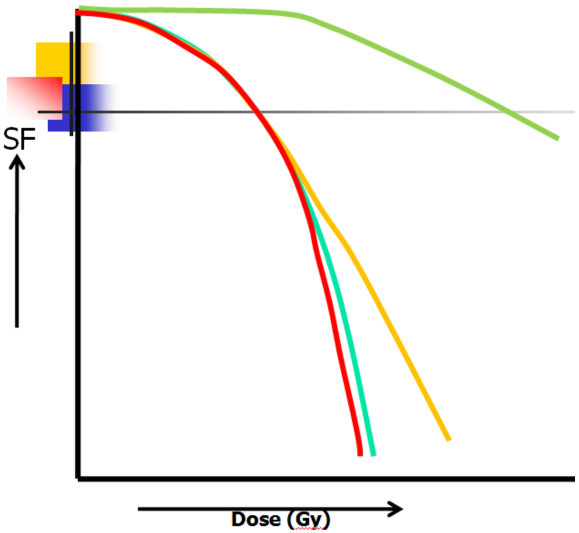
Law of Bergonie' and Tribondeau

"The radiosensitivity of a population of cells is inversely proportional to their degree of differentiation."

Radiobiology of Non Fractionated RT



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



- ❖Benign and Malignant Diseases

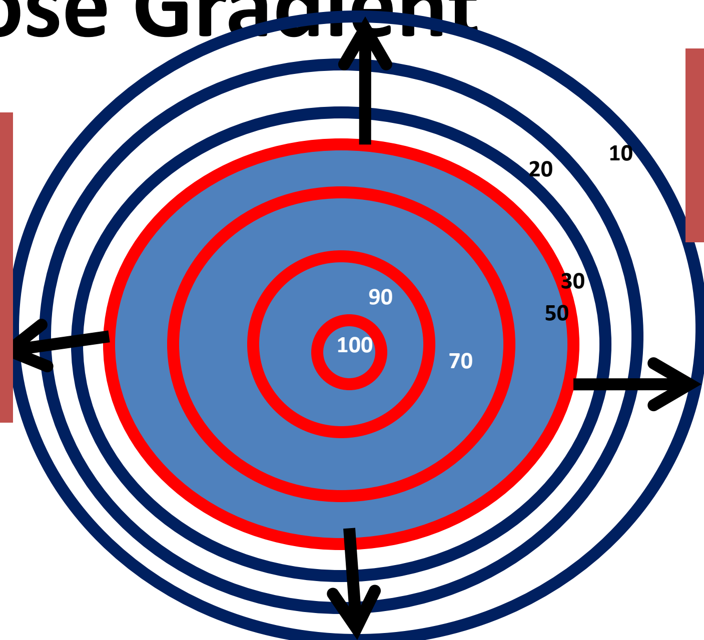
SRS and SBRT

1. Small Target usually tumor <3cm

2. Highest degree of conformality.

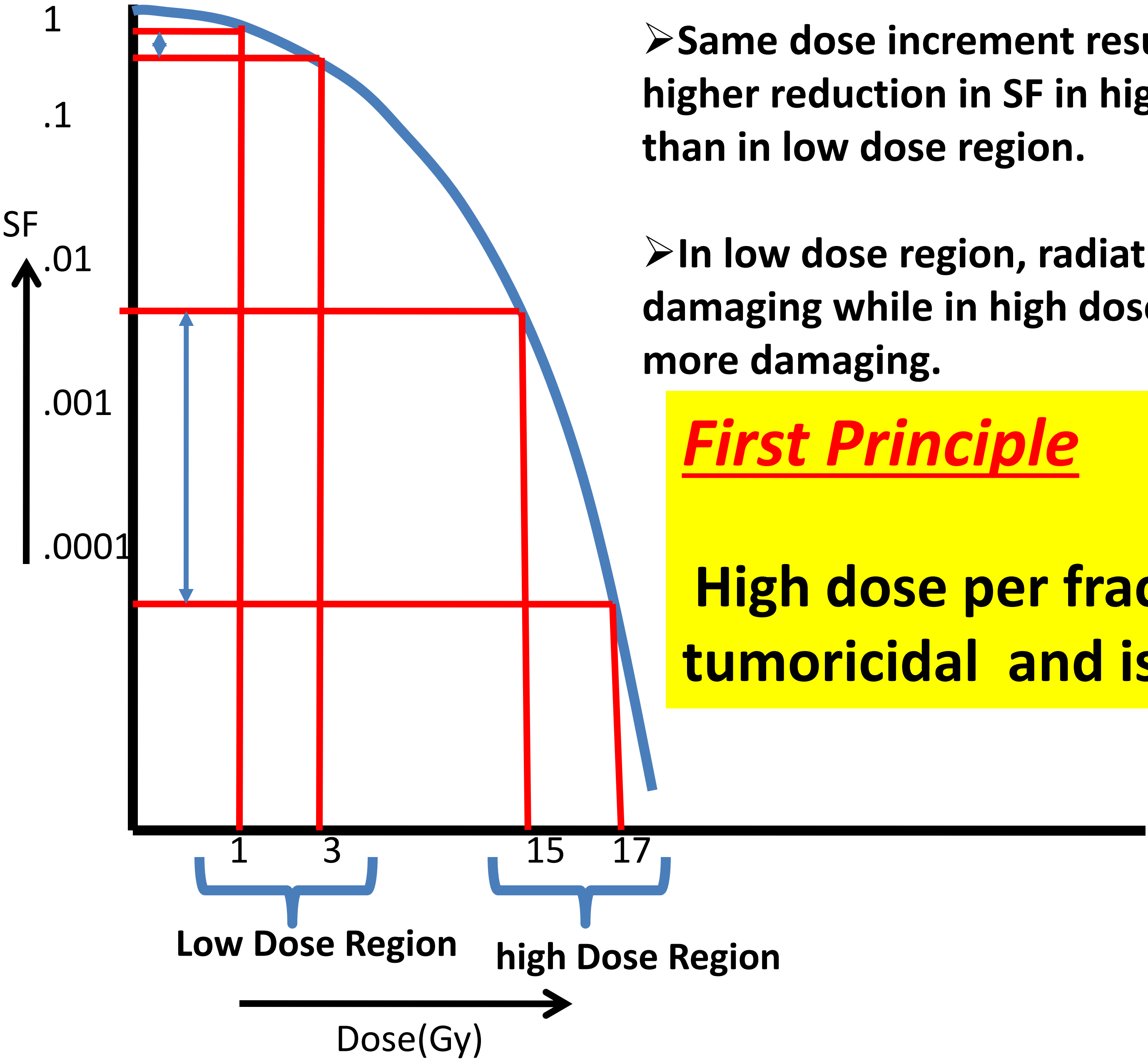
3. Steep Dose Gradient

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

Effect of high dose on Cell Survival Curve

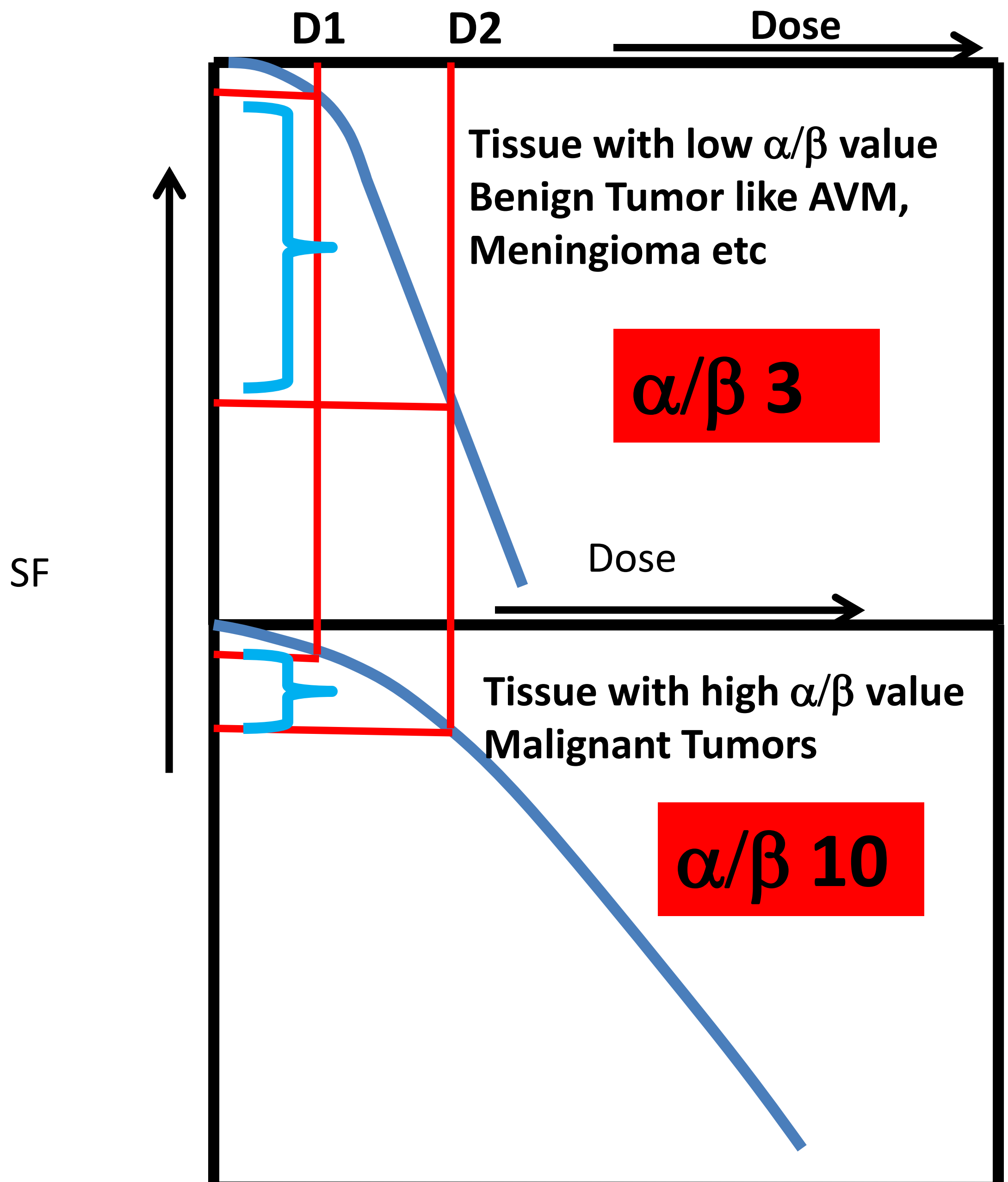


- Same dose increment result in much higher reduction in SF in high dose region than in low dose region.
- In low dose region, radiation is less damaging while in high dose region it is more damaging.

First Principle

High dose per fraction is more tumoricidal and is more damaging

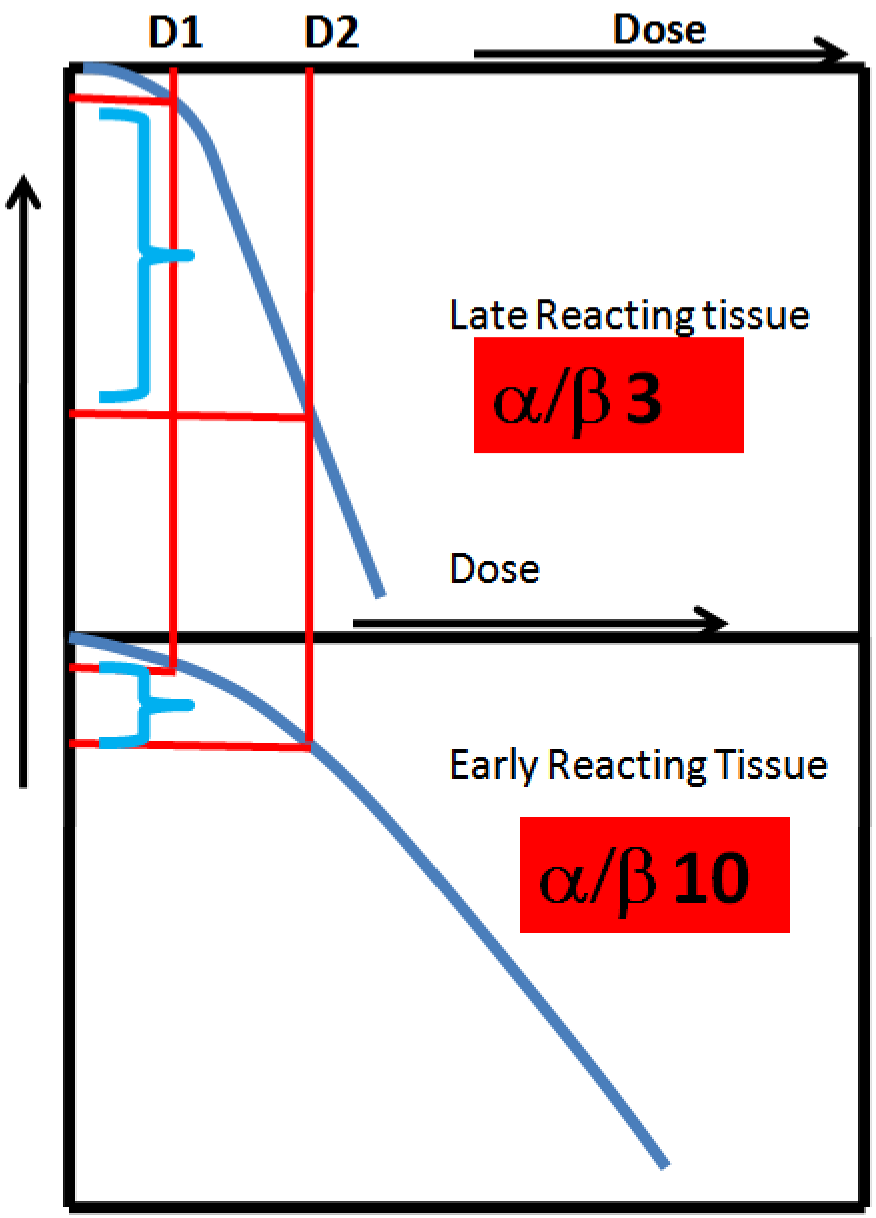
Non Fractionated RT More Effective For Benign Tumors

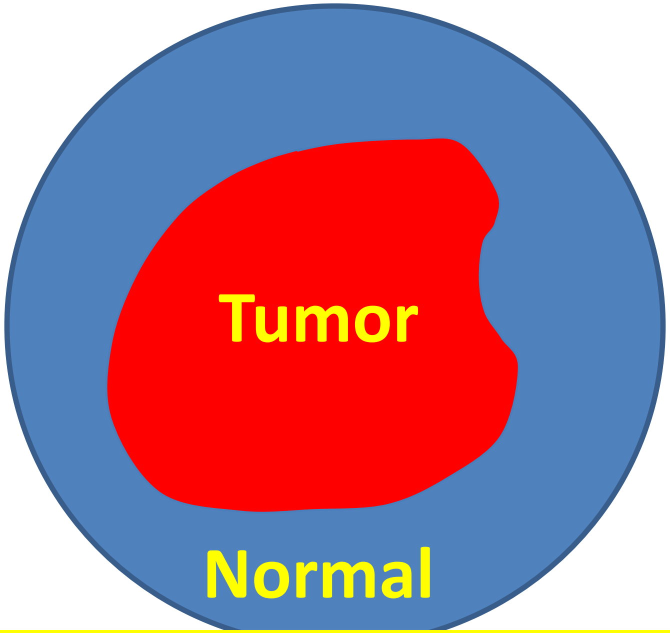


Second Principle

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





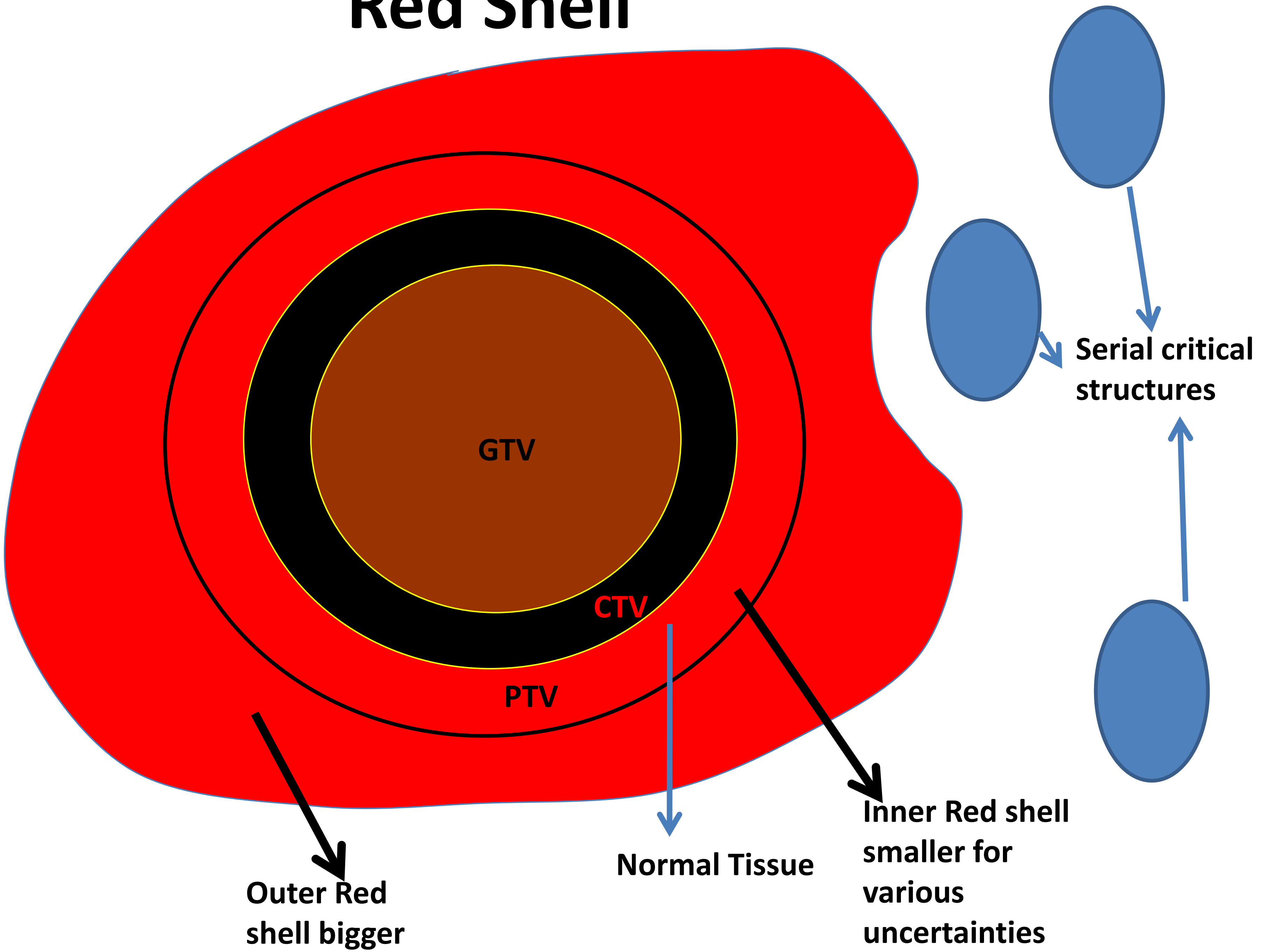
Third *Principle*

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

Red Shell

 I. J. Radiation Oncology ● Biology ● Physics Volume 77, Number 3, 2010

Red Shell



Clinical Significance of Red Shell

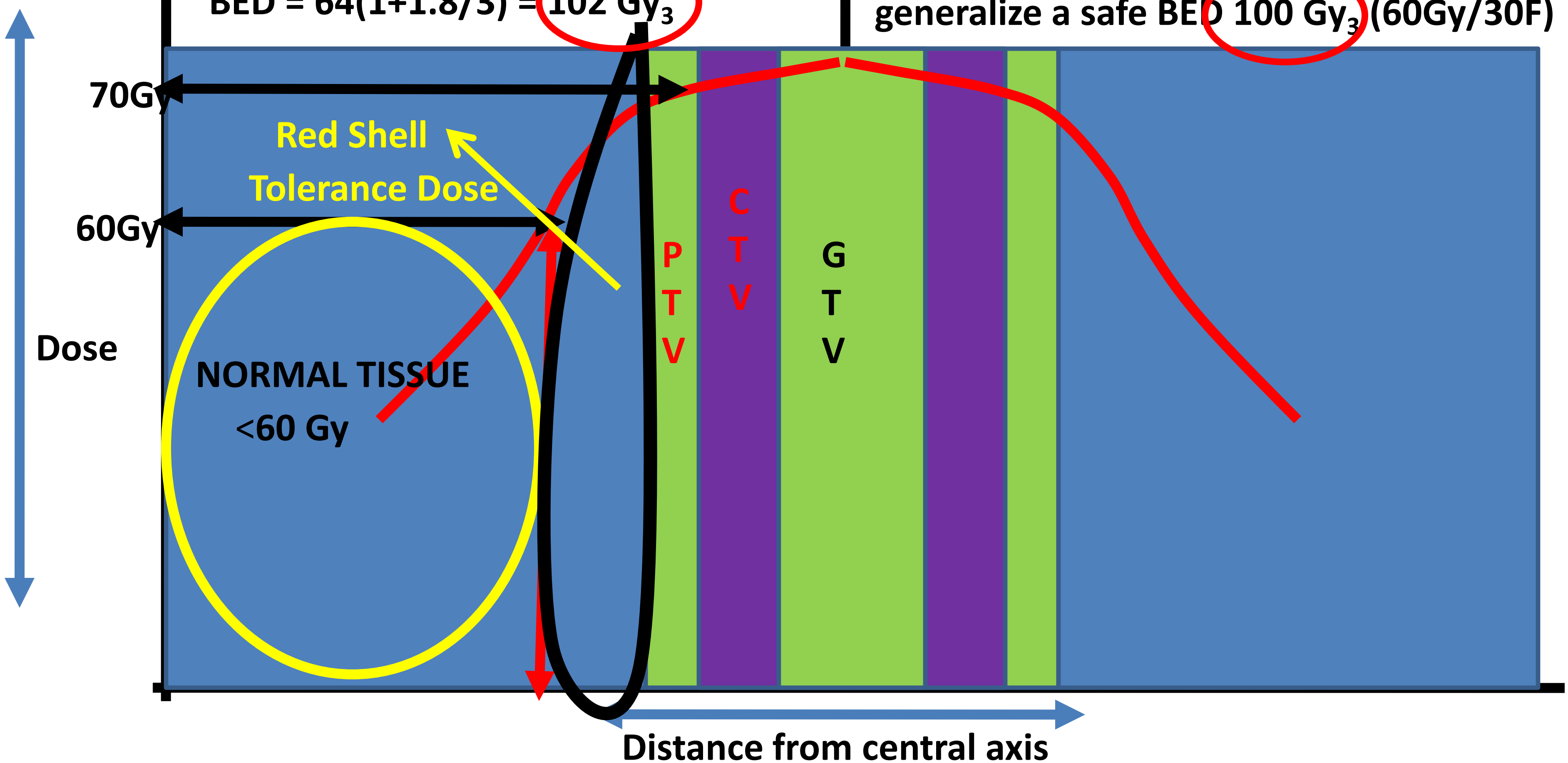
64 Gy in 35fx, d/f = 1.8 Gy

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

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

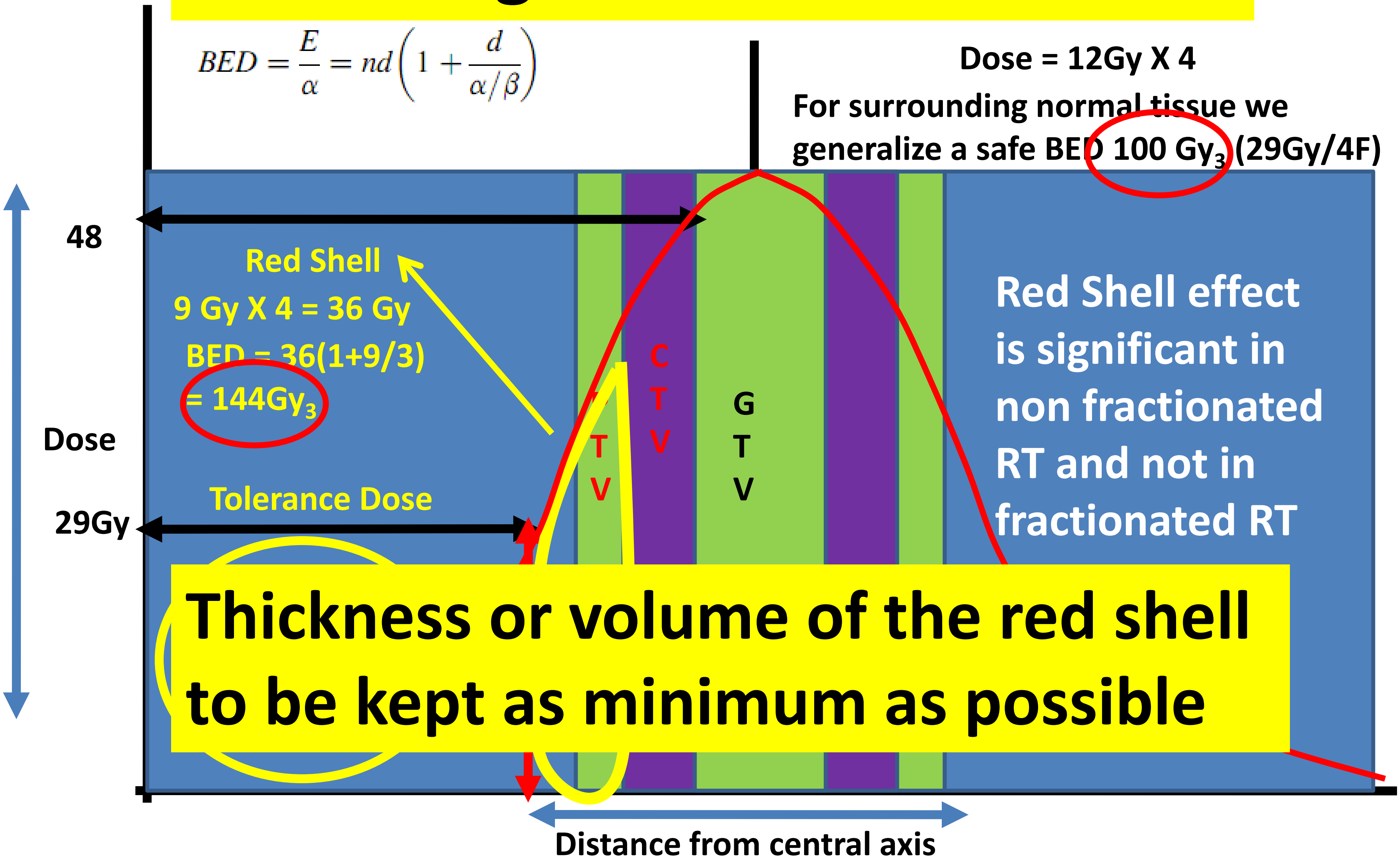
70 Gy/35fx/2Gy per fx

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

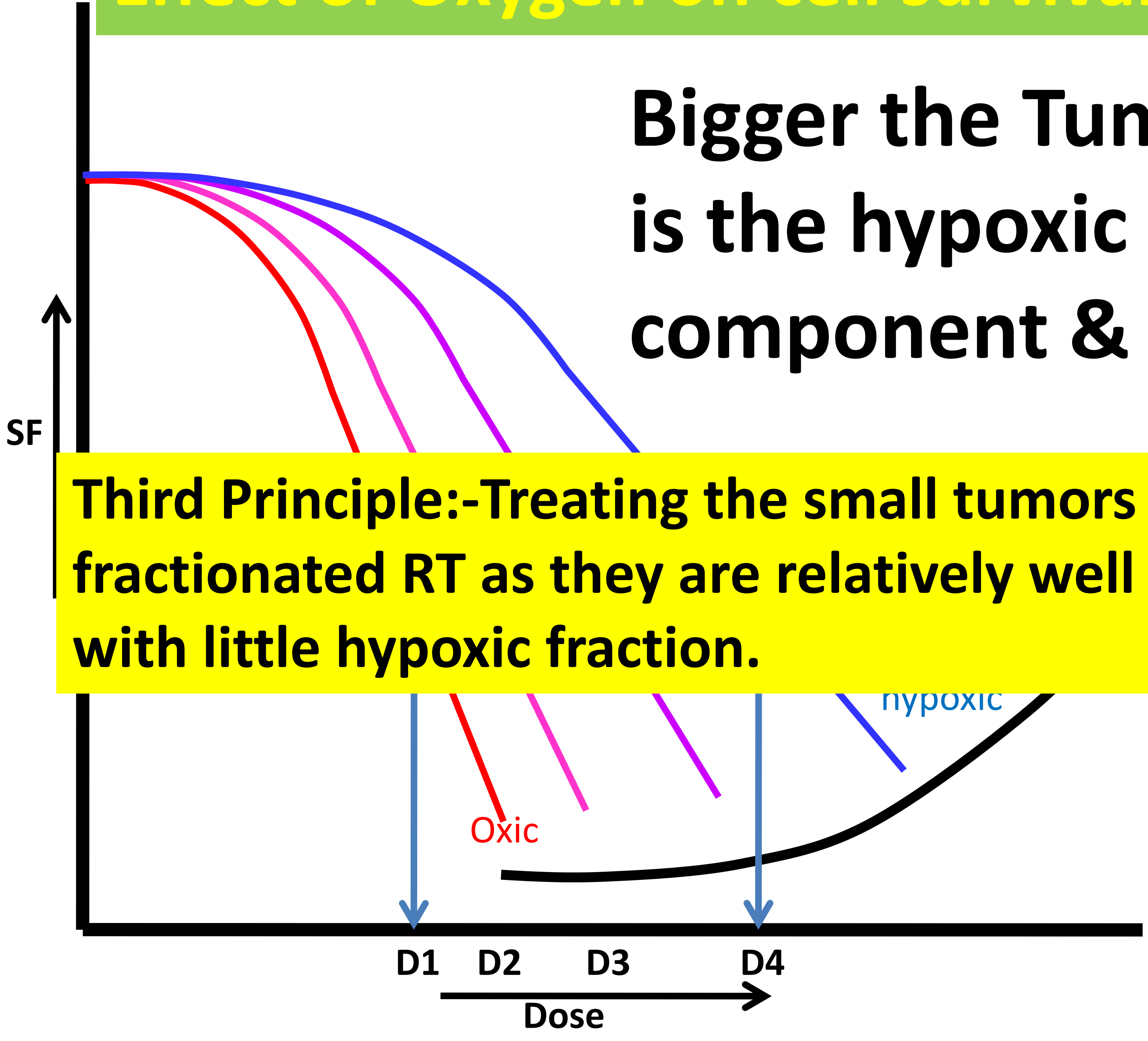
- ***So we can reduce the Volume of Red Shell thus damaging effect of Non fractionated RT on normal tissue by:-***
  - **Keeping the dose gradient very steep.**
    - **By multiple non-coplaner beams and careful planning**
  - **Keeping the target volume minimum.**
    - **By Treating early lesions only**
  - **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

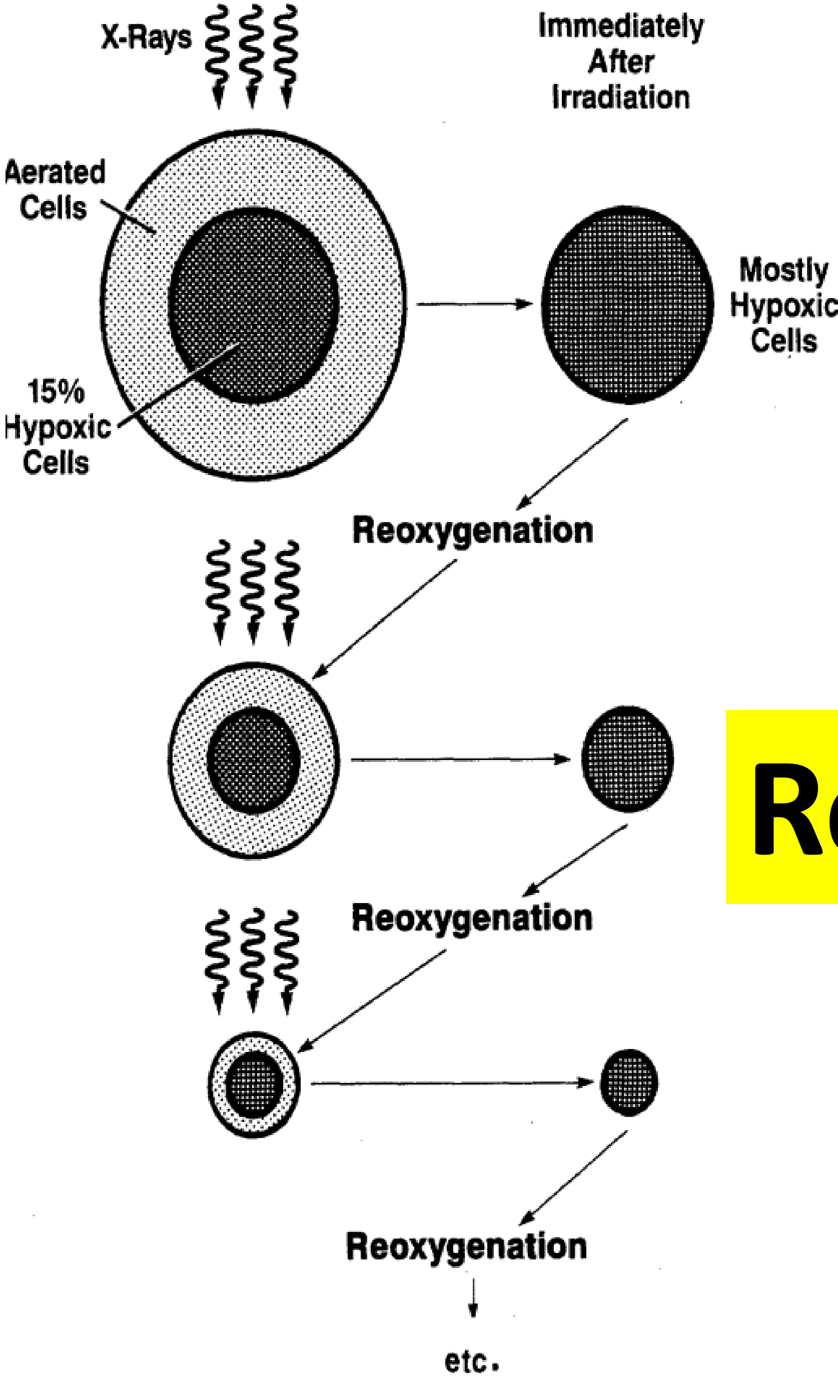
Effect of Oxygen on cell survival curve

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.

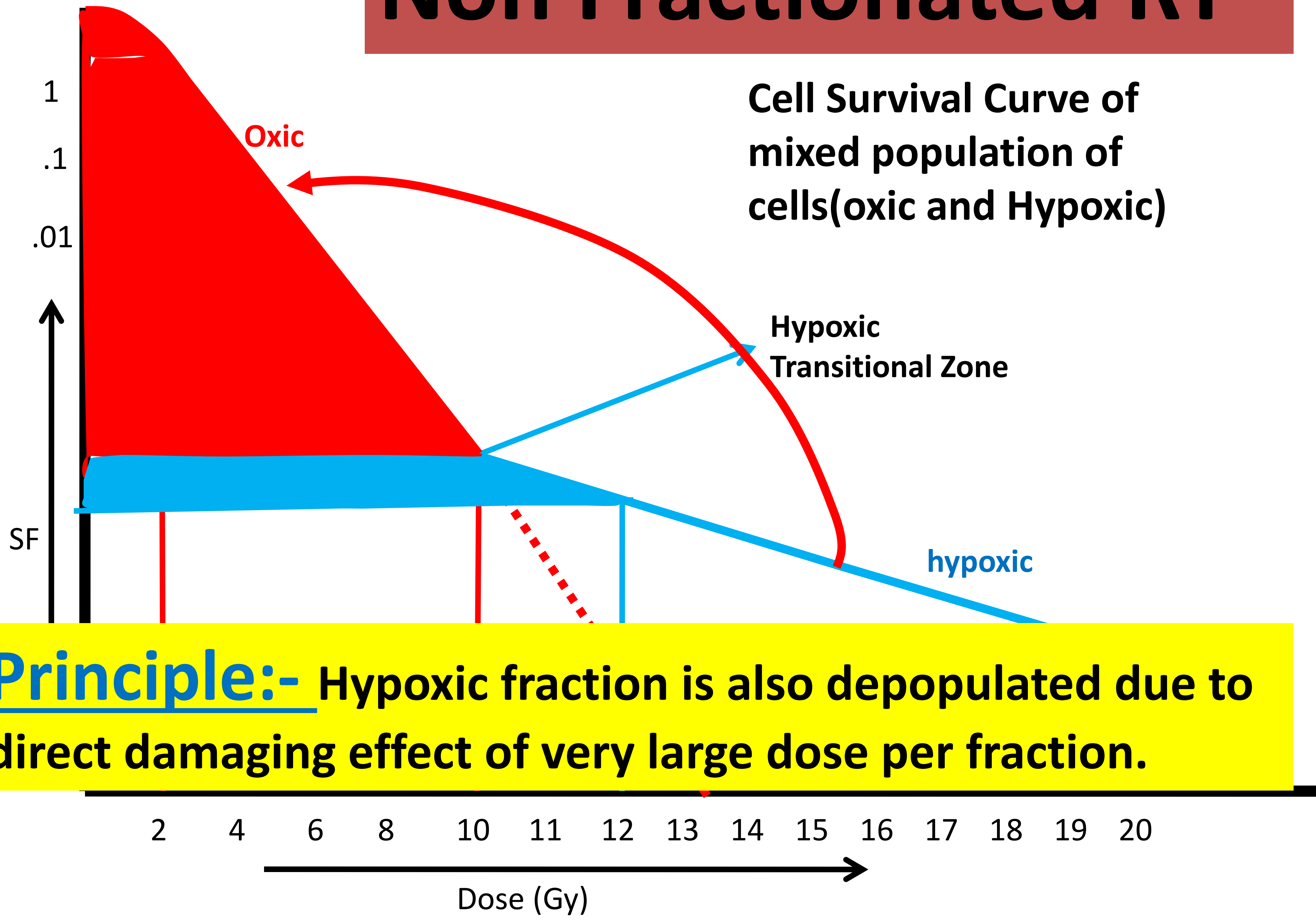
Fractionated RT



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.

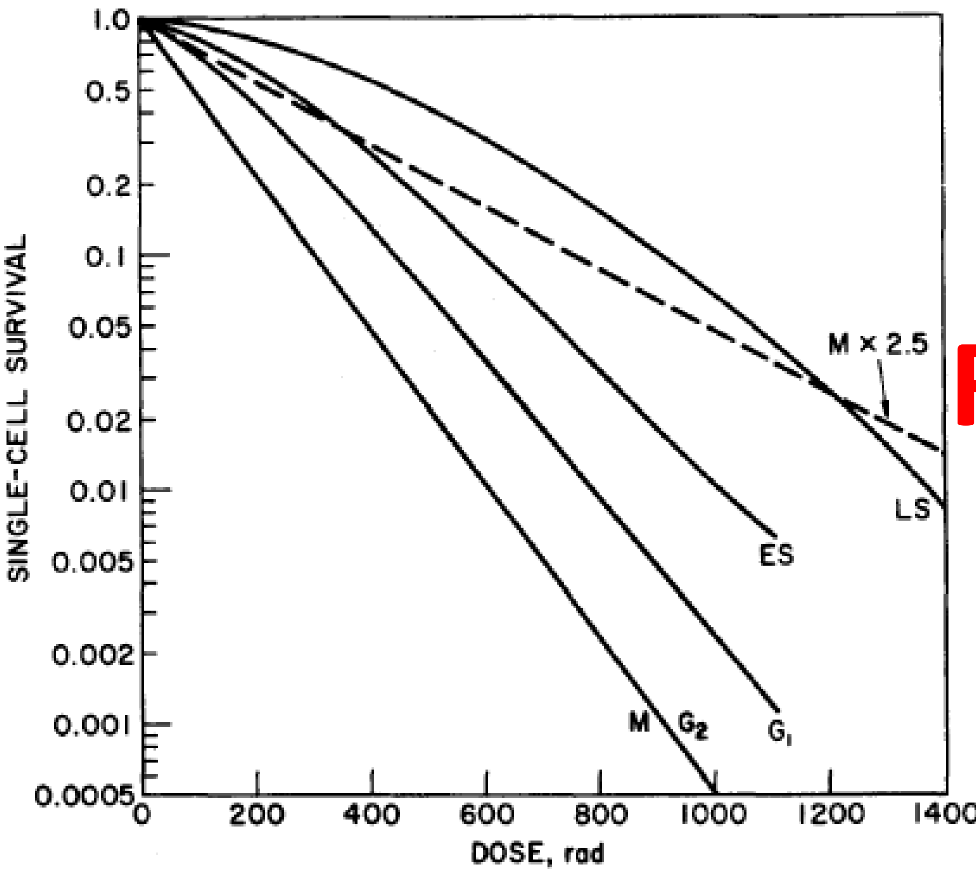
$$OER = \frac{D_0\,(\text{hypoxic}) \longrightarrow 6\text{ Gy}}{D_0\,(\text{aerobic}) \longrightarrow 2\text{ Gy}}$$

= 2.5 to 3 for x-rays and γ-rays

SRS/SRT Dose is > 12 Gy

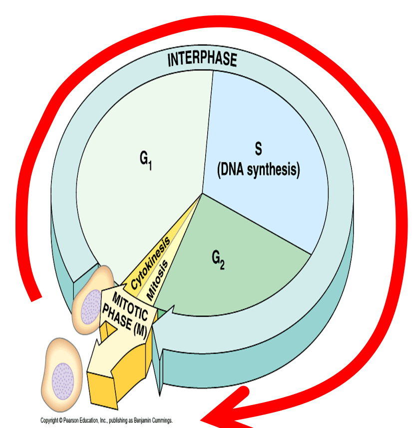
Redistribution or Reassortment

- G2, M-------Most sensitive
- Late S--------Most Resistant
- 5 fold difference in sensitivity.



- During fractionation, after each fraction of RT, cells in sensitive phase are killed and before next fraction, cells progress through cell cycle and again come to sensitive phase.
- This process is known as

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

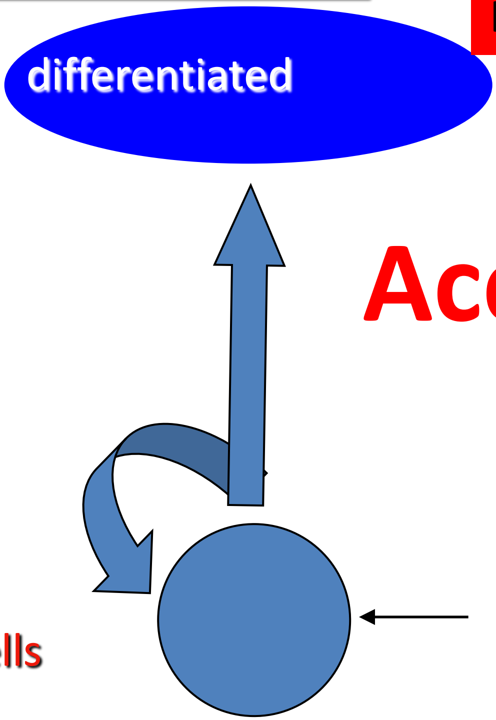
- There is 5 fold difference in survival after 200 rad

SRS/SRT Dose is > 12 Gy

Repopulation (Accelerated)

STEADY STATE → REGENERATION

Injury, physical or Radiation



Accelerated Repopulation.

stem cells

cell loss factor $\phi = 1$

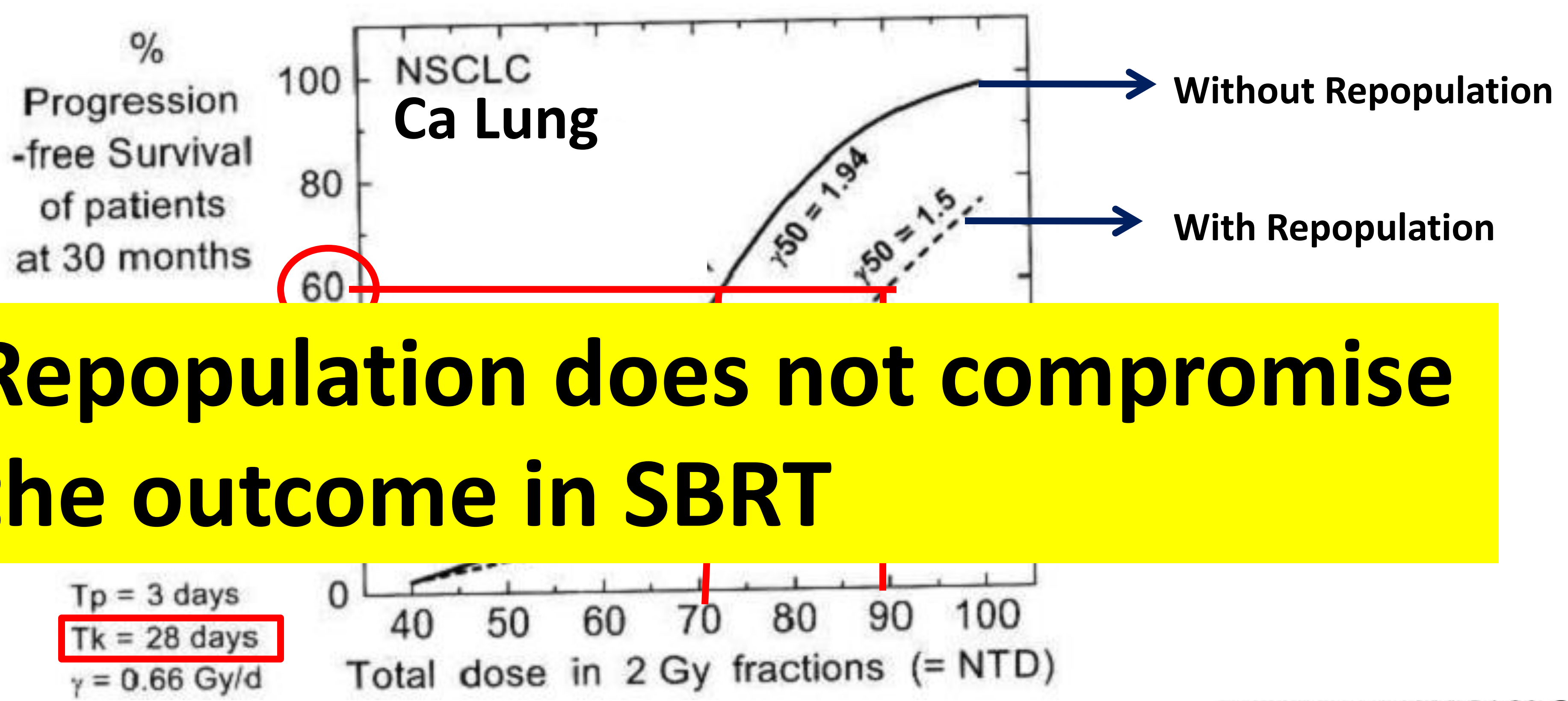
↓

Tissue will not Grow

Non Fractionated RT

Repopulation in NSCLC starts at 28 days

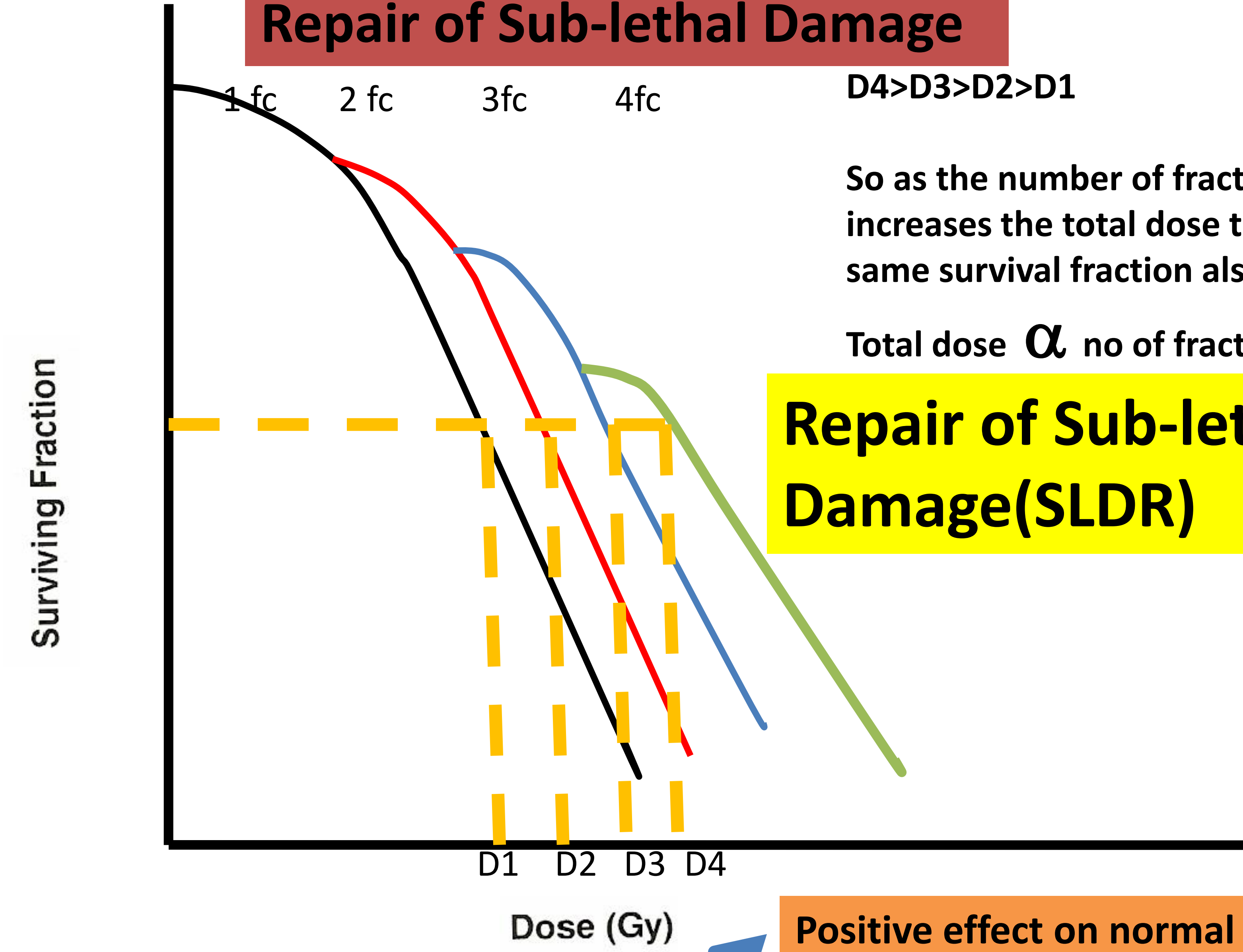
Most of the SBRT lung regimen are completed by two weeks



Repopulation does not compromise the outcome in SBRT

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

Repair of Sub-lethal Damage



D4>D3>D2>D1

So as the number of fraction increases the total dose to achieve same survival fraction also increases

Total dose α no of fractions

Repair of Sub-lethal Damage(SLDR)

Inter fraction repair

Completes in 4-8 hours

Positive effect on normal tissue

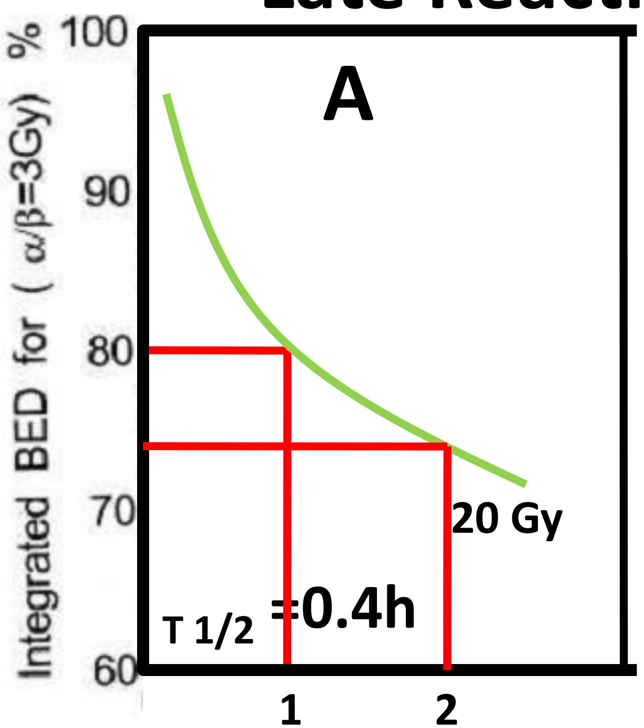
Negative effect on Tumor

Non Fractionated RT

Repair is not seen with high dose RT as in SRS/SBRT

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

Late Reacting Tissue



Positive effect on normal tissue

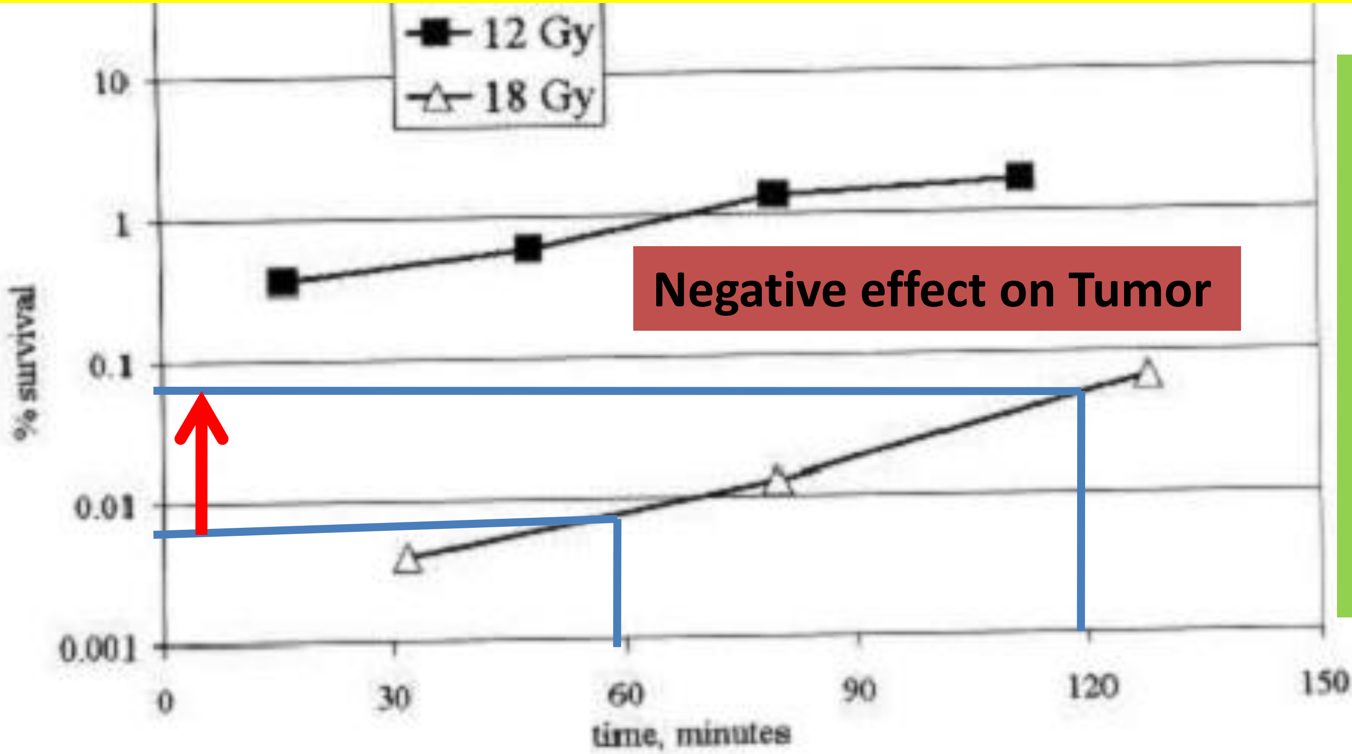
- **As the treatment delivery time increases the bio effective dose reduces**
- **Faster the repair more the loss of BED**

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

Non Fractionated RT

Effect on the Tumor

Survival fraction will increase with increase duration of radiation delivery



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

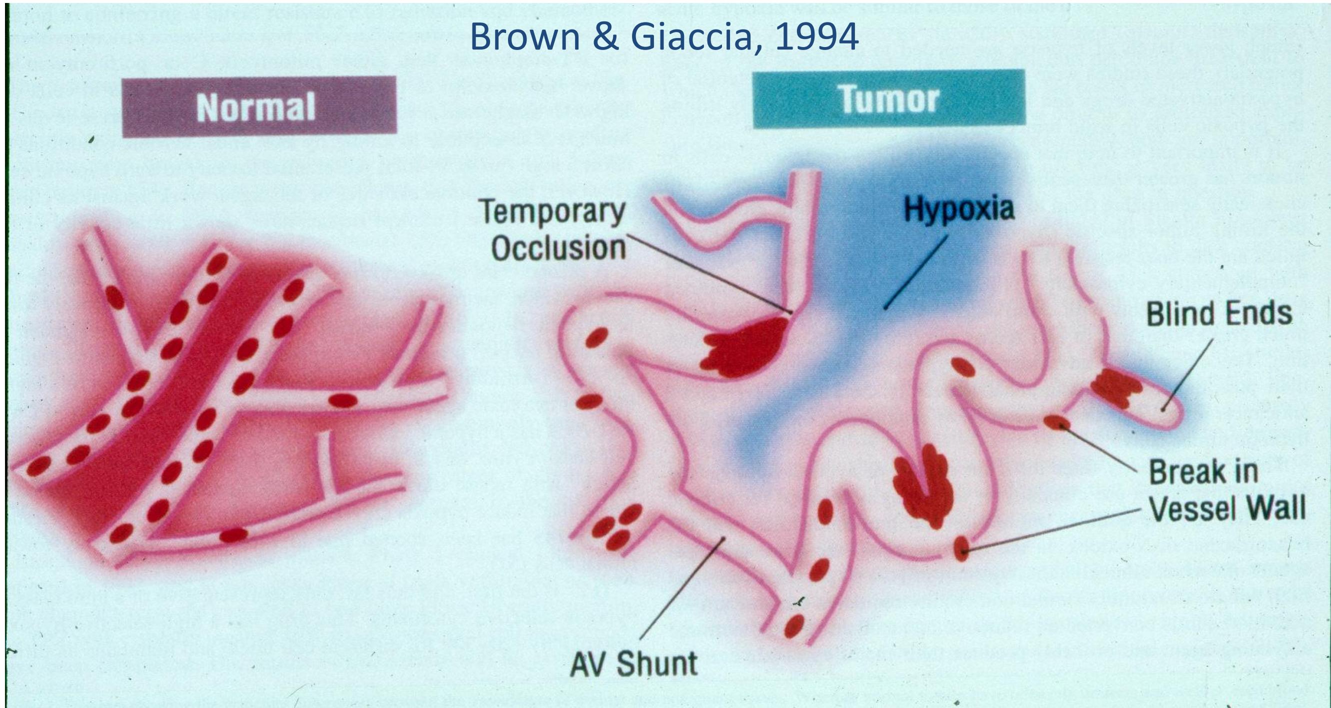
Benedict SH, Lin PS, *Int J Radiat Oncol Biol Phys* 1997;37:765–769.

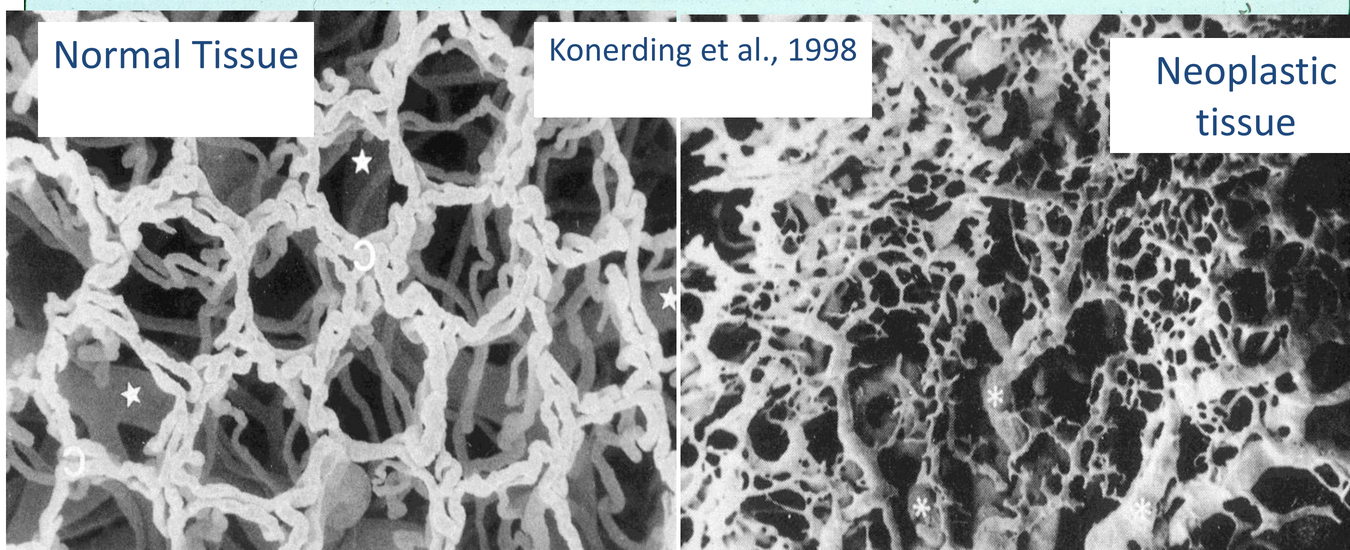
New Biology of High dose RT

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

Tumor Vasculature

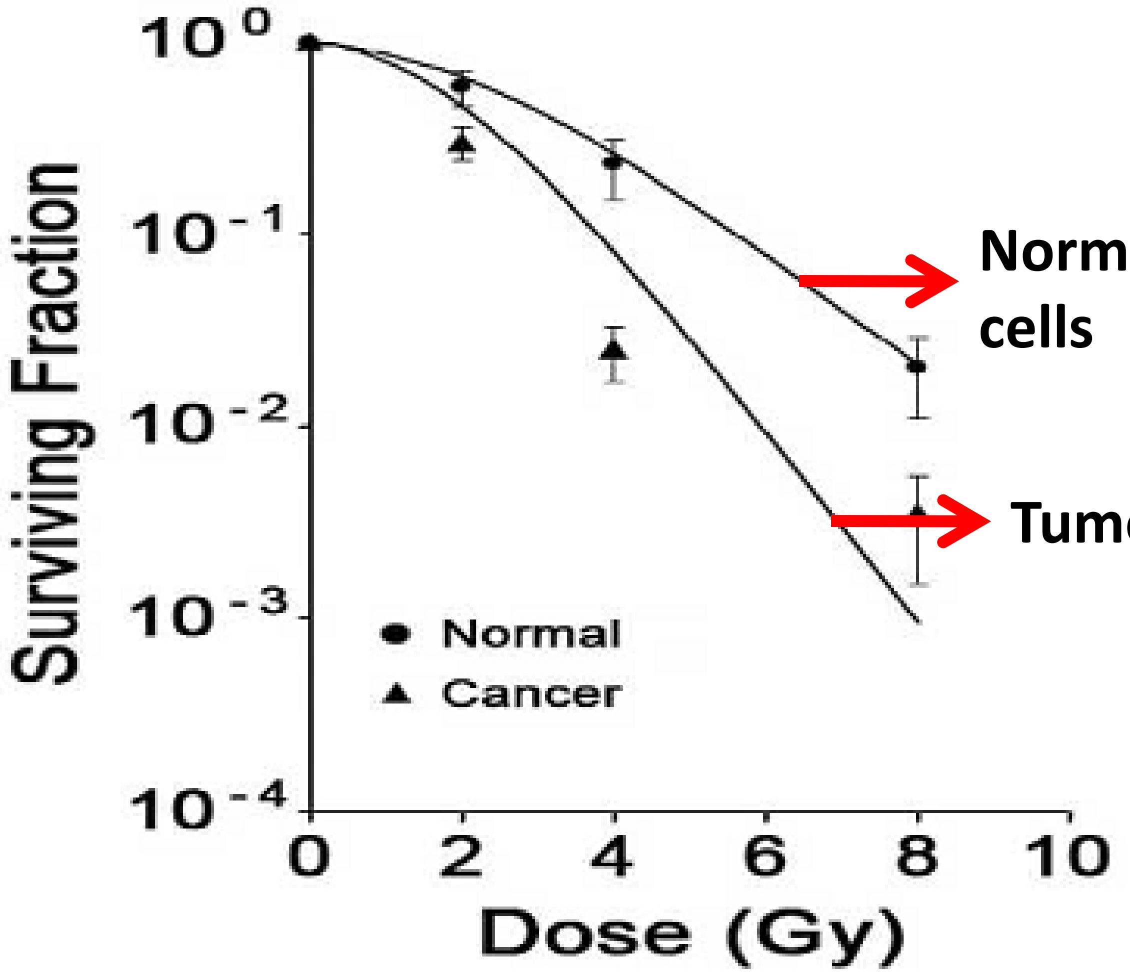
- The vascular network that develops in tumors is structurally abnormal
- Vessels are dilated, tortuous, elongated, with A-V shunts and blind ends
- The basement membrane is thin





Pre clinical Evidence

Tumor vasculature is more sensitive

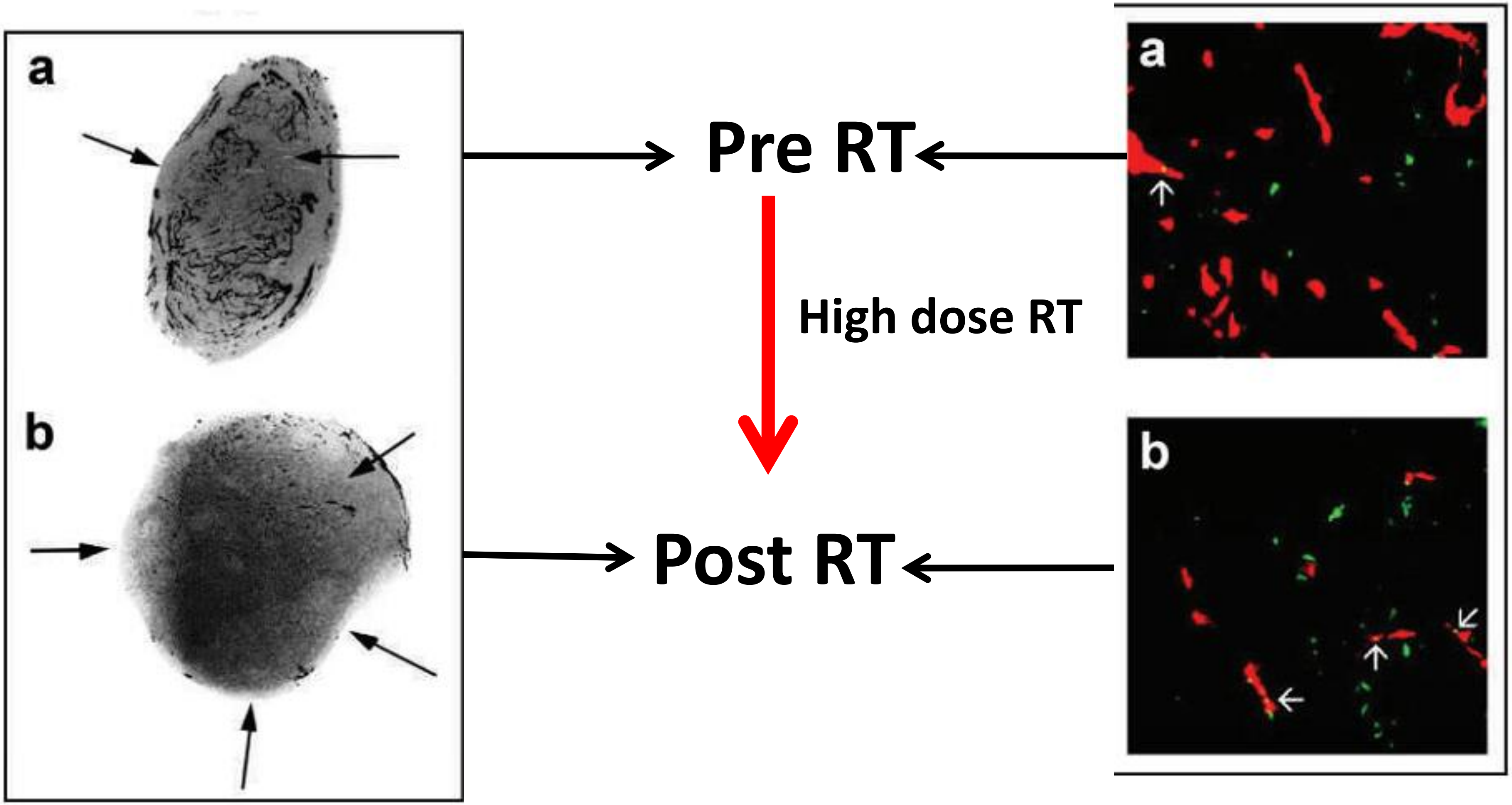


Normal tissue endothelial cells

Tumor endothelial cells

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

Vascular density in experimental tumor irradiated with high dose per fraction



Human Melanoma

Human Ovarian Ca

Pre clinical Evidence

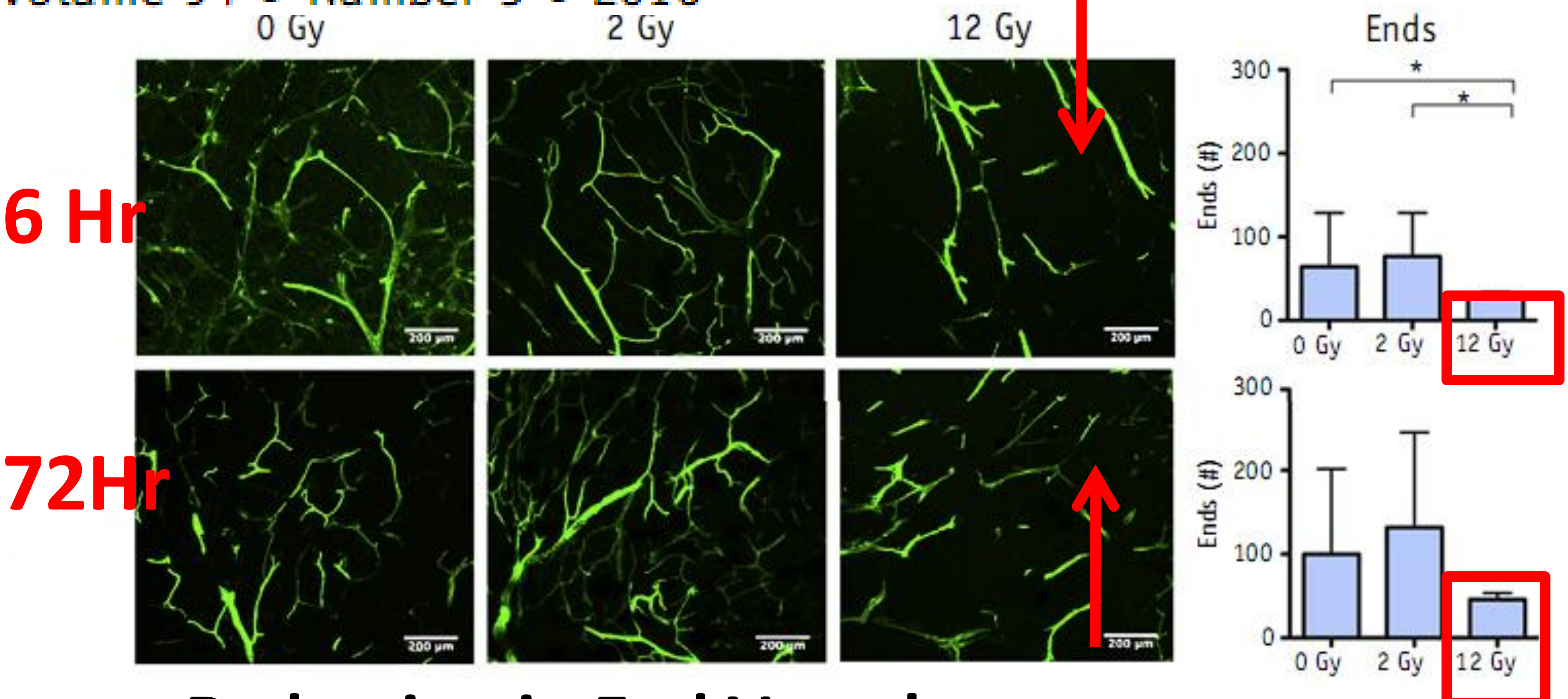
High-Dose, Single-Fraction Irradiation Rapidly Reduces Tumor Vasculature and Perfusion in a Xenograft Model of Neuroblastoma

CrossMark

Ashish Jani, MD,* Fauzia Shaikh, MD,* Sunjay Barton, BA,*
Callen Willis, BA,† Debarshi Banerjee, PhD,‡ Jason Mitchell, BA,†

International Journal of Radiation Oncology • Biology • Physics

Volume 94 • Number 5 • 2016



Reduction in End Vessels

High-Dose, Single-Fraction Irradiation Rapidly Reduces Tumor Vasculature and Perfusion in a Xenograft Model of Neuroblastoma

Ashish Jani, MD,* Fauzia Shaikh, MD,* Sunjay Barton, BA,*
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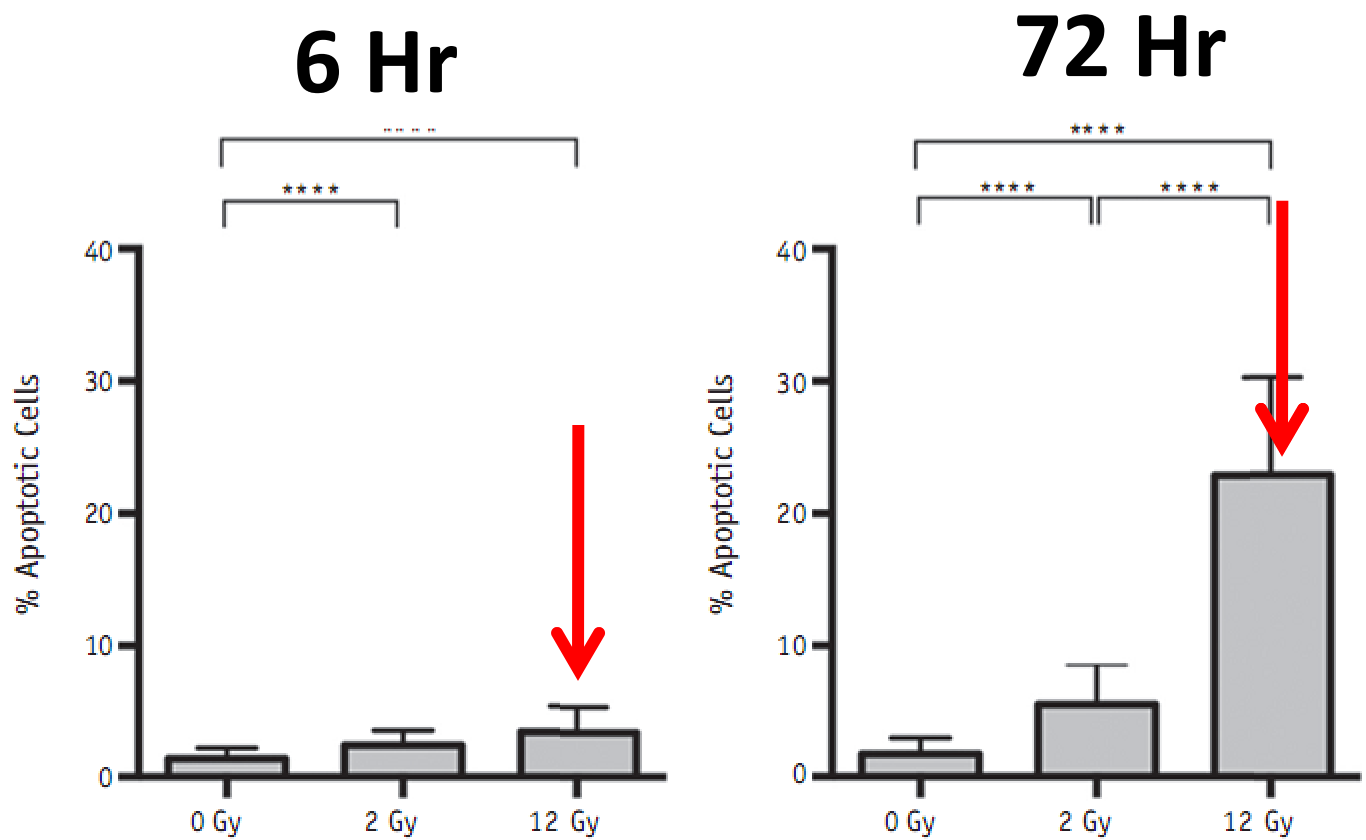
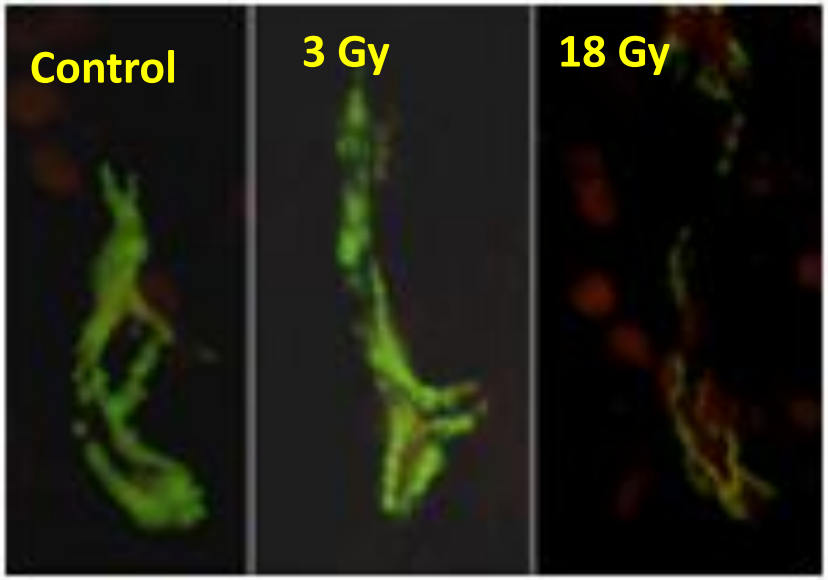


Increase in percentage apoptotic cells

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)

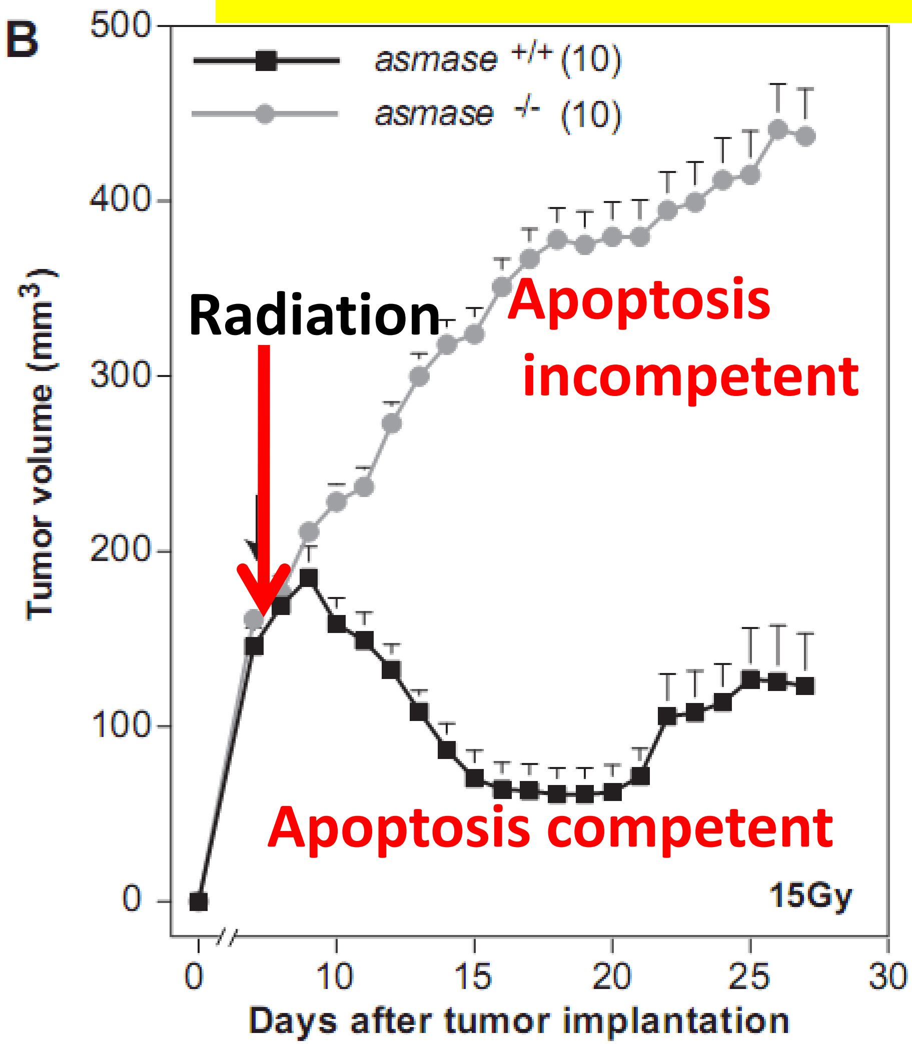


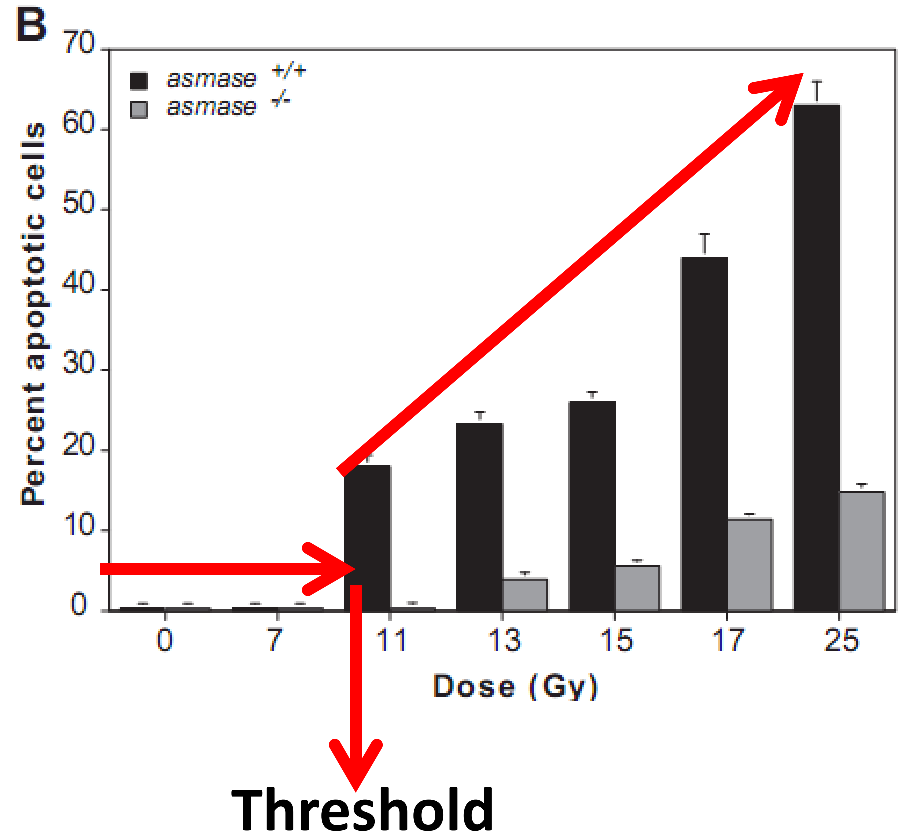
(L-R) control, 3 Gy fraction, 18 Gy fraction
Green = normal endothelium
Red = apoptosis

The currently trendy and possibly correct explanation:

Tumor response to high dose radiotherapy is largely driven by endothelial cell apoptosis

Fibrosarcoma and Melanoma Model





Monica Garcia-Barros, 16 MAY 2003 VOL 300 SCIENCE www.sciencemag.org

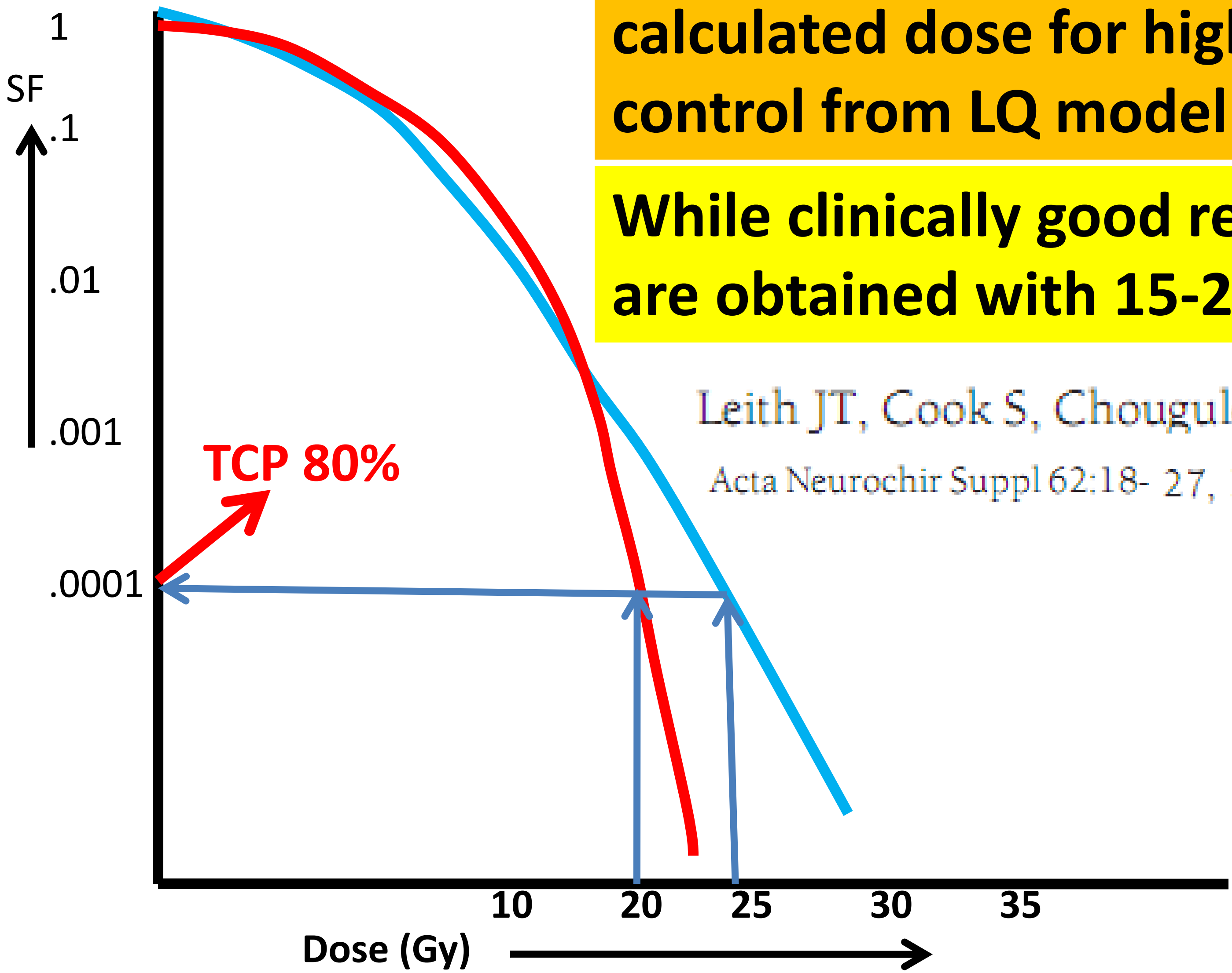
Clinical Evidence

SRS Metastatic Brain Lesions

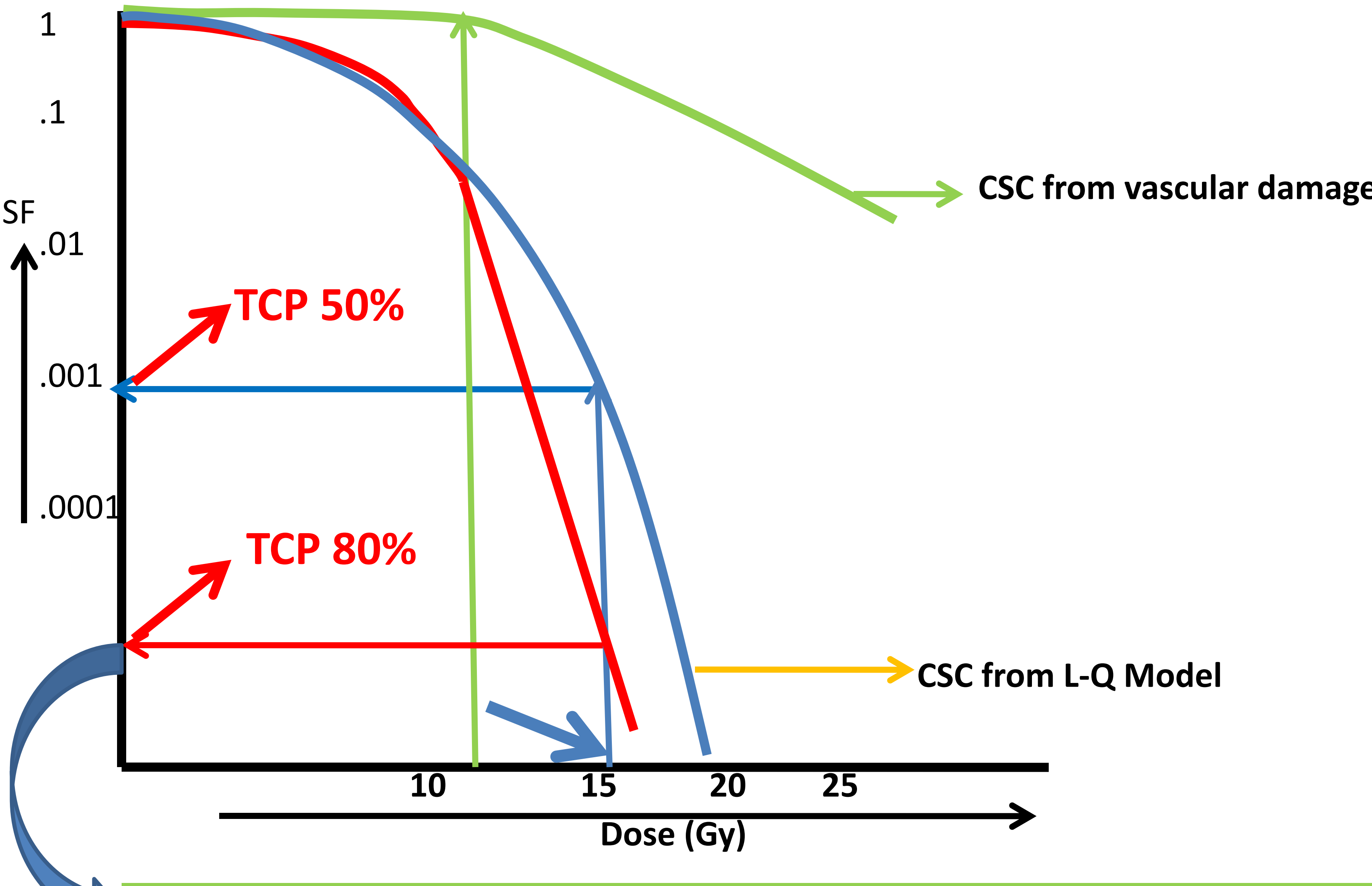
calculated dose for high tumor control from LQ model is 25-35 Gy.

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



Cell Survival Curve at High Dose



Actual SF because of DNA damage and vascular damage at high dose which is validated by excellent tumor control seen clinically than calculated from LQ model.

Extreme hypo fraction RT

↓

Endothelial Apoptosis

↓

Vascular Damage

↓

Cell Death

↑

3rd process of cell kill

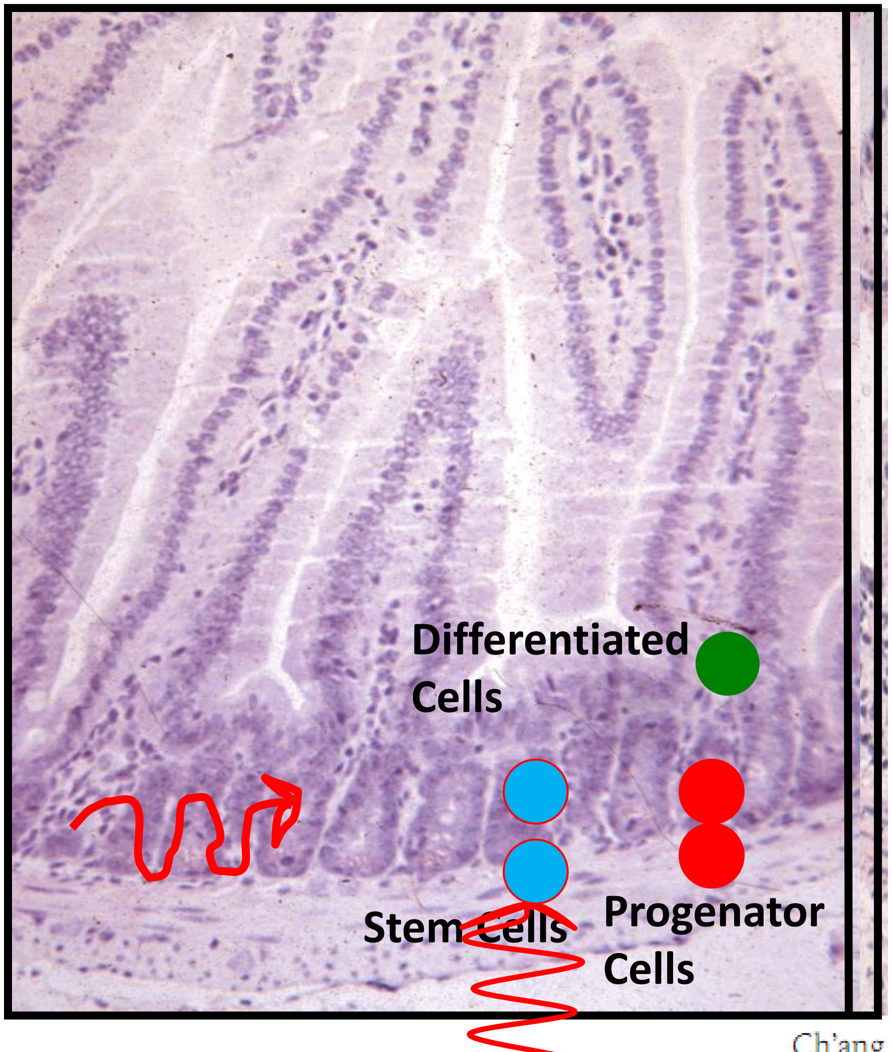
α and β cell kill

Stem Cell Death

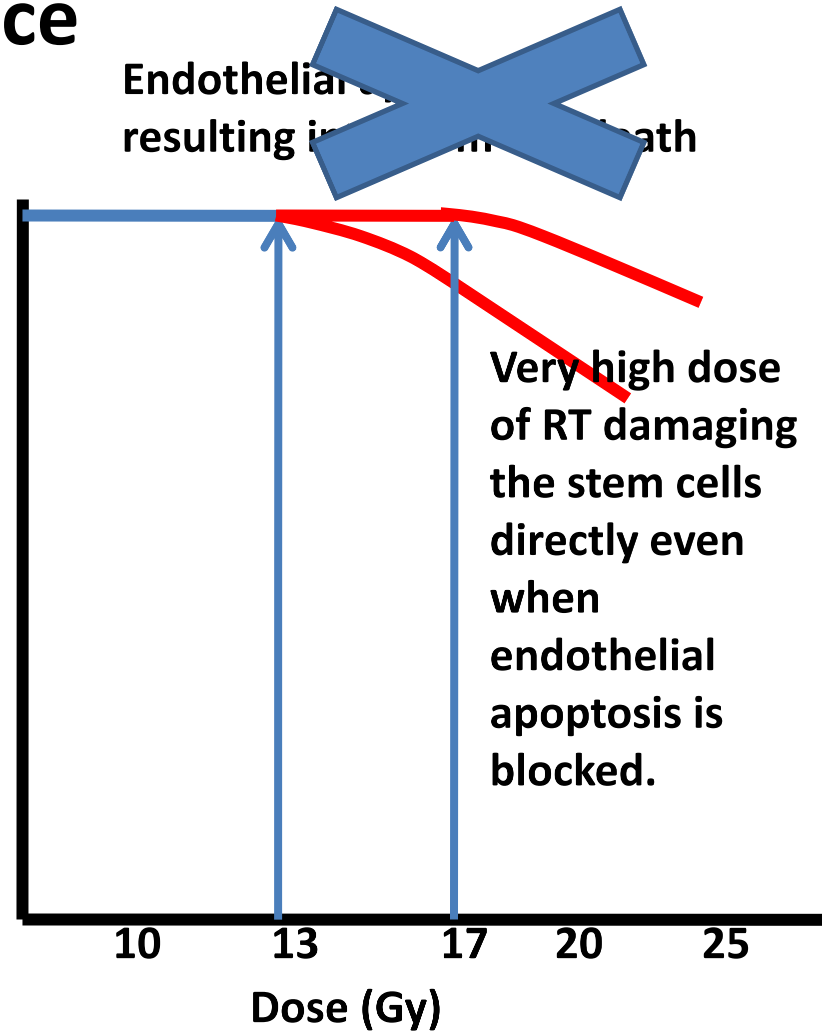
CD 133+ Glioma cells are relatively radioresistant

CD 44+ breast cancer cell lines

Jejunum Villi of Mice



Endothelial ...
resulting i... ...eath



They identified stem cell population in the crypts which die at very high doses

Ch'ang HJ, Maj JG, Paris F, et al: Nat Med 11:484-490, 2005

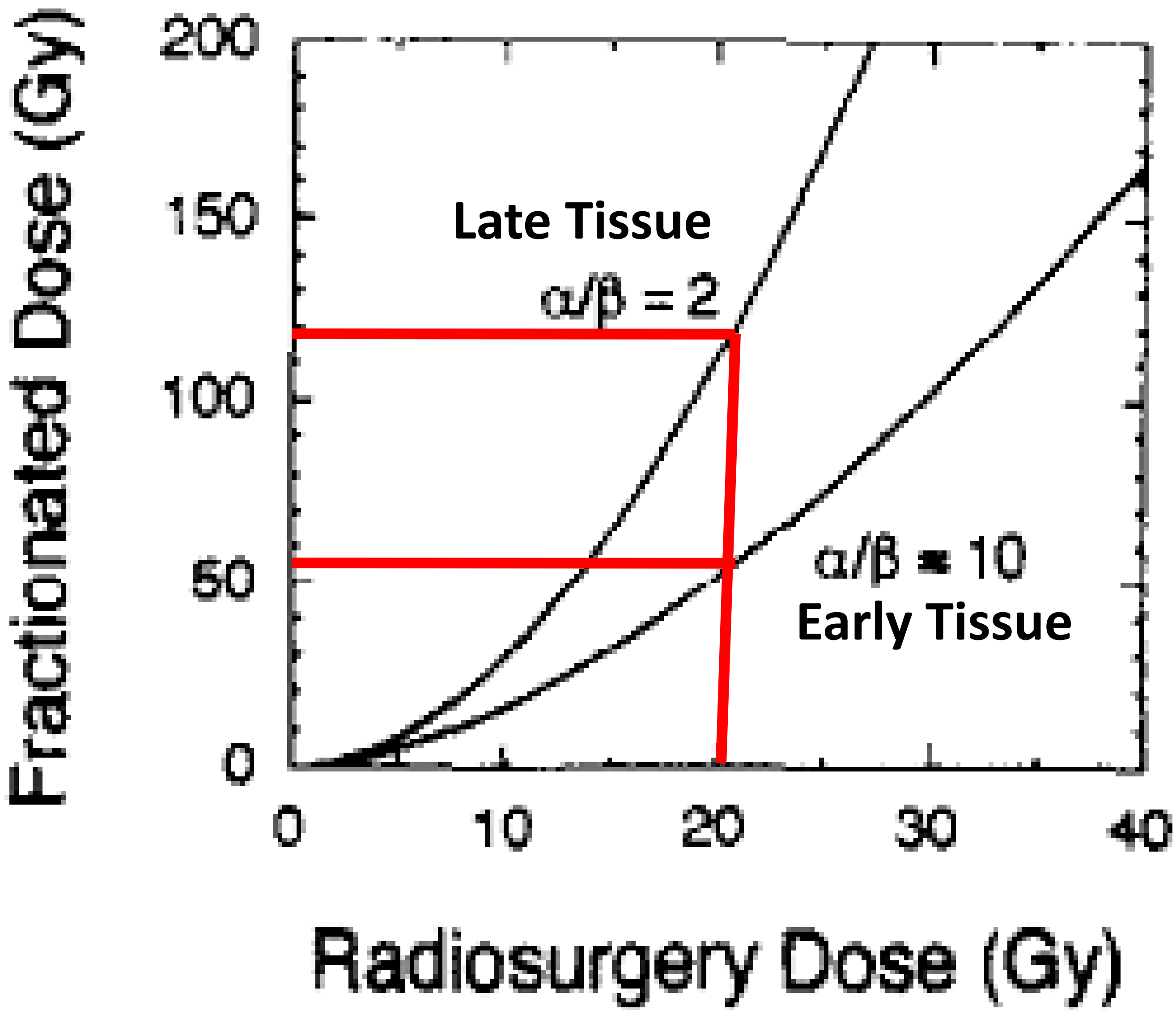
Cell death at High Dose RT

- **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

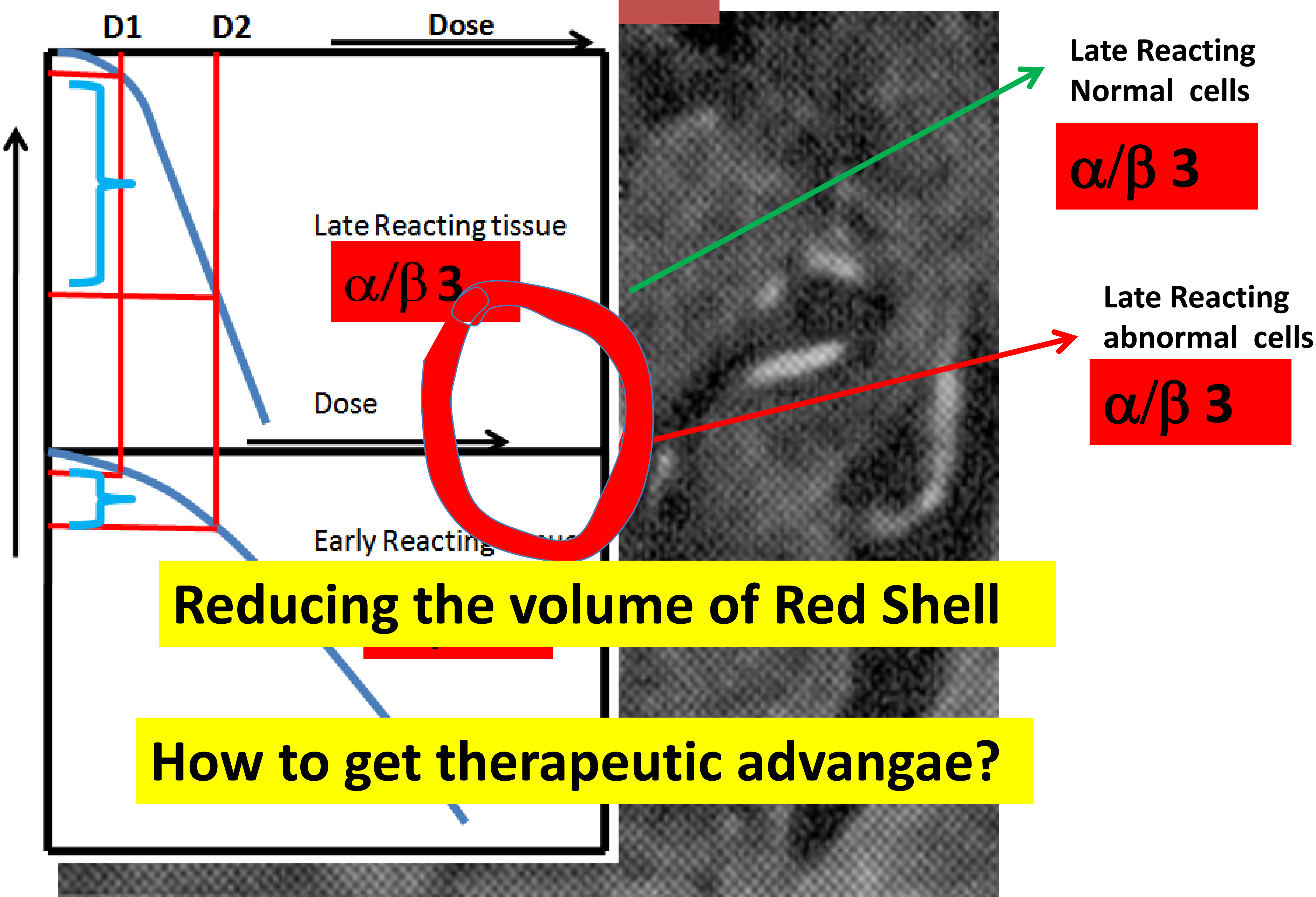
D. A. Larson *et al.* I. J. Radiation Oncology ● Biology ● Physics Volume 25, Number 3, 1993



Intracranial SRS

- 4 types of situations
  - Late Reacting target embedded into late reacting normal tissues eg AVM
  - Late Reacting target surrounded by late reacting normal tissues eg Meningioma
  - Early reacting target embedded in late reacting normal tissues eg Low grade Astrocytoma
  - Early reacting target surrounded by late reacting normal tissues eg metastasis

Meningioma

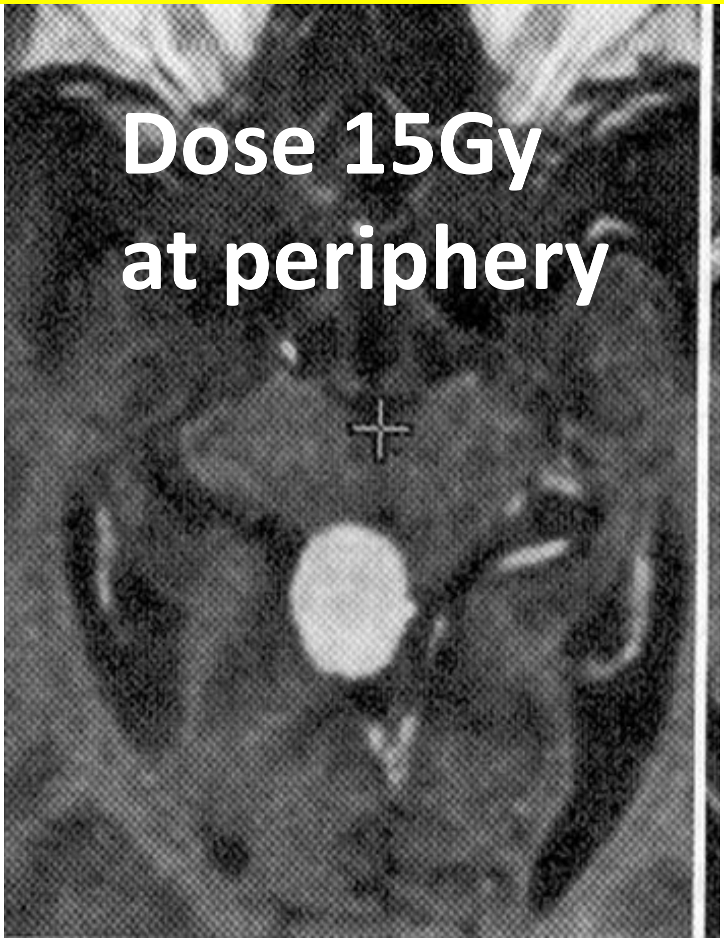


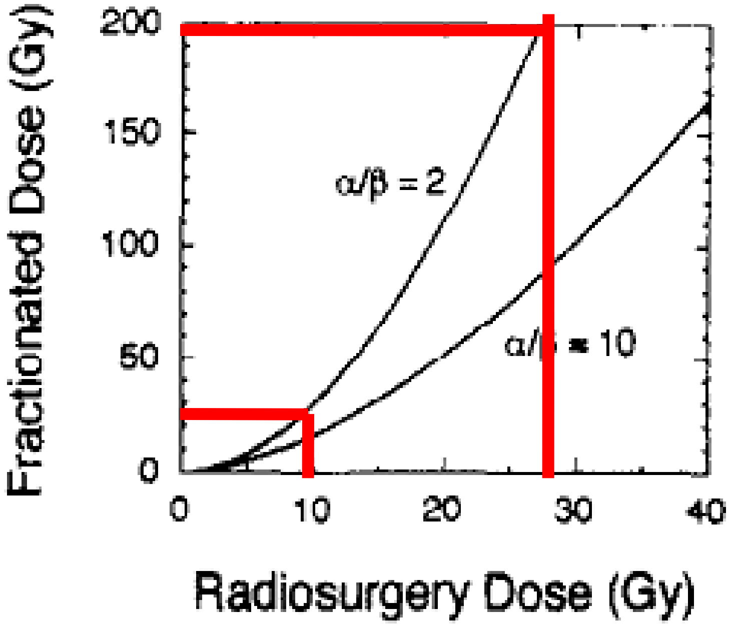
Reducing the volume of Red Shell

How to get therapeutic advangae?

Meningioma

Therapeutic Advantage with high tumor dose and less normal tissue doses



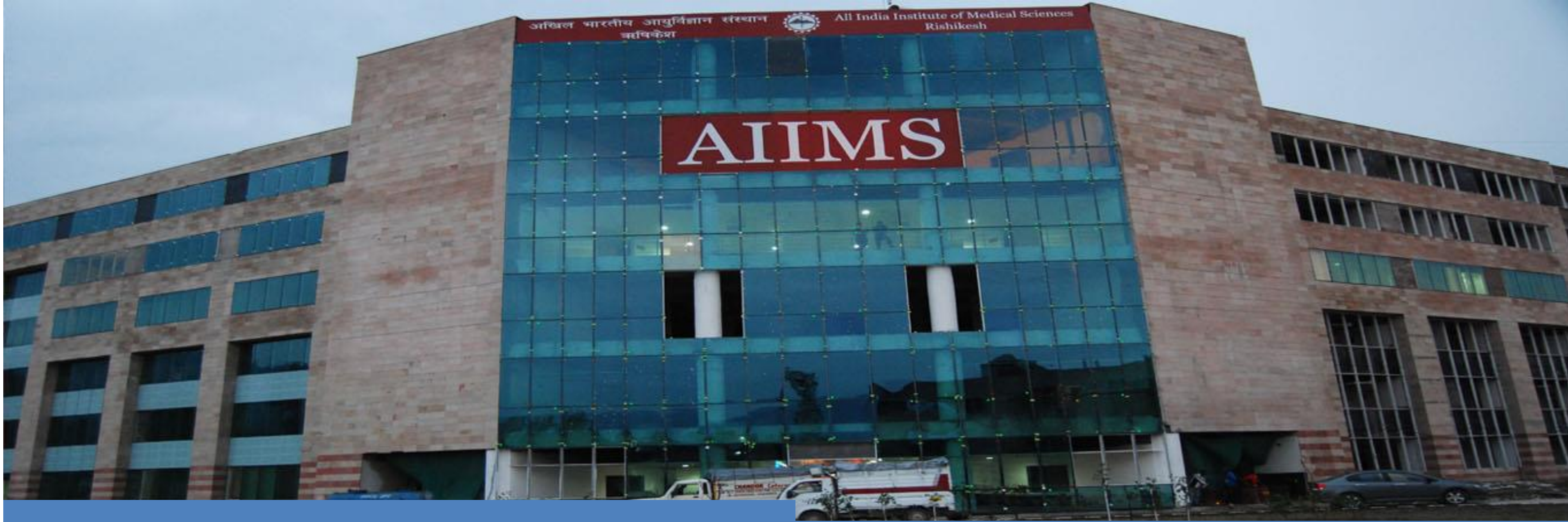


Dose outside the Tumor will reduce to 10 Gy within few mm ≈ EQD_2 30 Gy in fractionated regimen

Dose = 15 Gy at Periphery will rise inside the tumor to 25-30 Gy ≈ 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.**



Thanks

Greetings From Rishikesh