Radiation Dose Response

LQ model, RBE, LET, OER, TCP & NTCP

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Radiotherapeutic Paradigm

- The basic goal of Radiotherapy- Kill the enemy (TUMOUR) but prevent collateral damage (NORMAL TISSUES).

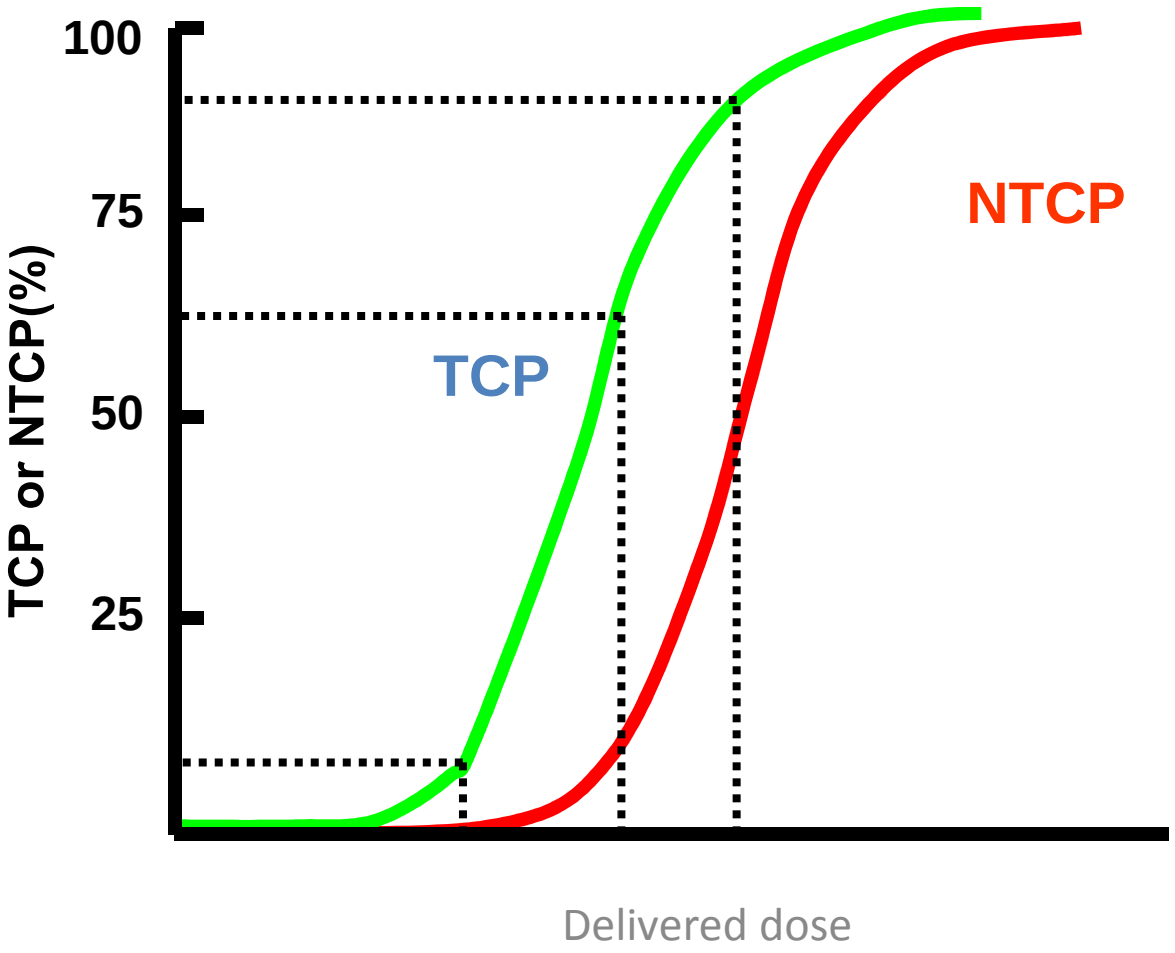
TUMOUR CONTROL AND NORMAL TISSUE COMPLICATIONS

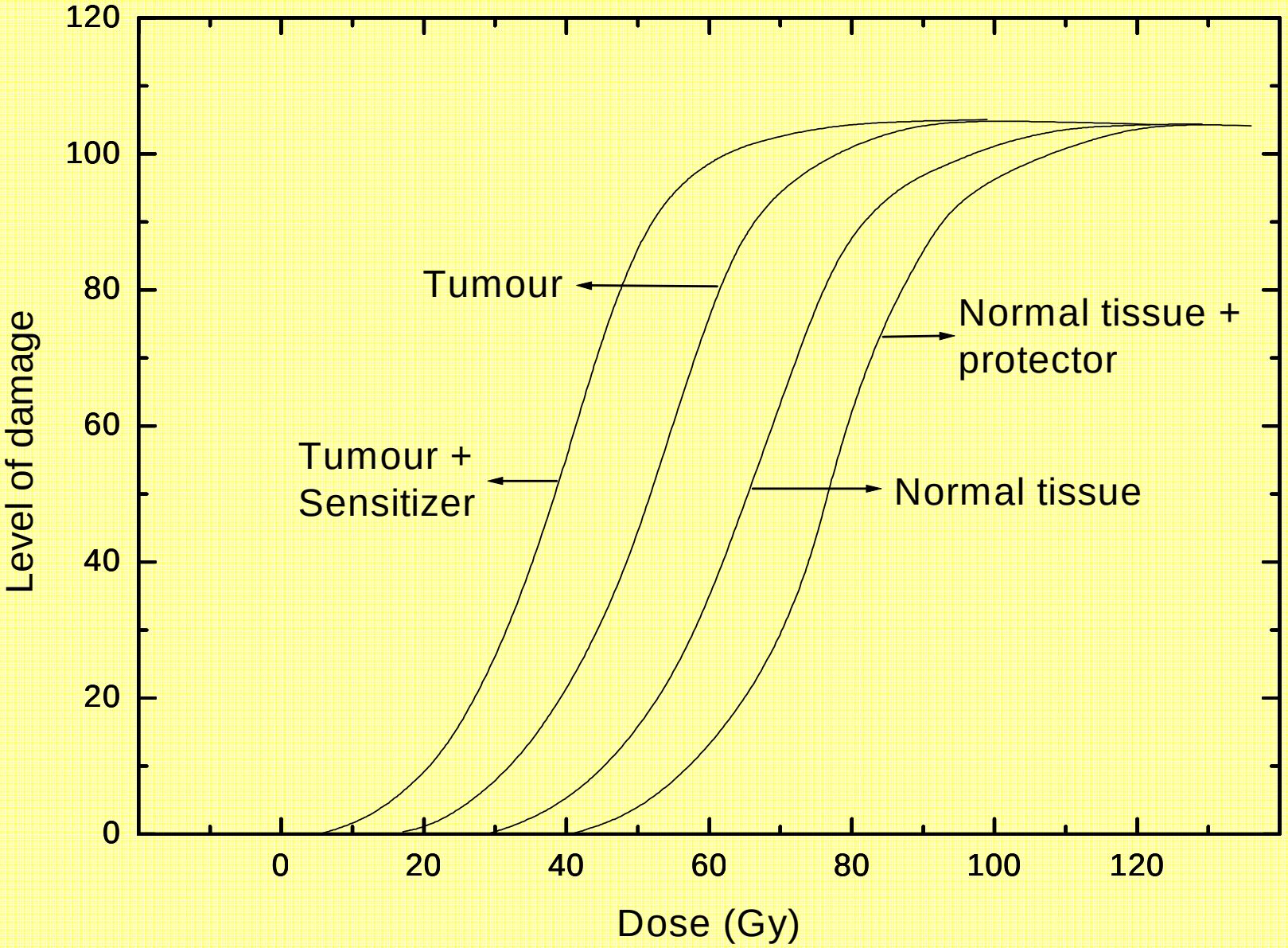
- Repair of sublethal damage
- Redistribution
- Repopulation
- Reoxygenation
- Radiosensitivity

OUR WEAPONS

- Total dose
- Overall treatment time
- Fraction size
- Radiation technique
- Type of radiation
- Sensitisation or protection

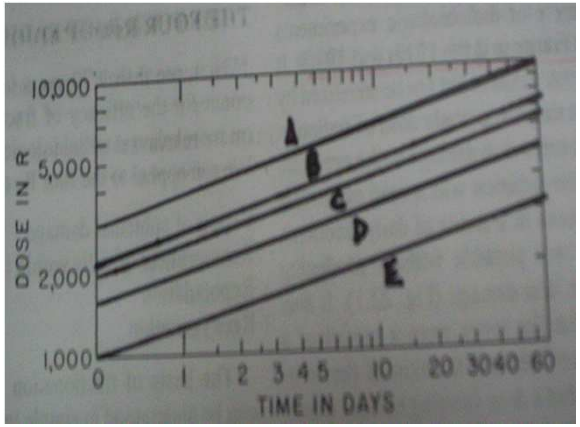
What we want to achieve..




120
100
80
60
40
20
0
Level of damage
0
20
40
60
80
100
120
Dose (Gy)
Tumour
Tumour +
Sensitizer
Normal tissue +
protector
Normal tissue

The early days….

Coutard's experiment 1934



Strandqvist's curves 1944

Ellis' Nominal Standard Dose 1969-73

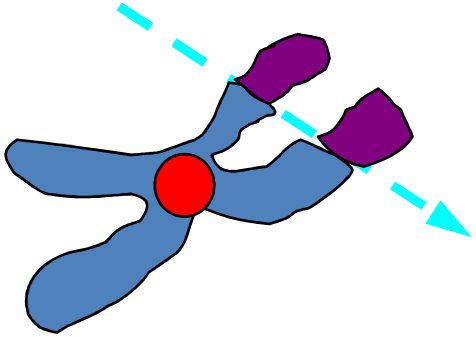
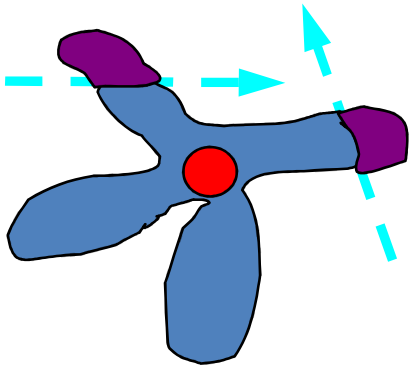
Total dose = (NSD) $T^{0.11}N^{0.24}$
No. of fractions N
Overall treatment time T

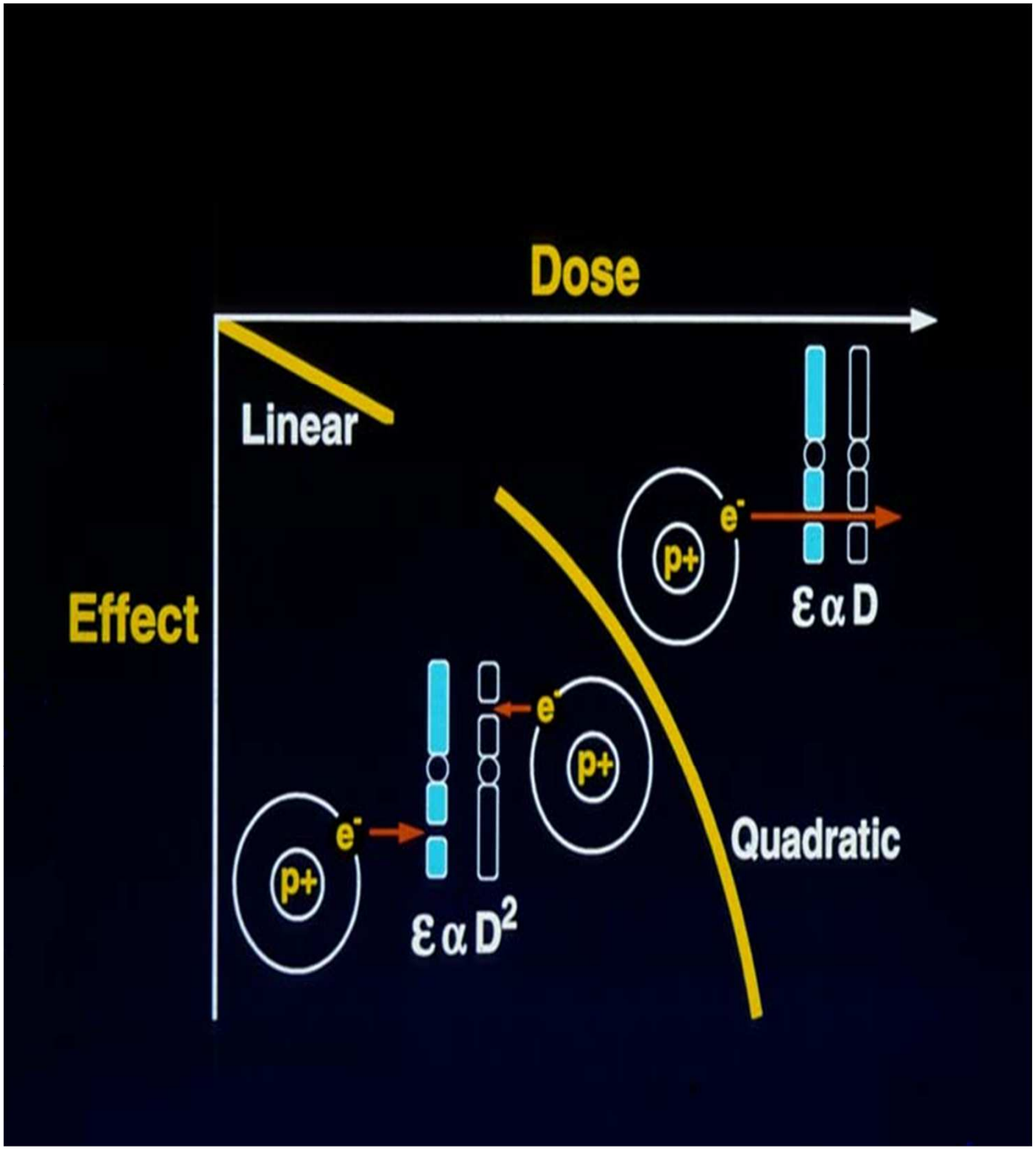
Linear Quadratic Model

- Mechanistically based model
- Calculates radio-therapeutic iso-effect doses for different fractionation schemes

Assumptions

- Basic lesion which is responsible for radiation induced cell death is the di-centric exchange type chromosomal aberration .
- Equal dose fractions are equally effective, independent of the preceding or following dose fractions.
- Complete repair between two fractions.

Type A damage	*Type B damage*
	
Always lethal	Not always lethal
Amount of damage is always proportional to dose.	For instantaneous exposures, the amount of damage is always proportional to square dose.
Amount of damage is independent of dose rate and exposure time.	Amount of damage is additionally dependent on dose-rate and exposure time. For any given dose, as exposure time increases, the amount of Type B damage is reduced.



Two component of cell killing by radiation, one dependent by the dose and the other one proportional to the square of the dose

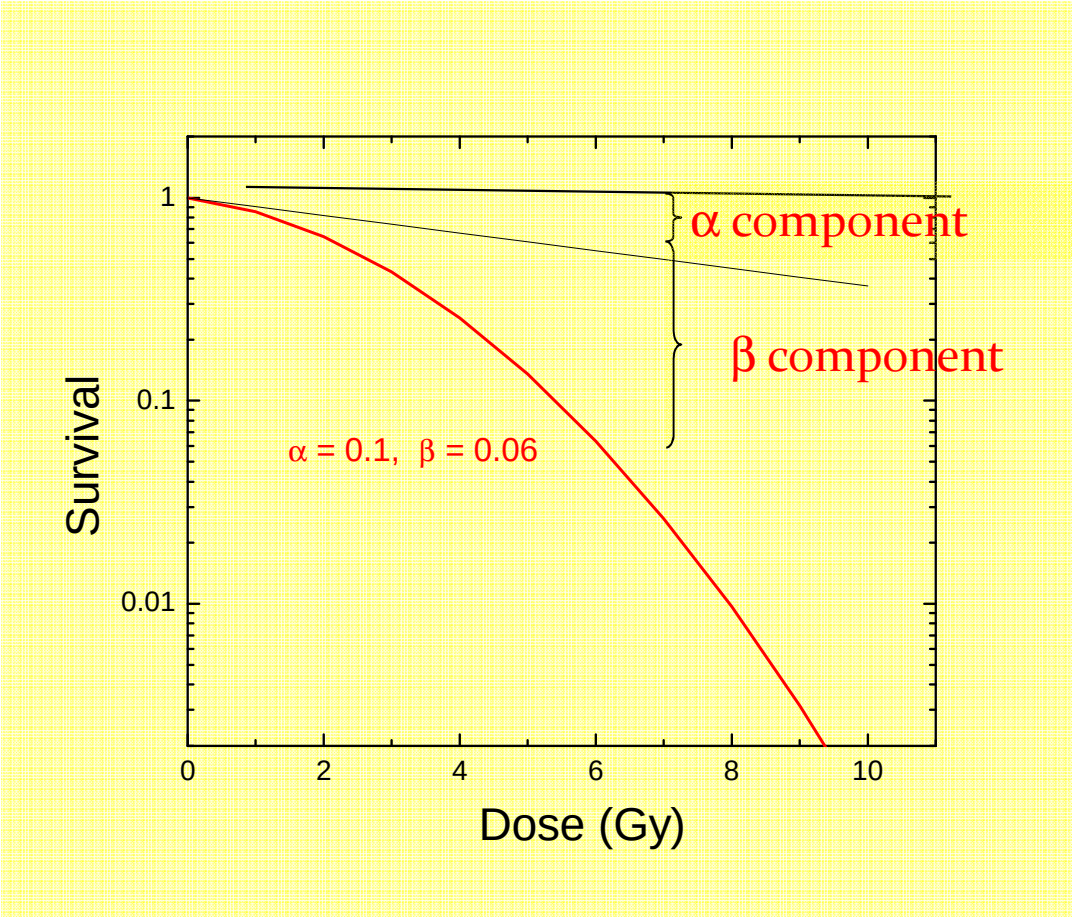
-cell survival curve is continuously bending

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

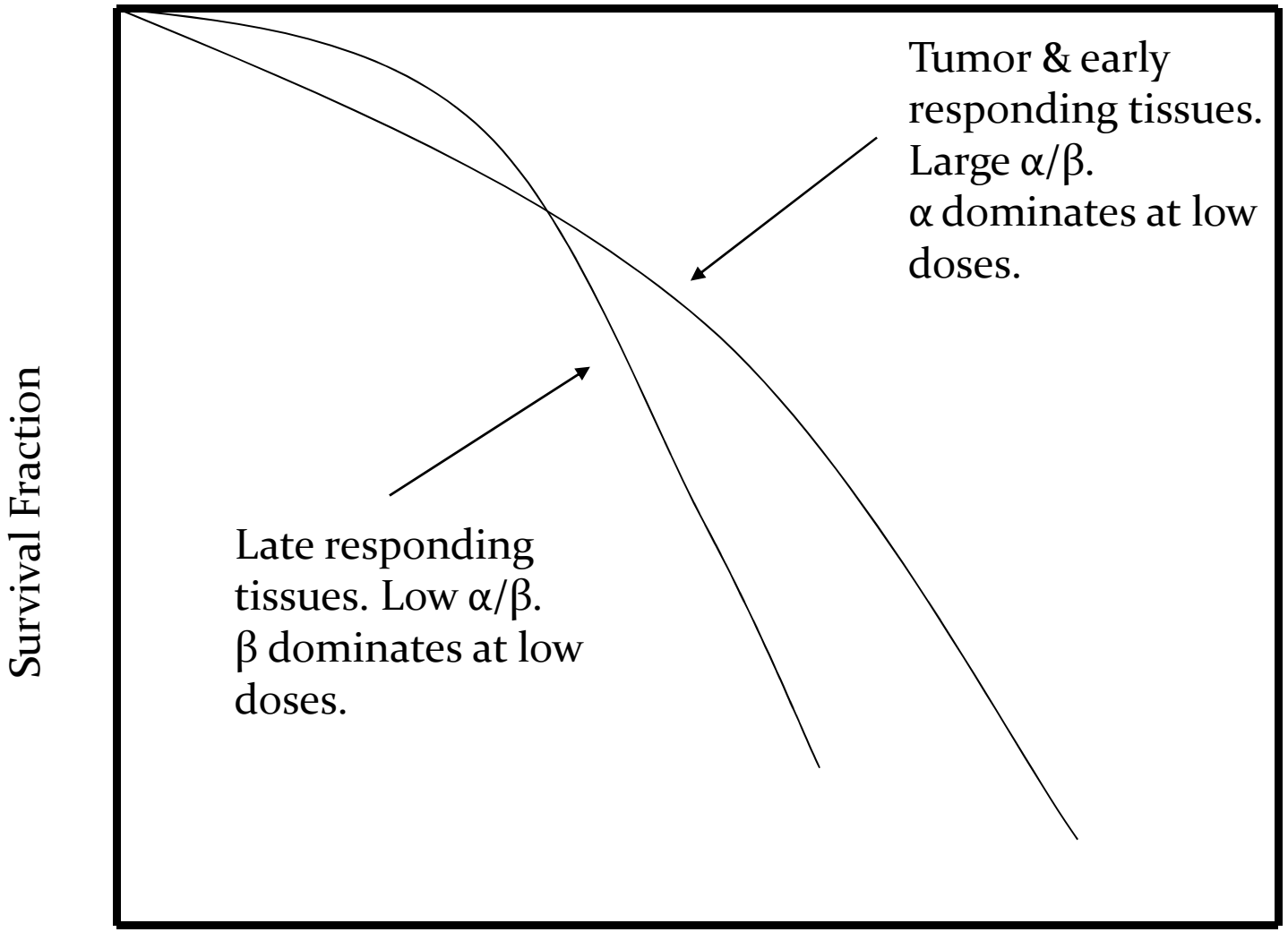
α and β = Constant.
S = Survival, D = Dose.

α/β Ratio

- Defines the dose at which cell killing by linear and quadratic components are equal.
- α/β ratio is thus the measure of how soon the survival curve begins to bend over significantly.
- Late responding tissue have low α/β ratio and early responding tissue have more α/β ratio .



Dose Response Relationship



PARAMETERS	α/β ratio	Dose Response Curve	Isoeffect Curve Shape	Dose fractionation
Acutely Responding Normal tissues & Tumors	High 10-20 Gy	Steep	Shallow	Less sensitive
Late Responding normal Tissues	Low 1-6 Gy	Shallow	Steep	Marked sparing

α/β VALUES FOR EARLY AND LATE REACTING TISSUES

TISSUE	**α/β VALUE**
EARLY REACTIONS	
SKIN (DESQUAMATION)	9 – 12
JEJUNUM	6 – 10.7
COLON	8 – 13
TESTIS	12 – 13
TUMOR BED (45 DAYS)	5.6 – 6.8
LATE REACTIONS	
SPINAL CARD (CERVICAL)	1.5 – 3
LUMBAR	3.7 – 4.9
COLON (WEIGHT LOSS)	3.1 – 5
KIDNEY (PIG)	1.7 – 2
LUNG (LD_{50})	2 – 6
LUNG (BREATING RATE)	1.9 – 3.1
BLADDER (FUNCTION)	5 – 10

α/β VALUES FOR HUMAN TUMORS

HUMAN TUMORS	**α/β VALUE**
HEAD AND NECK	14.5
VOCAL CARD	13
OROPHARYNX	16
BUCCAL MUCOSA	6.6
TONCIL	7.2
MASOPHARYNX	16
SKIN	8.5
MELANOMA	**0.6**
LIPOSARCOMA	**0.4**
SKIN (EARLY REACTIONS)	8 – 12
ORAL MUCOSA (EARLY REACTIONS)	8 – 15
SKIN (LATE REACTIONS)	1.7 – 2.8
MUSCLE/VASCULATURE/CARTILATURE	3.5
SPINAL CARD	< 3.3
LUNG	< 3.3

Use of the LQ model in external beam radiotherapy:

- Calculate ‘equivalent’ fractionation schemes
- Comparing different fractionation schemes
- Correcting treatment gaps
- Changing overall treatment time
- Changing time interval between dose fractions
- Changing dose per fraction
- Re-irradiation
- Double trouble
- Allowance for tumour proliferation

Biological Effective Dose (BED)

- Allow for the quantitative assessment of the biological effects associated with different patterns of radiation delivery.
- Is a measure of the biological dose delivered to a tumour or organ.
- The theoretical dose, which, if delivered in infinitely small fractions, would produce the same biological endpoint as that under consideration
- BED is a measure of effect in units of Gy_x, where the suffix x indicates the value of α/β assumed in the calculation.

Derivation of BED formula

- $E = \alpha D + \beta D^2$.

$= \alpha\ nd + \beta\ nd^2$

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

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

$= \alpha\ (nd)\ (1 + d/\ \alpha/\beta)$

$E / \alpha = nd\ (1 + d/\ \alpha/\beta)$

BED = Total dose X Relative effectiveness.

nd = total dose $1+d/\alpha/\beta$= relative effectiveness

Calculating Isoeffective relationship

Describe range of fractionations schedules that are isoeffective

$$\frac{D_2}{D_1} = \frac{\alpha/\beta + d_1}{\alpha/\beta + d_2}$$

D_1 = initial known total dose ,
d_1 = initial dose / fraction
D_2 = total dose to be calculated for new dose schedule
d_2 = new dose / fraction

EQUIVALENT EFFECTIVE DOSE (EQD)

Simple way of calculating isoeffective relationship is To convert into equivalent dose in 2 Gy fraction EQD2

- $EQD2 = D \left[\frac{d + \alpha/\beta}{2 + \alpha/\beta} \right]$

Example

We want to change current practice of palliative radiotherapy in advanced head neck cancer from 40Gy/16# to 4Gy/# due to logistic reason

Excluding late effects from calculation

What would be total dose needed to achieve same effective dose to that of current practice.

- Let us suppose D1=40Gy d1=2.5Gy

  D2=? And d2= 4Gy .

  We want D1 and D2 isoeffective thus,

  BED equation can be modified to

  $$D2/D1 = d1 + \alpha/\beta \,/ d2 + \alpha/\beta$$

  $$D2/D1 = d1 + 10/d2 + 10$$

  $$D2/40 = 2.5+10 \,/4+10$$

  $$D2 = 40 \text{ X}12.5 \,/\, 14$$

  $$= 35.72 \text{ Gy.}$$

Comparison of different fractionation schemes

- Different fractionation schemes can be compared by comparing their BED for acute and late effects

- This is obviously only valid for one tissue/tumour type with one set of alpha, beta values

Clinical examples.

- Comparison of various treatment schedules for head neck cancer.
- *For calculation purpose for early effect and tumor (10 Gy), late effect (2Gy).*

- Treatment **1(conventional)** = 70Gy/35#/ 7 weeks @ 1#/day , 2Gy/#.

- Treatment 2 (**Hyperfractionation)** = 80.5Gy /70#/7weeks @ 2# /day , 1.15Gy/#.

- Treatment 3 (**Conco boost**) = 54Gy/30#/6weeks 1.8Gy/# with conc boost 18Gy/12# , 1.5Gy/3 during same period.

- Treatment 4 (**CHART**) = 54Gy/36#/12day @ 3#/day , 1.5Gy/#

Treatment 1(conventional) = 70Gy/35#/ 7 weeks @ 1#/day , 2Gy/#.

- **Early effect**

  BED = nd (1+ d/ α/β)

  = 70 (1 + 2/10)

  = 70 (1.2) = 84.

- **Late effects**

  = 70 (1+ 2/2)

  = 140

Using the formula we will see that…..

Arm	Early	Late
Conventional	84	140
Hyper#	89.6	126.8
Conco Boost	84.4	134.1
CHART	62.1 ★	94.5 ★

Allowance for tumour proliferation

- An alternative to put time scale in BED formulae.
- Crude method based on the assumption that rate of cellular proliferation remains constant throughout the overall treatment time.
- $N = N_o e^{\lambda t}$

  N = number of clonogens at time t.

  No = initial clonogens.

  λ = constant = 0.693 / T pot.
- Thus after modification
- BED = $nd (1+ d/ \alpha/\beta) - (0.693/ \alpha) (t / Tpot)$

Arm	Early Effect	Proli. correction	Corrected dose for time
Conventional	84	22.64	61.36
Hyper#	89.6	22.64	67.16
Conco Boost	84.4	19.4	65
CHART	62.1	5.55	56.5

Double trouble

- Dosimetric hotspots receive not only higher total dose but also higher dose per fraction

- Withers called it *double trouble*

Biological effect of a hotspot is relatively more
Important for late effects than for tumour control

Unplanned gaps in treatment

- Gaps negative therapeutic effect (strongest for sq.ca. of head & neck, uterine cervix)

- Options
  - accelerating treatment after gap
  - hyper fractionation
  - delivering remaining in hypofractionated dose/fr

Example

Pt of colorectal ca planned to receive RT 5Fraction of 5 Gy from Monday to Friday, no Treatment on Wednesday..

Planned to deliver isoeffective tumour dose by increasing size of last 2 # . α/β =10 Gy for colorectal Gy

$$EQD_2 = 15\left[\frac{5 + 10}{2 + 10}\right] = 18.75 \text{ Gy}$$

$$EQD_2 \text{ (New)} = 2x\left[\frac{x + 10}{2 + 10}\right]$$

$$2x * \left[\frac{x + 10}{12}\right] = 18.75$$

$$2x^2 + 10 = 18.75 * 12$$

$$2x^2 + 20x - 225 = 0$$

$$x = -b + \sqrt{\frac{b2 - 4ac}{2a}} = -20 + \sqrt{\frac{(20)^2 - 4+2+-226}{2*2}}$$

$$= 6.7$$

Limitations of LQ model

- The LQ model from which the BED concept is derived does not intrinsically include an **allowance for the volume effect**. The methods for assessing volume effects are complex (e.g. integrated BED, EUD, NTCP and TCP)

- Limitation for **reirradiation**.

- Applies best within **dose range of 2-8 Gy** /#
  application beyond that is not established

Inaccuracy due to incorrect estimation of α/β

Important in tissues with low α/β

- Since curve is steep, wide variation of SF with little change in dose/#
- So any in accuracy in α/β estimation leads to amplified differences in isoeffective dose prediction

No application to treatment given in single dose per fraction

Lacks time factor

Time Dose Parameters

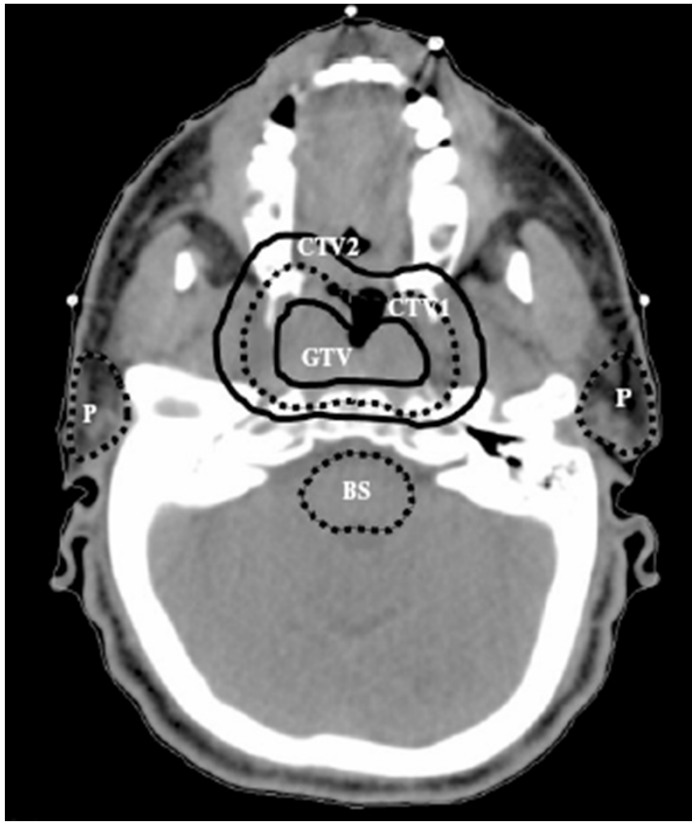
- Time dose parameters determining normal tissue tolerance are:
  - Total dose.
  - Overall duration of treatment.
  - Size of dose per fraction.
  - Frequency of dose fractionation.
- Size of dose per fraction and fractionation frequency determine the rate of dose accumulation.
- Intensity of acute reaction depends upon rate of cell kill & cell survival through proliferation of surviving stem cells which, depends on dose accumulation.
- At the peak of acute reaction, further irradiation will not increase the intensity of acute reaction, but will increase the time to heal.

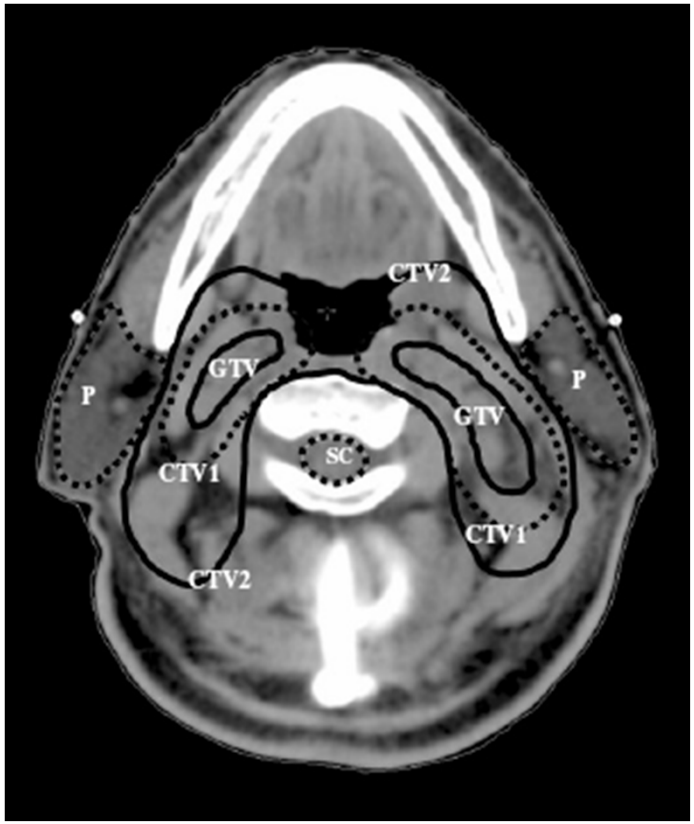
Time Dose Parameters

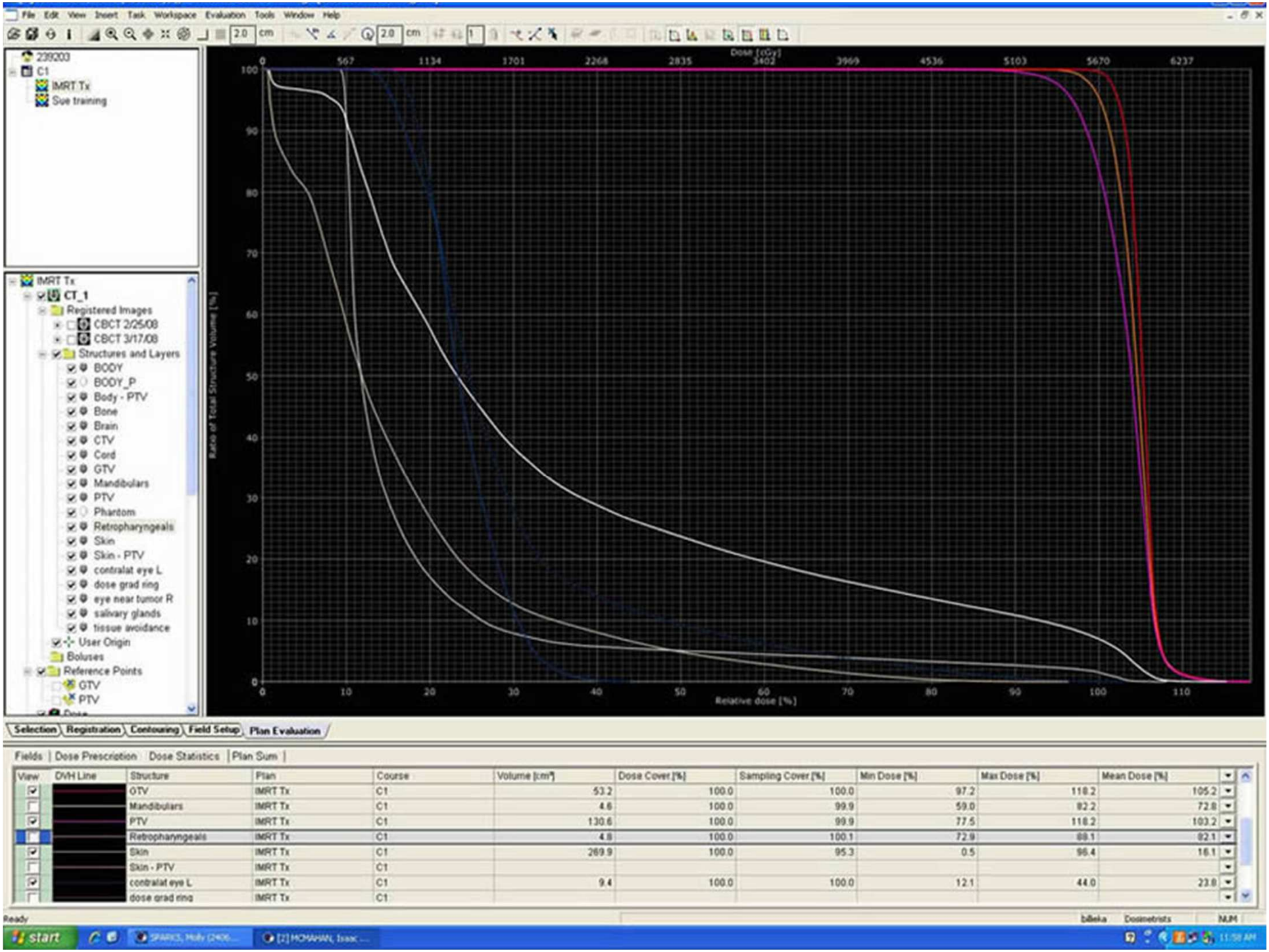
- Late reaction occurs in tissues with slow cellular turnover like mature connective tissue and parenchymal cells of organs. Eg. Spinal Cord.
- No depletion of cells in late reacting tissues even if full course of RT is complete.
- Hence overall Rx time as well as dose accumulation has little role in severity of late reaction.
- Instead severity of late reaction is dominated by size of dose per fraction and interfraction interval.
- Time interval is necessary for complete repair of sublethal damage. Recommended time interval is at least six hours.
- As overall treatment time increases the probability of tumor control decreases / isoeffective dose for tumor control increases.

The era of IMRT….

- Target and critical organ





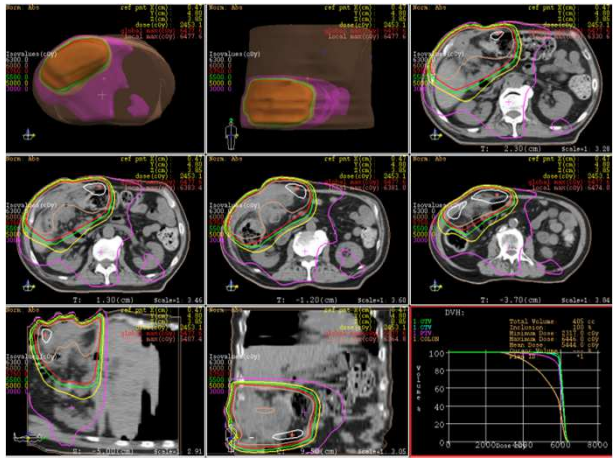


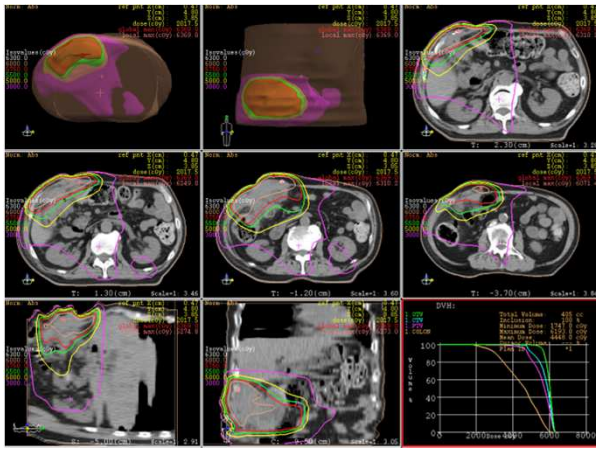
View	DVH Line	Structure	Plan	Course	Volume [cm³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [%]	Max Dose [%]	Mean Dose [%]
☑		GTV	IMRT Tx	C1	53.2	100.0	100.0	97.2	118.2	105.2
☐		Mandibulars	IMRT Tx	C1	4.6	100.0	99.9	59.0	82.2	72.8
☑		PTV	IMRT Tx	C1	130.6	100.0	99.9	77.5	118.2	103.2
☐		Retropharyngeals	IMRT Tx	C1	4.8	100.0	100.1	72.9	88.1	82.1
☑		Skin	IMRT Tx	C1	269.9	100.0	95.3	0.5	96.4	16.1
☐		Skin - PTV	IMRT Tx	C1						
☑		contralat eye L	IMRT Tx	C1	9.4	100.0	100.0	12.1	44.0	23.8
☐		dose grad ring	IMRT Tx	C1						

- Do the DVH parameters really predict the tumour control and normal tissue complications?

- This led to the development of more probabilistic models predicting tumour control or normal tissue complication probabilities.

- They essentially aimed at making plan evaluation easier between two close High Precision plans.





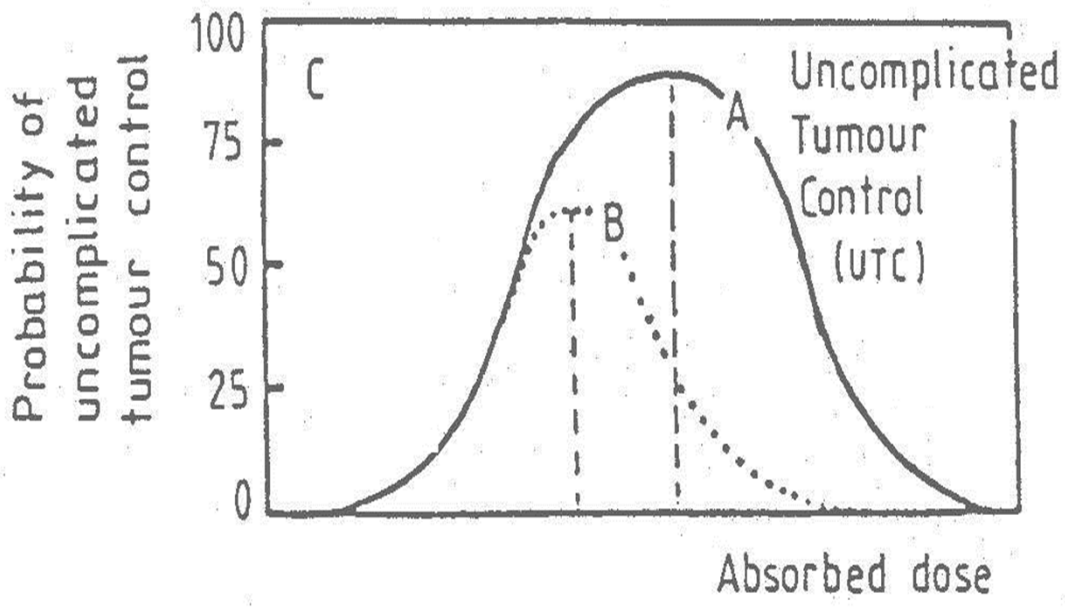
TCP 32.28
NTCP 61.30%

TCP 26.83
NTCP 14.91%

Tumour **C**ontrol **P**robability

- The probability of uncomplicated tumor control (P_{UTC}):

P_{UTC}=TCP(1-NTCP)



Normal **T**issue **C**omplication **P**robability

- These models aim to predict the probability of a complication as a function of the dose or biologically equivalent dose and volume

Normal Tissue Complication Probability

- Functionally, the whole organ does not fail if some part of it is destroyed

- Withers suggested that the tolerance of tissues depends on the ability of the remaining clonogenic cells to maintain a sufficient number of mature cells suitably structured to maintain organ function

Normal tissue complication probability

- Organ function depend upon the aggregation of cells into functional sub-units (FSUs)

- FSUs in an organ can be organized in series or parallel
  - Series: gastrointestinal tract and spinal cord, damage in one portion of the organ may produce total organ fail
  - Parallel: lung or kidney, function is often maintained since the undamaged part operates independently from the damage part

Normal tissue complication probability

- Volume dependence

- A lot to a little or a little to a lot ?
  - Whether it is better to give a lot to a little as unconventional treatment, or a little to a lot as in 3D and IMRT

Models for NTCP

- Homogeneous dose distribution
  - Empirical model
    - Probit model : Lyman (1985)
    - Logistic model
  - Tissue architecture model

- Inhomogeneous dose distribution
  - Effective dose method : Lyman and Wolbarst (1987)
  - Effective volume method : Kutcher and Burman (1989)
  - Integral probability model : Schultheiss et al. (1983)

Probit model (Lyman)

$$NTCP = 1/\sqrt{2\pi}\int_{-\infty}^{t}\exp(-t^2/2)dt$$

$$v = V/V_{ref}$$

$$t = (D - TD_{50}(v))/(m \cdot TD_{50}(v))$$

$$TD_{50}(v) = TD_{50}(1)\cdot v^{-n}$$

$TD_{50}(1)$: the tolerance dose for reference volume irradiation

m : the steepness slope of the dose response curve

V_{ref} : the reference volume

n : tissue-specific parameter

Tolerance Data: Emami *et al.*, 1991

Lung

Vol	1/3	2/3	3/3
$TD_{5/5}$	**4500**	**3000**	**1750**
$TD_{50/5}$	**6500**	**4000**	**2450**

$TD_{5/5}$ is the dose to the partial organ that would have a 5 % probability of complication in 5 years.

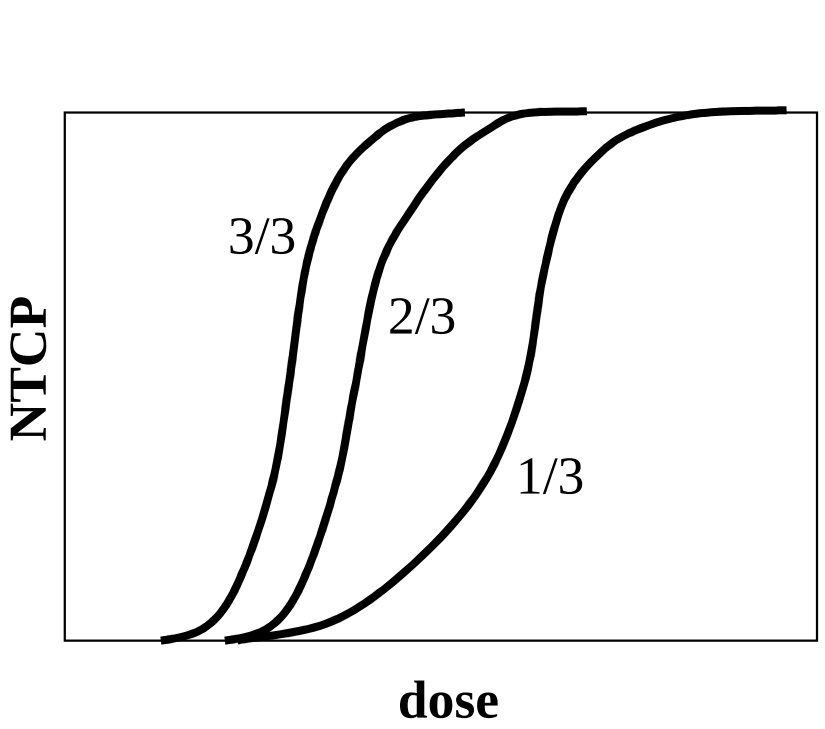
$TD_{50/5}$ is the dose to the partial organ that would have a 50 % probability of complication in 5 years.

Fitting of Tolerance Data: Burman *et al.*, 1991
Lung, brainstem, optic nerve

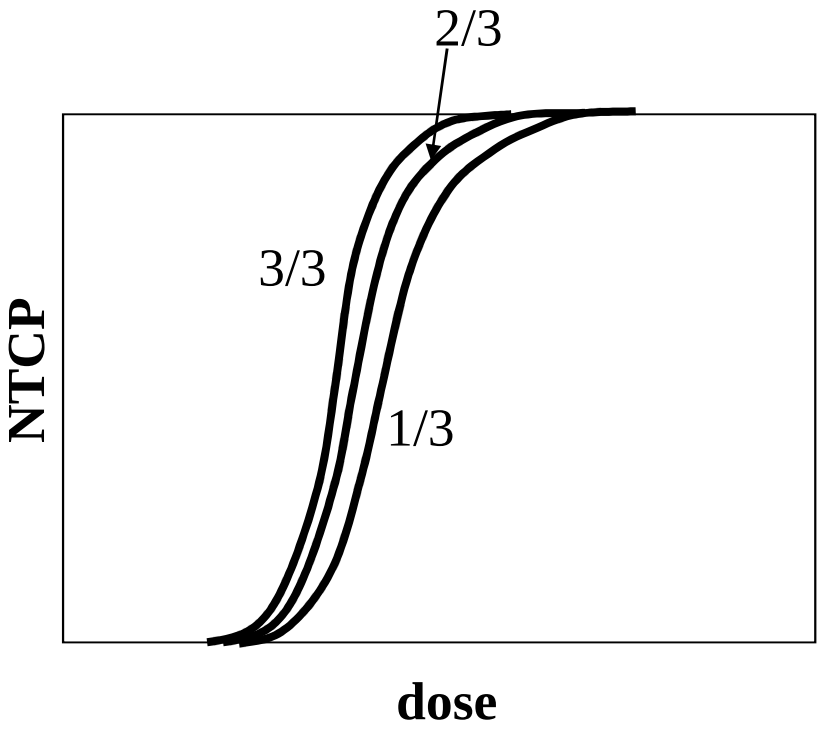
organ	n	m	TD50	end point
Lung 0.87	0.18	24.5	Pneumonitis	
Brainstem	0.16	0.14	65	necrosis/infarction
Optic nerve	0.25	0.14	65	blindness

	$TD_{5/5}$			$TD_{50/5}$		
organ	1/3	2/3	1	1/3	2/3	1
Lung 45	30	17.5	65	40	24.5	
(fitted data)	45	24	17	64	35	25
Brainstem	60	53	50	-	-	65
(fitted data)	60	53	50			65
Optic nerve	-	-	50	-	-	65
(fitted data)	-	-	50	-	-	65

NTCP vs. dose, fixed partial irradiated volume



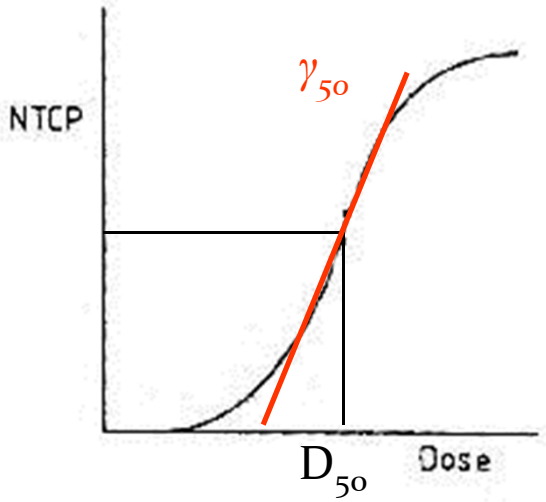
Large volume effect, n → 1.0



small volume effect, n → 0.0

Logistic model

$$NTCP(D,1) = \frac{1}{1+(D_{50}/D)^{k}}$$



D_{50} : the dose resulting in a 50% complication probability for some spec complication or end point

k : $4\gamma_{50}D_{50}$ (γ_{50} : slope of D_{50})

Effective dose method

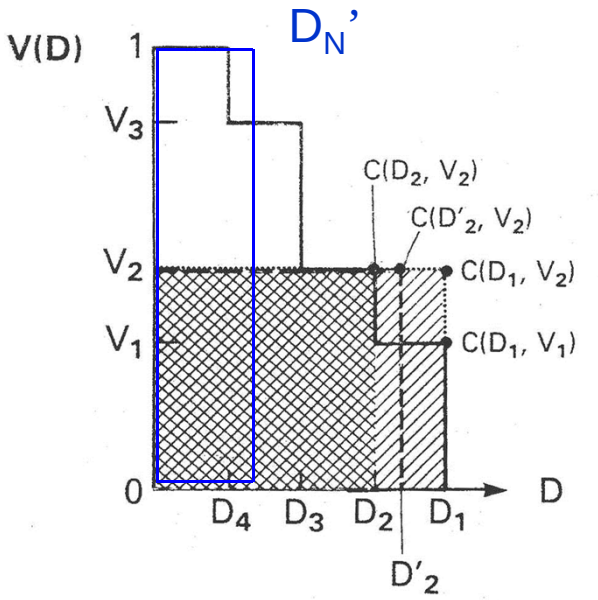
$$D_2^{'} = D_2 + (V_1 / V_2).(D_1 - D_2)$$

$$D_3^{'} = D_3 + (V_2 / V_3).(D_2^{'} - D_3)$$

$$\vdots \quad (N-1)\,step$$

$$D_N^{'} = D_N + (V_{N-1} / V_N).(D_{N-1}^{'} - D_N)$$

Lyman model or logistic model

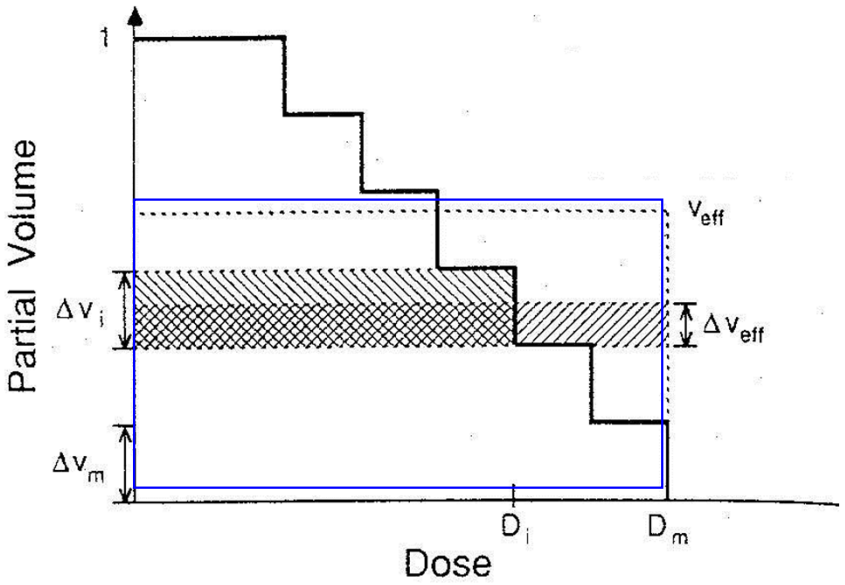


From Lyman et al. 1987

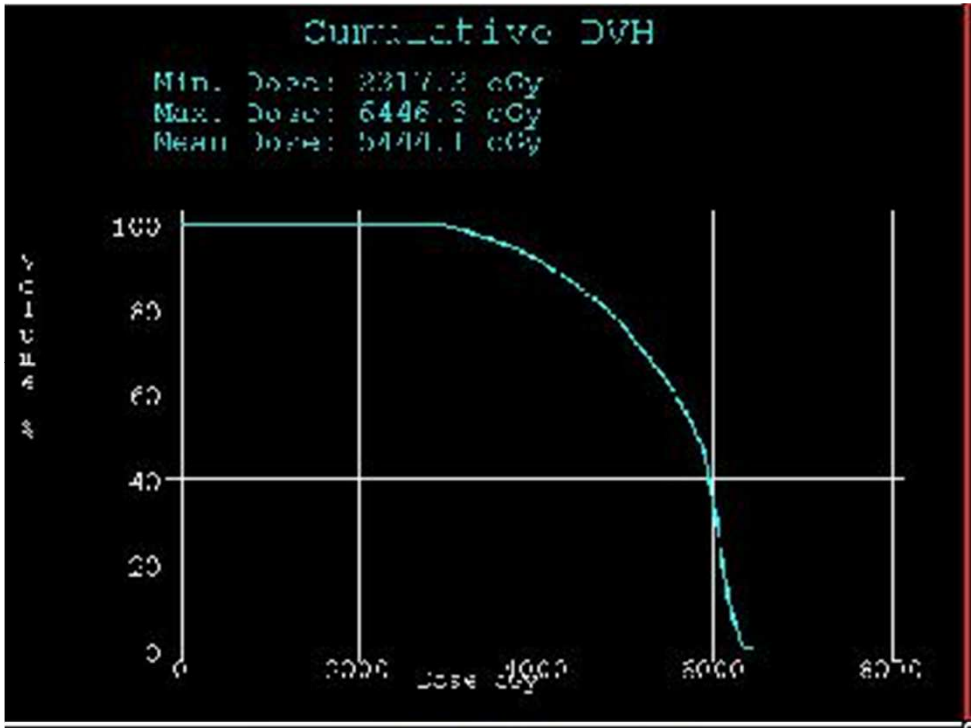
Effective volume method

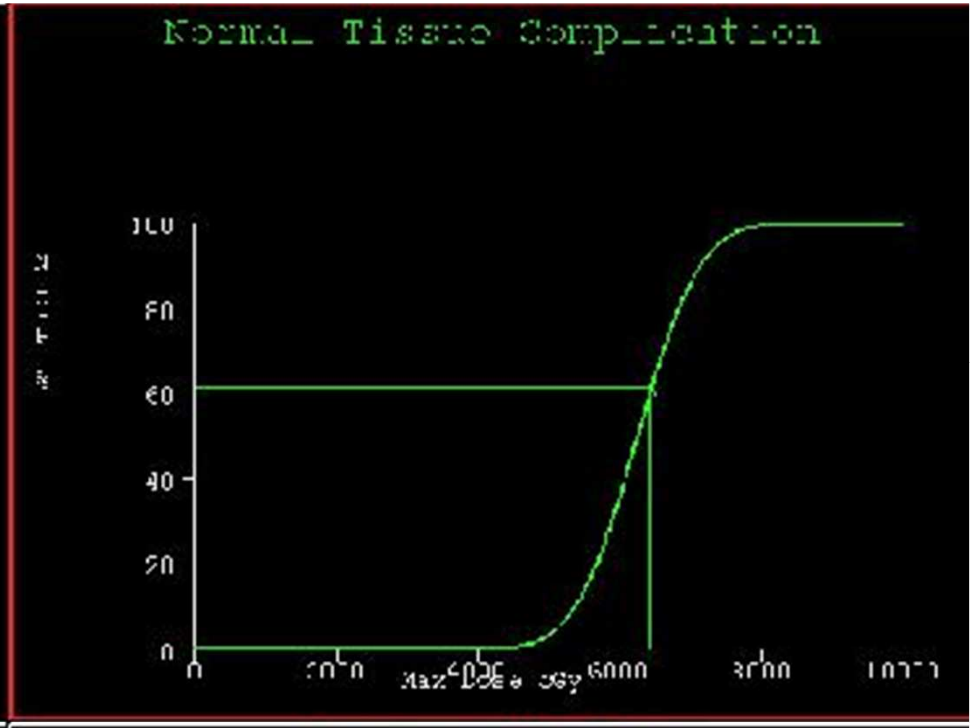
$$V_{eff} = \sum_i V_i (D_i / D_{\max})^{1/n}$$

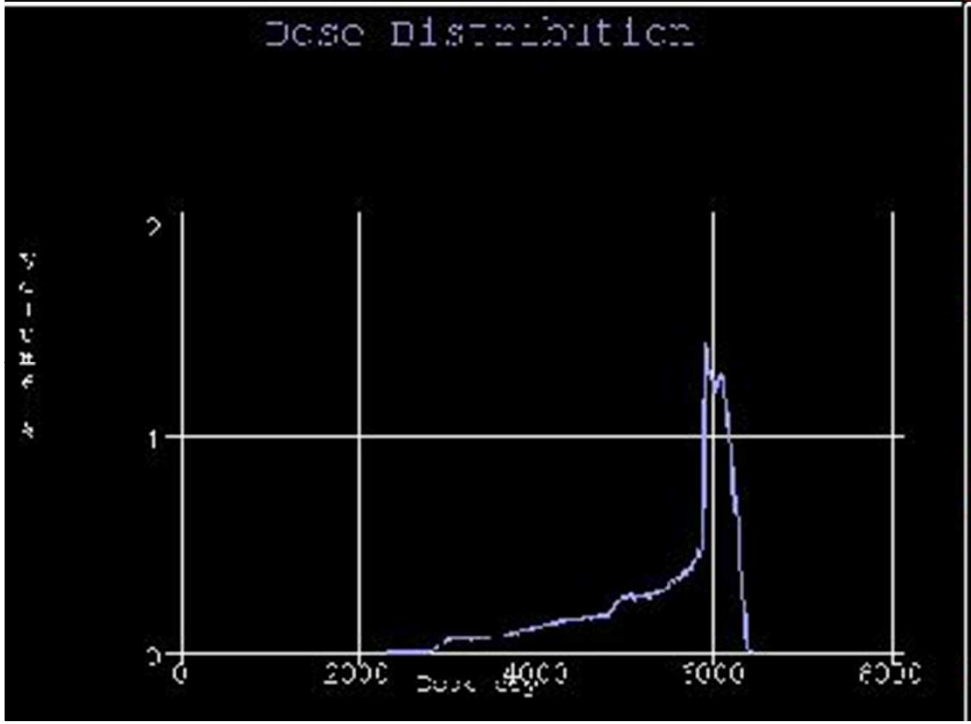
Lyman model or
logistic model

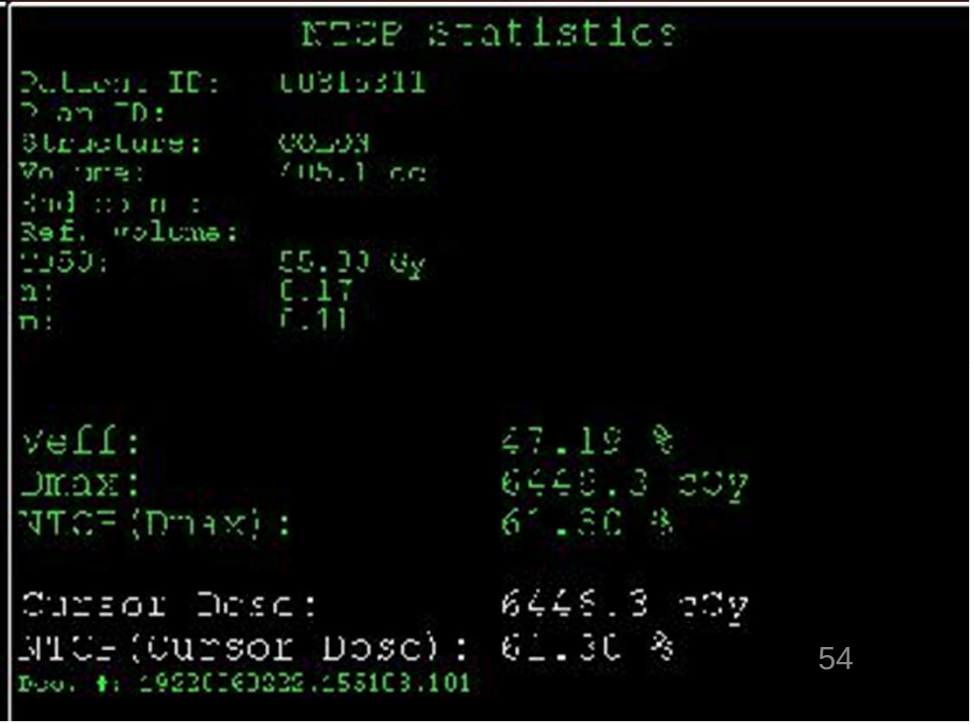


From Kutcher et al.1989


Cumulative DVH
Min. Dose: 2317.2 cGy
Max. Dose: 6446.3 cGy
Mean Dose: 5447.1 cGy
100
80
60
40
20
0
0
2000
4000
6000
8000
Dose cGy


Normal Tissue Complication
100
80
60
40
20
0
0
2000
4000
6000
8000
10000
Max Dose cGy


Dose Distribution
2
1
0
0
2000
4000
6000
8000
Dose cGy


NTCP Statistics
Patient ID: 00816311
Plan ID:
Structure: COLON
Volume: 705.1 cc
Endpoint:
Ref. volume:
TD50: 55.00 Gy
m: 0.17
n: 0.11
Veff: 47.19 %
Dmax: 6446.3 cGy
NTCP(Dmax): 61.30 %
Cursor Dose: 6446.3 cGy
NTCP(Cursor Dose): 61.30 %

Disadvantages of NTCP models

Lymen's model only applies to fractional volumes receiving uniform doses. In practice it is never the case. Modern systems describes dose to an organ in terms of DVH.

DVH needs to be transformed into into a single point dose:

Method 1: DVH is transformed into an equivalent dose given to the whole volume

Method 2: DVH is transformed into a fractional volume that received the maximum dose in DVH

(ASSUMTION: Each fractional volume will follow the same dose-volume relationship as the whole organ).

Use of NTCP in clinical decision making is highly controversial.

Dose is not the most important….

Two identical doses may not produce identical responses due to other modifying factors

1.Physical factors

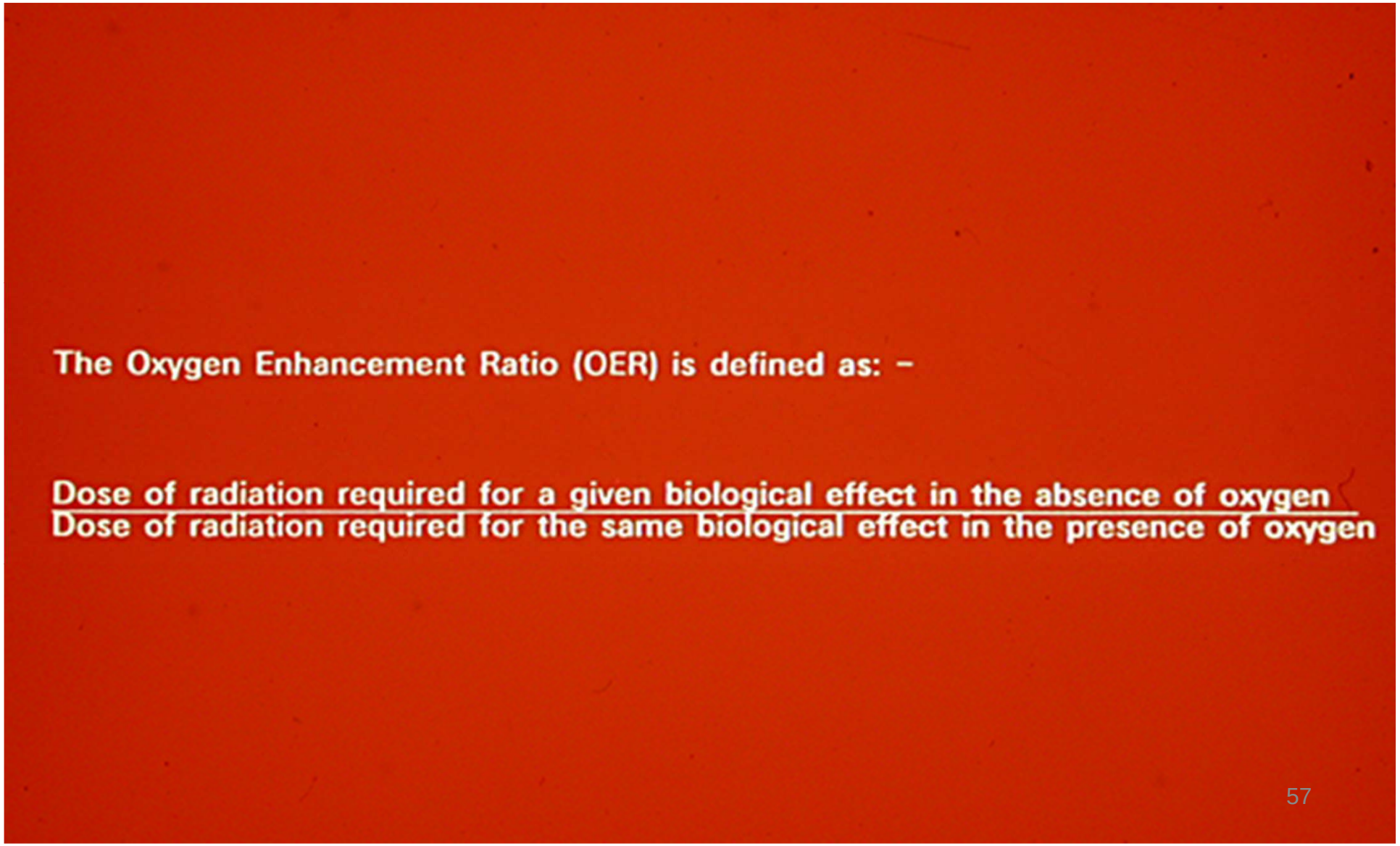
- **Linear energy transfer**
- **Relative biologic effectiveness**
- **Fractionation & protraction**

2. Biological factors

- **Oxygen Effect-Oxygen enhancement ratio**
- **Age**
- **Recovery**
- **Chemical Agents**

OER: Oxygen Enhancement Ratio

Definition



OER

- for sparsely ionizing radiation (i.e., x-rays)

  for a synchronous cell population: OER varies from according to cell cycle phase

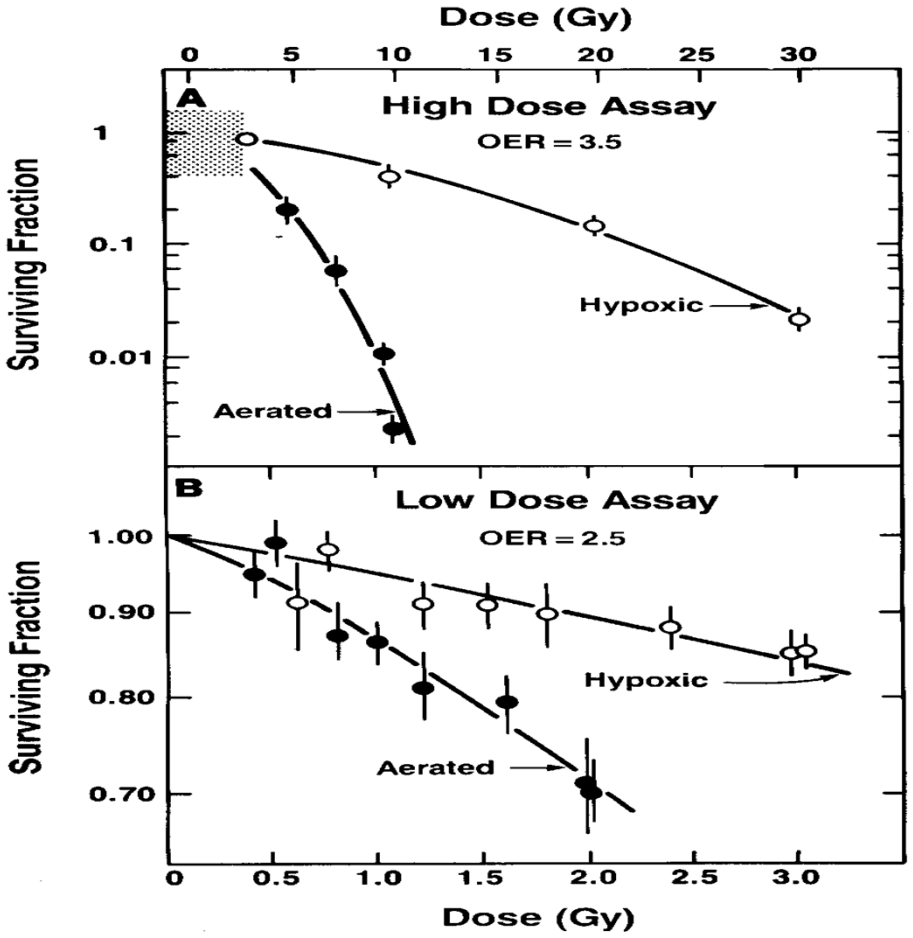
  S phase: 2.9

  G2 and M phases: 2.3

  G1 phase: 2.6

  for an asynchronous cell population: OER varies according to radiation dose

OER & radiation sensitivity



Palcic et al Rad Res 1984

for radiation of low ionizing density (i.e x-rays): OER 2.5-3.

for radiation of intermediate ionizing density (*i.e.*, neutrons): OER is 1.6 and is much smaller than for x-rays.

for densely ionizing radiation (*i.e.*, α-particles): OER is 1 – that is, there is no oxygen effect

OER for X-RAYS

- ***at low doses* (*i.e.*, < 200 cGy)**
  - OER ~ 2.5
  - *rationale*
  - cells in G1, G2, or M phase are more radiosensitive than cells in S phase

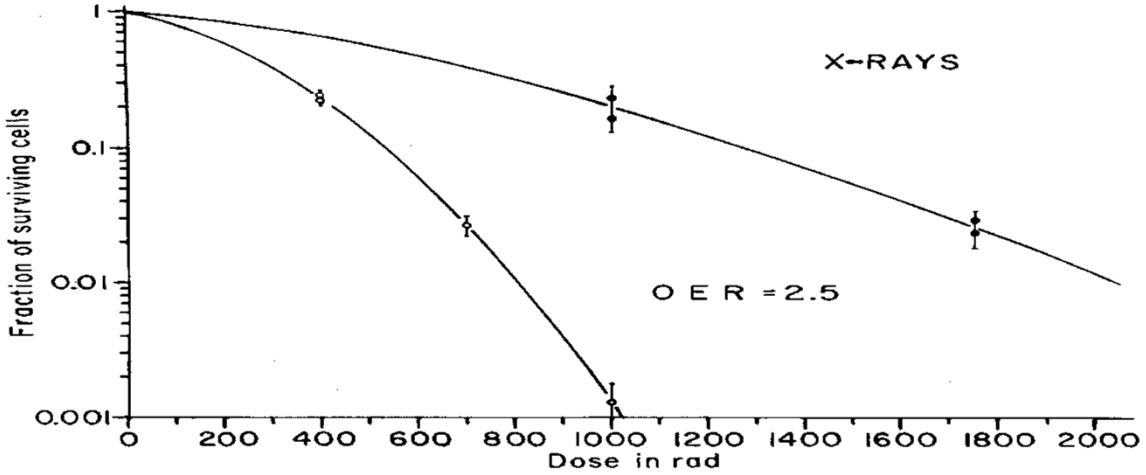
    OER tends to be lower for cells in G1, G2, or M phase than cells in S phase

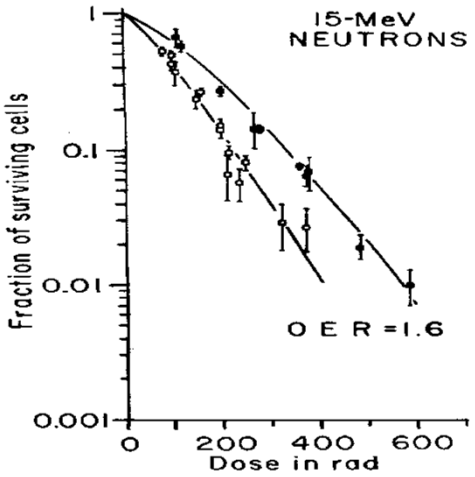
    therefore, at low doses, cells in radiosensitive phases constitute most of the killed cells, and OER is low.

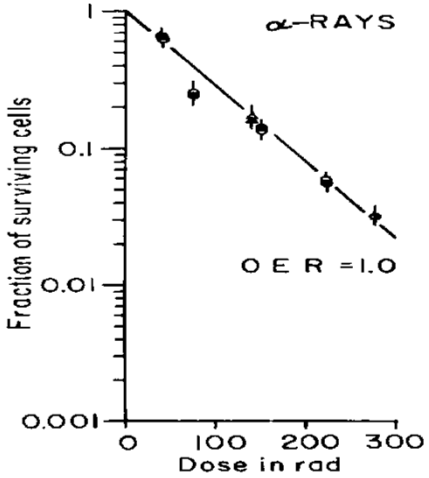
- ***at high doses* (*i.e.*, > 200 cGy)**
  - OER ~ 3 – 3.5
  - *rationale*:

    at high doses, an increasing proportion of radioresistant cells are killed, and OER is therefore observed to increase

OER & LET







Oxygen effect is large for sparsly ionizing radiation e.g X-rays

Oxygen effect is absent for densly ionizing radiation.

Oxygen effect is Intermmediate for neutrons.

according to radiation type: OER decreases as LET increases

LET: Linear Energy Transfer

Definition: introduced by Zirkle

- **Energy deposited per unit of track length of soft tissue.**
- **LET = d*E*/d*l***
- ***Where:***

  d*E* is the average energy locally imparted to the medium by a charged particle of a specified energy in traversing a distance of length d*l.*

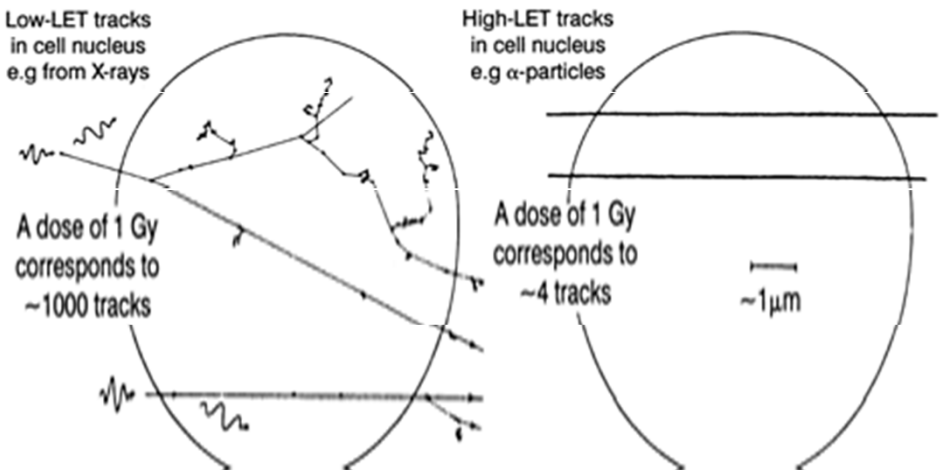
- **Units: KeV/um**

- **What LET tells us is that the number of ionization events increase as the LET increases and decrease as the LET decreases**

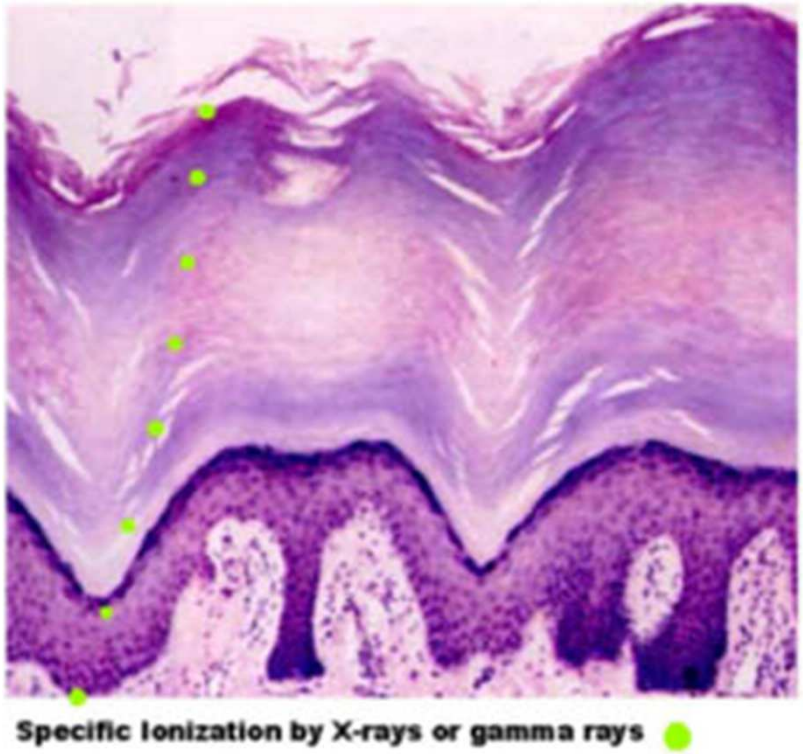
- **Track average = equal track length**
- **Energy average = equal energy increments.**

LET

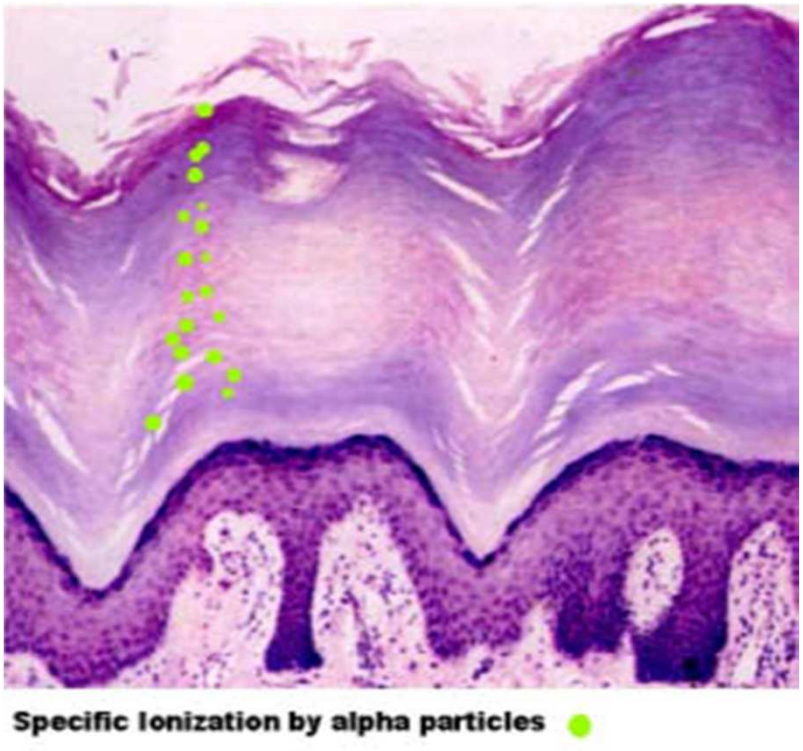
- Sparsely ionizing: x-rays gamma rays.
- Densly ionizing: Alfa particles, protons, neutrons
- A measure of average ionization density.



LET



The specific ionization of low LET radiation such as x-rays and gamma rays do not create ion pairs close together.



The specific ionization of particulate radiations (e.g. alpha particles) is high as ionization occurs more frequently and at closer intervals along the radiation's path.

LET

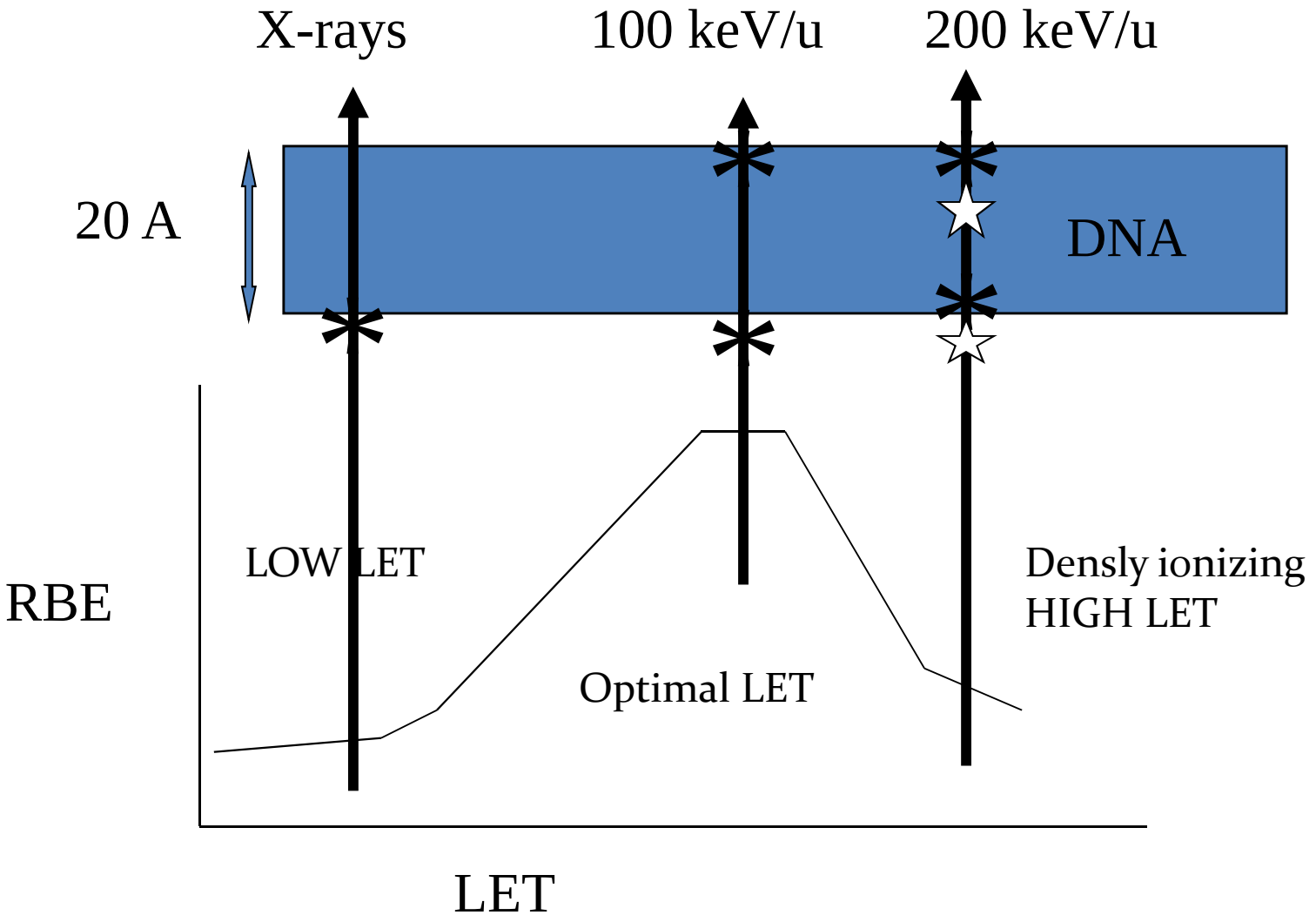
- As the energy of a photon of electromagnetic radiation increases its LET decreases, for example a 25-MeV photon will impart a LET of approximately 0.2 keV/μm.

- X-rays and gamma rays are highly penetrating radiations as such do not easily give up their energy and are considered low LET radiations.

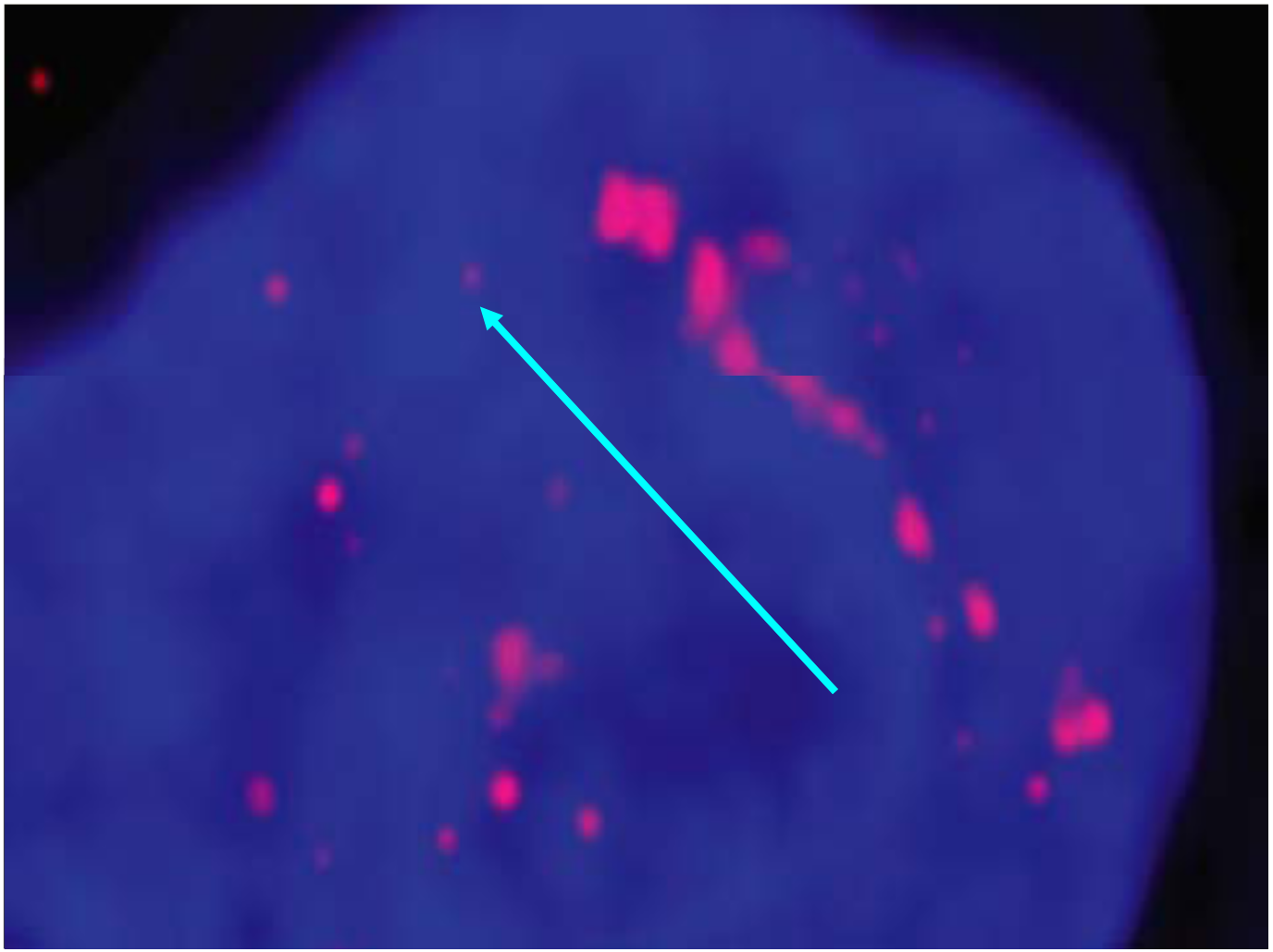
- Less penetrating radiations such as particulate radiation, photoelectrons, alpha particles, and beta radiation are high LET radiations.

so LET is inversely proportional to energy and range of travel

RBE &LET (phenomenon of overkill effect)



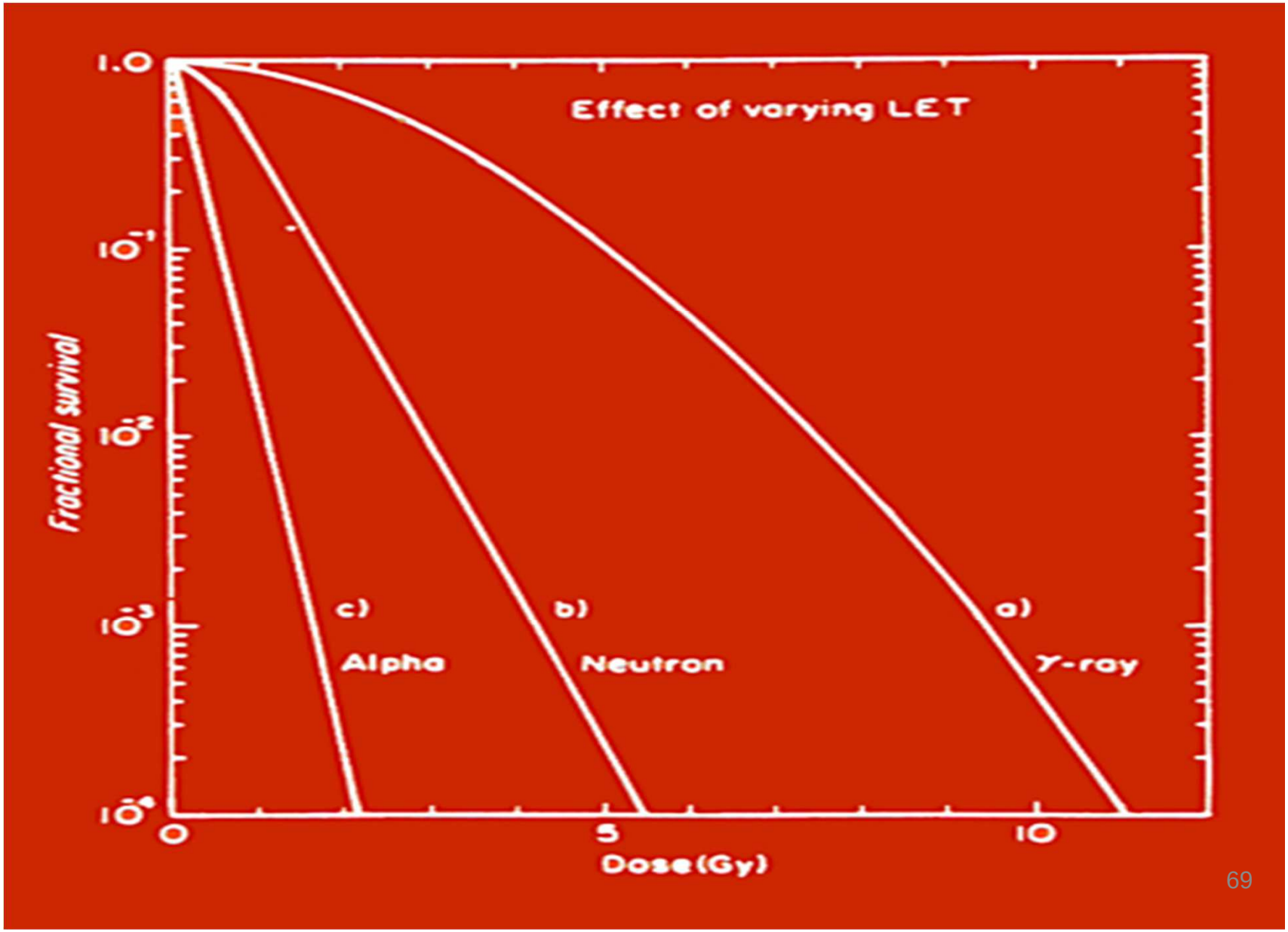
Initial DNA damage from an alfa- particle, measured by histone H2AX accumulation



LET

- Measure of the rate at which energy is transferred from ionizing radiation to tissue.
- Another way of expressing radiation quality & determining the value of the tissue weighting factor (WT)
- **A simple way to indicate the quality of radiation.**

Effect of varying LET on surviving fraction



Rationale of High LET beams

(1) **Hypoxic** cells

-are very resistant to low-LET radiation
-less resistant to high-LET radiation

(2) **Slowly proliferating** cells

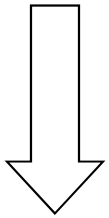
in the Go or G1 phase resistant to low-LET radiation
but not so resistant to high-LET

(3) **Repair of sub lethal damage**

-Less repair of sub-lethal damage after high-LET radiation,
-high-LET treatments resemble large dose-per-fraction of X rays.

Jack F. Fowler *International Journal of Radiation Applications and Instrumentation. Part D. Nuclear Tracks and Radiation Measurements, Volume 16, Issues 2-3, 1989, Pages 89-95*

High-LET



- Neutrons
- Heavy ions
- Light ions
- Protons

Radiotherapy and Oncology xx (2008) xxx–xxx
www.thegreenjournal.com

Original article

Energetic heavy ions overcome tumor radioresistance caused by overexpression of Bcl-2

Nobuyuki Hamada[a,b,c,*,1], Takamitsu Hara[a,b,c,1], Motoko Omura-Minamisawa[d], Tomoo Funayama[c], Tetsuya Sakashita[c], Sakura Sora[a,b,c], Yuichiro Yokota[c], Takashi Nakano[b,e], Yasuhiko Kobayashi[a,b,c]

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Abstract

Background and purpose: Overexpression of Bcl-2 is frequent in human cancers and has been associated with radioresistance. Here we investigated the potential impact of heavy ions on Bcl-2 overexpressing tumors.

Materials and methods: Bcl-2 cells (Bcl-2 overexpressing HeLa cells) and Neo cells (neomycin resistant gene-expressing HeLa cells) exposed to γ-rays or heavy ions were assessed for the clonogenic survival, apoptosis and cell cycle distribution.

Results: Whereas Bcl-2 cells were more resistant to γ-rays (0.2 keV/μm) and helium ions (16.2 keV/μm) than Neo cells, heavy ions (76.3-1610 keV/μm) yielded similar survival regardless of Bcl-2 overexpression. Carbon ions (108 keV/μm) decreased the difference in the apoptotic incidence between Bcl-2 and Neo cells, and prolonged G_2/M arrest that occurred more extensively in Bcl-2 cells than in Neo cells.

Conclusions: High-LET heavy ions overcome tumor radioresistance caused by Bcl-2 overexpression, which may be explained at least in part by the enhanced apoptotic response and prolonged G_2/M arrest. Thus, heavy-ion therapy may be a promising modality for Bcl-2 overexpressing radioresistant tumors.

Keywords: Bcl-2; Radioresistance; Heavy ions; Linear energy transfer; G_2/M arrest

High-LET radiation enhanced apoptosis but not necrosis regardless of p53 status.
Takahashi A, Matsumoto H, Yuki K, et al. IJROBP 2004;60:591–7.

RBE: Relative Biological Effectiveness

- RBE : $\frac{\text{Dose of standard Radiation to produce a given effect}}{\text{Dose of test radiation to produce the same effect}}$

- Standard radiation, by convention, is X-radiation in the 200- to 250-kVp range or 60Co gamma rays

- For diagnostic X-rays, RBE = 1

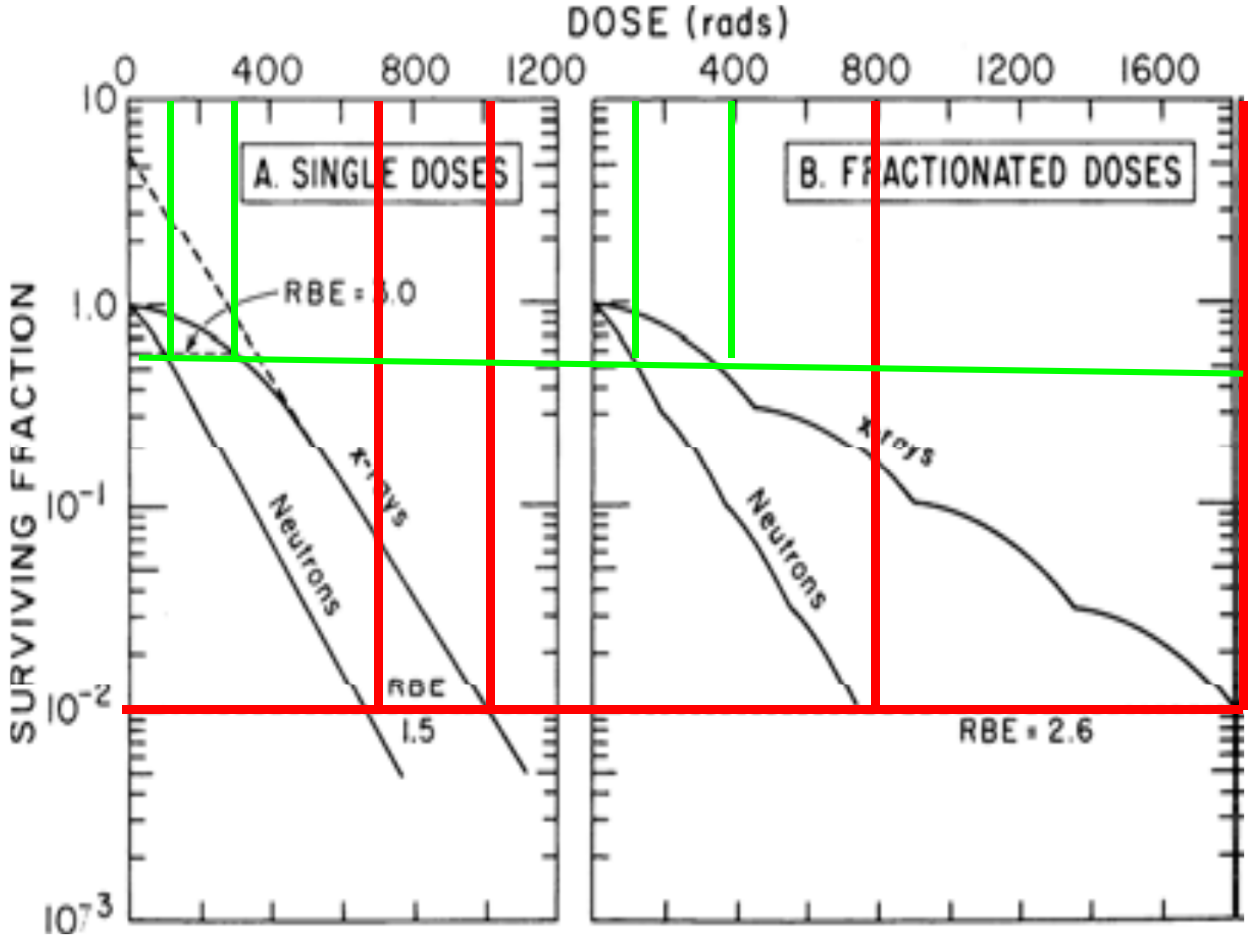
Factors which influence the RBE

RBE depends upon:

- radiation dose (dose per fraction) ,dose rate
- radiation quality (LET)

  RBE increases with increase in LET up to a maximum at ~100keV /micron, and thereafter decreases due to the “overkill” effect.
- biological system or endpoint
- conditions, *e.g.* oxygenation

Effect of dose and dose per fraction on the RBE



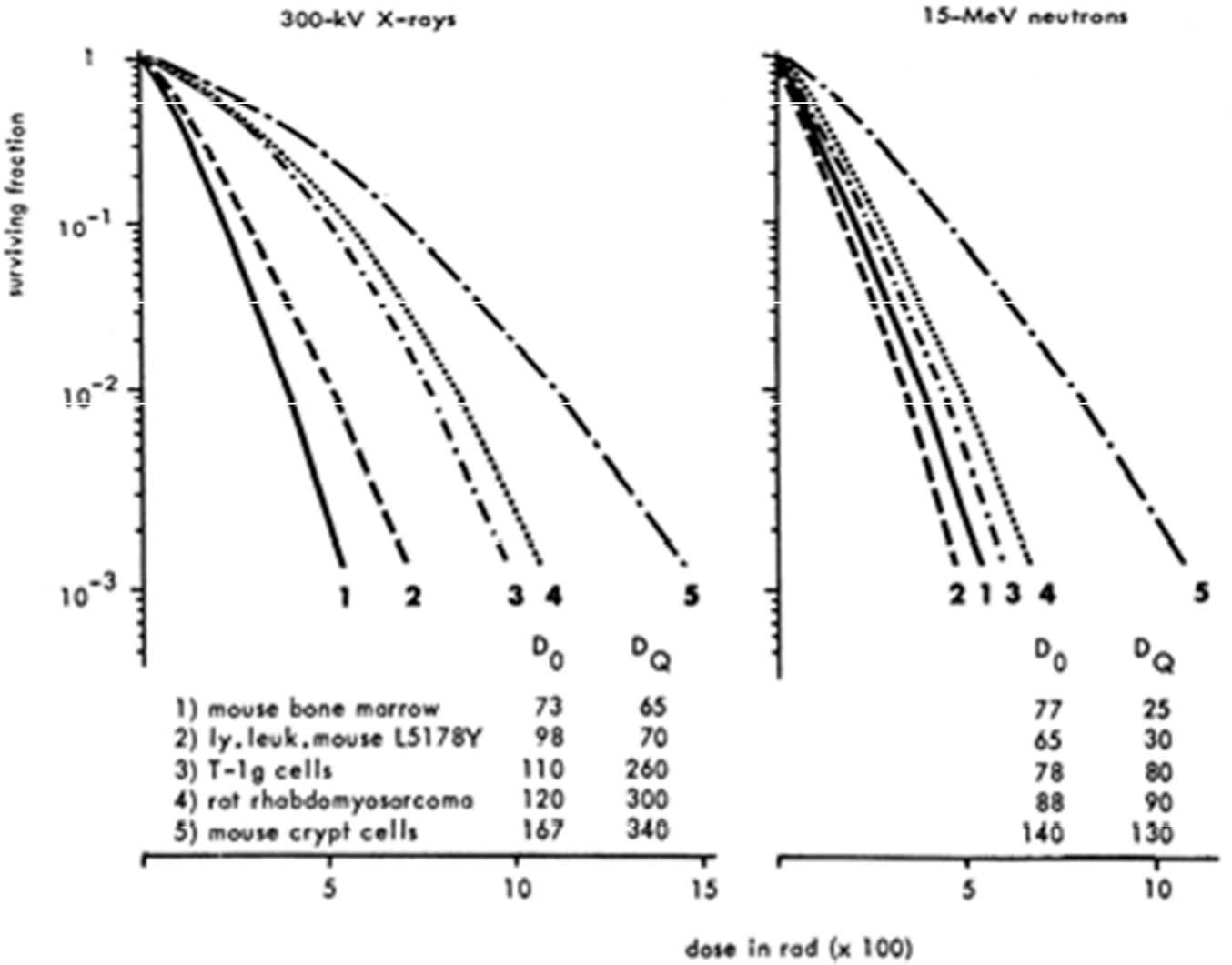
Dependence of RBE on the type of cell irradiated

- In general, cells which exhibit large shoulders in their X-ray survival curves will show large RBEs for neutrons.

- Conversely, cells with *little, if any, shoulder* will have *low RBE's* for nutrons

- But there are exceptions, due to the different interaction mechanisms between low- and high-LET radiations *e.g.* cell-cycle effect.

Dependence of RBE on type of cell irradiated



Applications of RBE in Radiation Protection

Radiation Weighting Factor (WR)

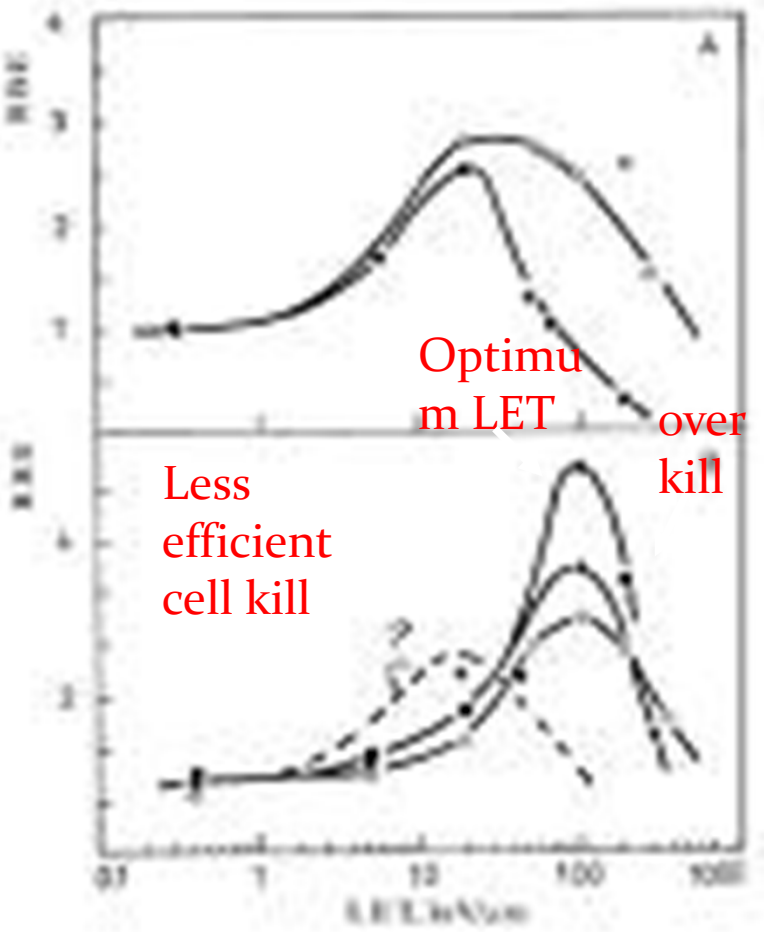
Equivalent Dose = dose x WR

where WR is a “rounded” value of the RBE.

A “rounded” (approximate) RBE needs to be used to cover all biological systems, doses, and endpoints.

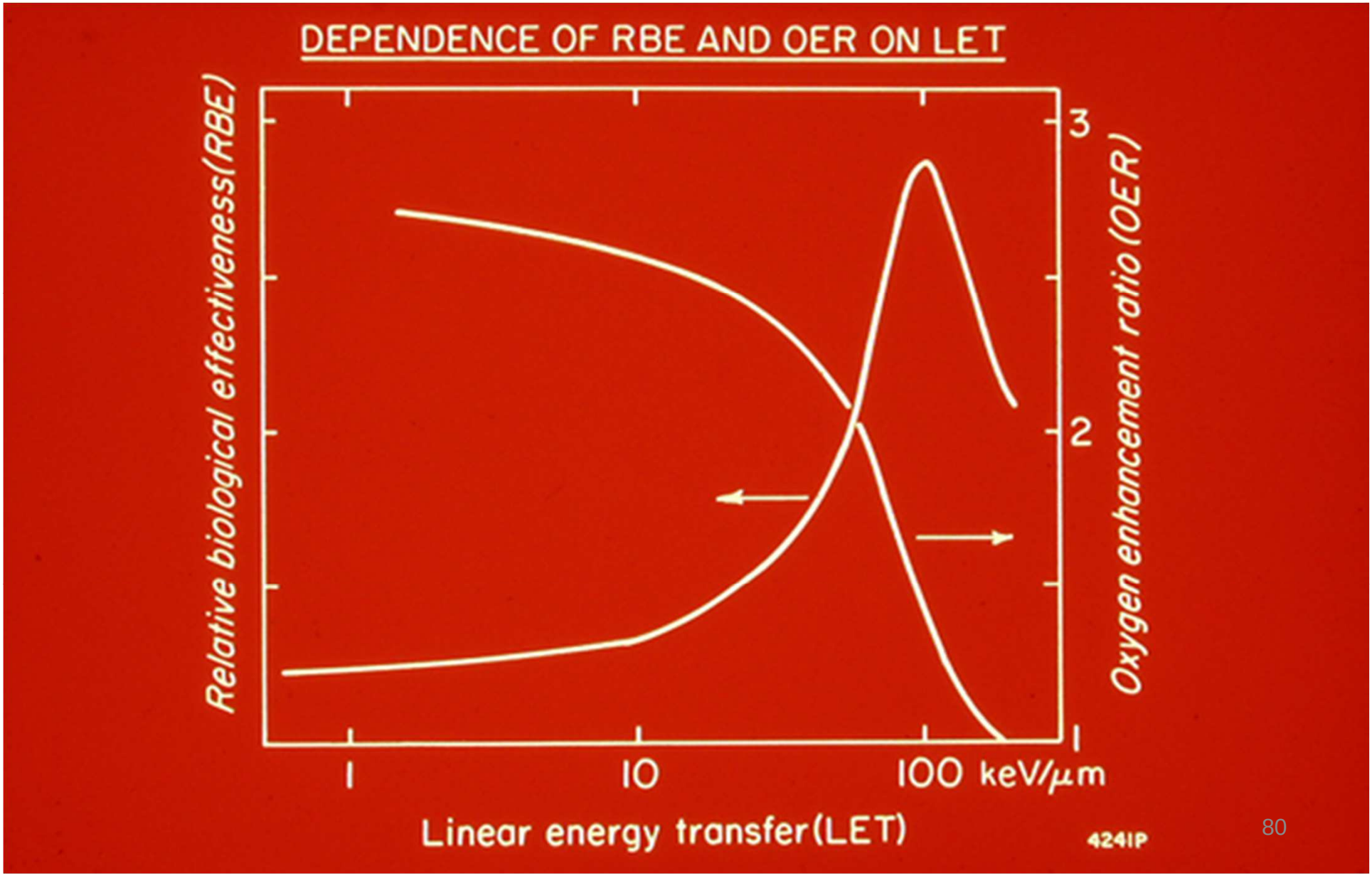
Relationship Between LET & RBE

- LET & RBE



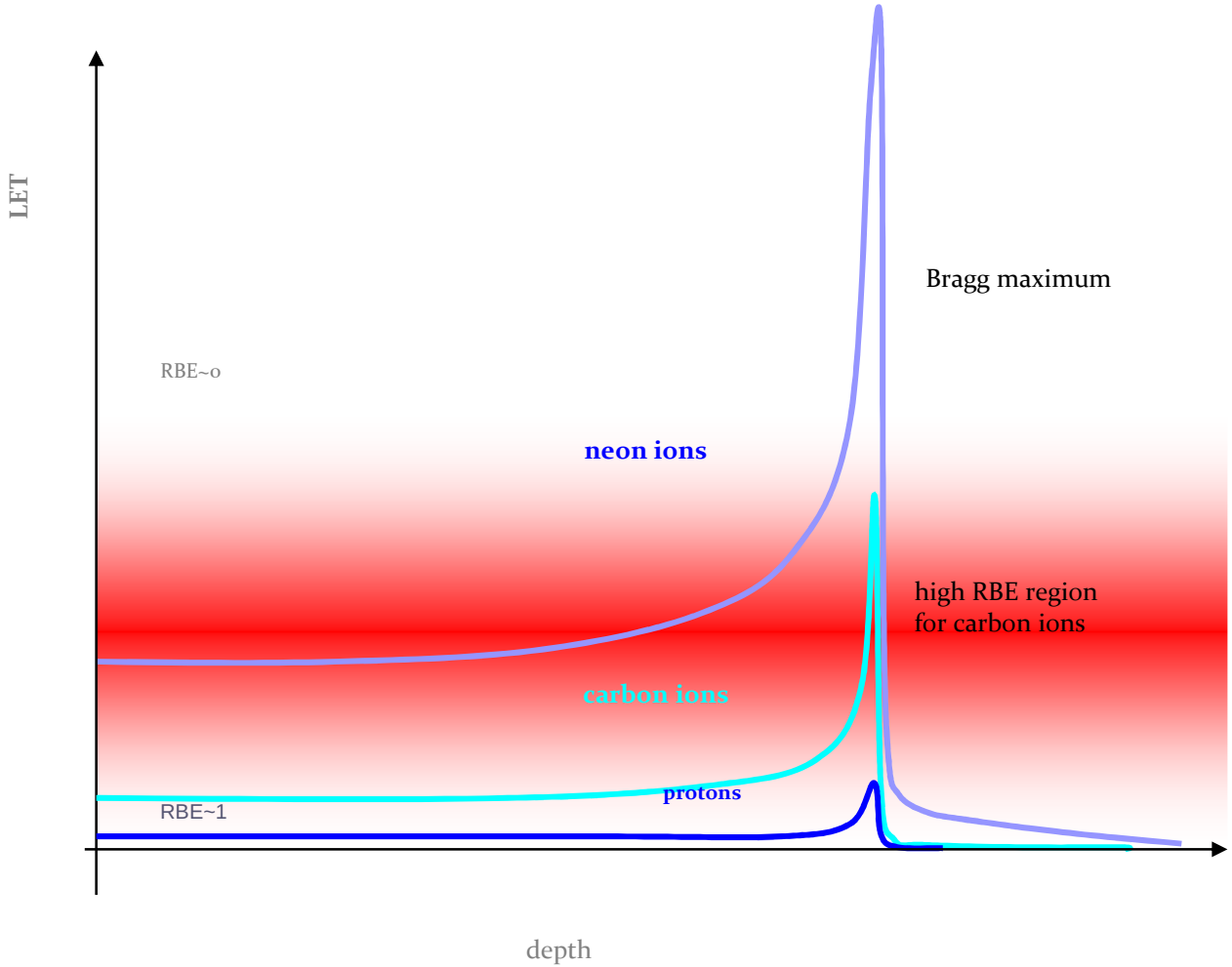
Type of Radiation	LET	RBE
25-MV x-rays	0.2	0.8
60Co X-rays	0.2	0.9
1-MeV electrons	0.3	0.9
Diagnostic X-rays	3.0	1.0
10-MeV protons	4.0	5.0
Fast Neutrons	50.0	10
5-MeV alpha particles	100.0	20

Relation between LET, RBE & OER



LET for proton, carbon and neon ions along their path

For carbon ions the maximum RBE is in the tumour region, neon ions produce an "overkill-effect" inside the target volume where the Bragg maximum is situated. The density of the red colour indicates the increased RBE for carbon



Particle Therapy

- **First proposed the use of protons and heavier ions for therapy in 1946**

Robert Wilson

(March 4, 1914– January 16, 2000)

- Protons - positively charged particles
- hydrogen atom → electrical field → separated into protons and electrons
- protons →vacuum tube in LA & proton energy boosted to about 7 MV
- proton beam→ synchrotron →accelerated 70 to 250 MeV → enough energy to place at any depth
- beam passes series of magnets →shape, focus, and direct the beam to patient

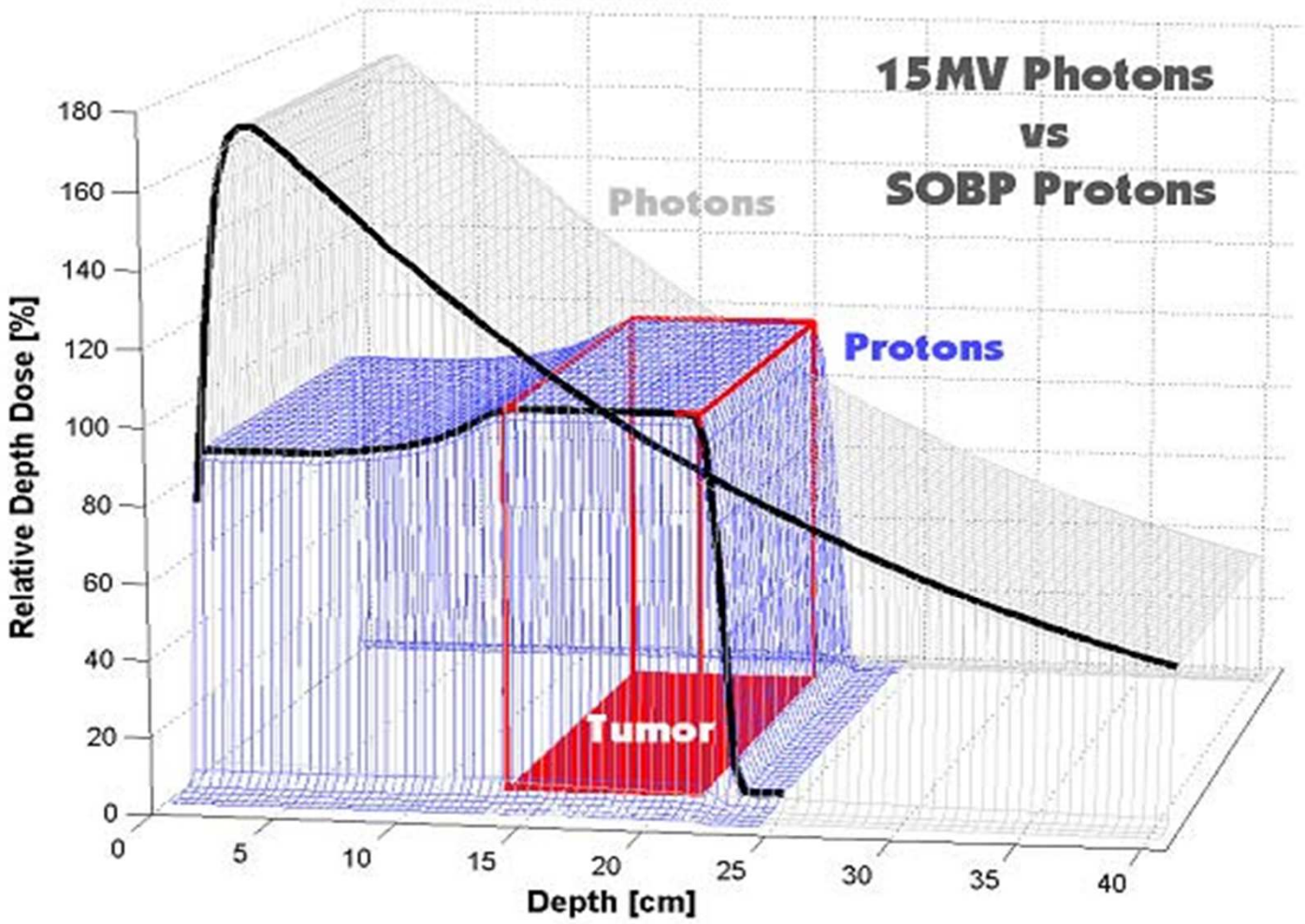
Accelerators for High RBE Radiations

- Two types of accelerators : cyclotron or a synchrotron
- Cyclotrons → fixed energy, higher energy ≈ 250 MeV
- Synchrotron → varied energies, usually in the range of -50 – 70 MeV

SOBP

- Individual Bragg peaks → too narrow to use
- Summed up and spread out (SOBP) to a useful plateau

SOBP


15MV Photons
vs
SOBP Protons
Photons
Protons
Tumor
Relative Depth Dose [%]
180
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
Depth [cm]

Useful applications of the proton beam

1) ***Zero dose beyond the Bragg peak.***

-Stop the beam in front of sensitive healthy structures.

Eye tumours –

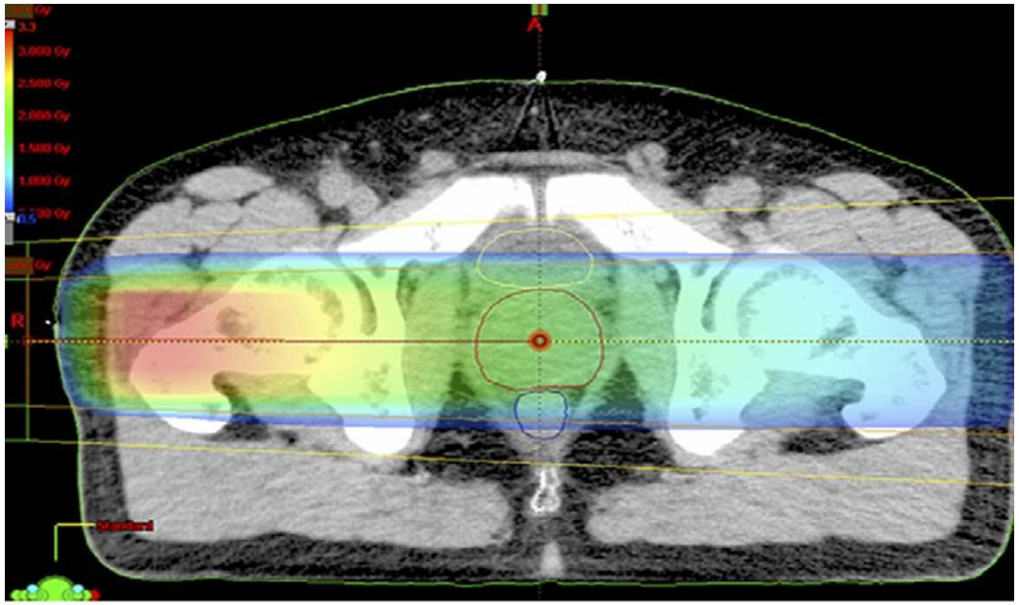
2) ***Low integral dose outside of the target volume.***

-Treatment of large tumours by reducing the dose burden outside the target volume and give more dose to the target.

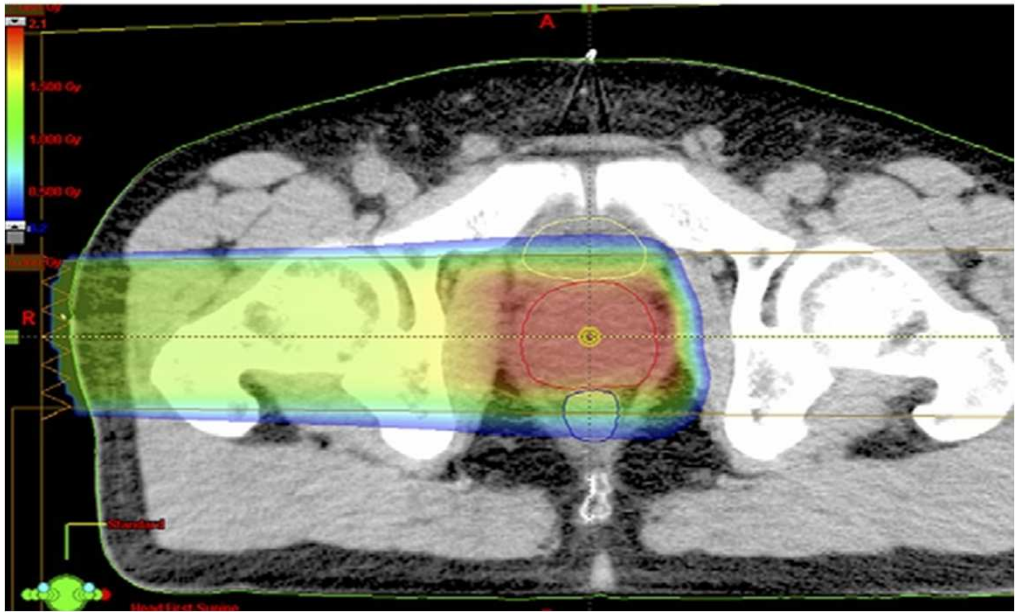
3) Protons are ***charged*** *particles.*

--Magnetic deflection of the beam - active dynamic scanning of the beam.

-For treatment of tumours with complex geometrical shape - conformal therapy.

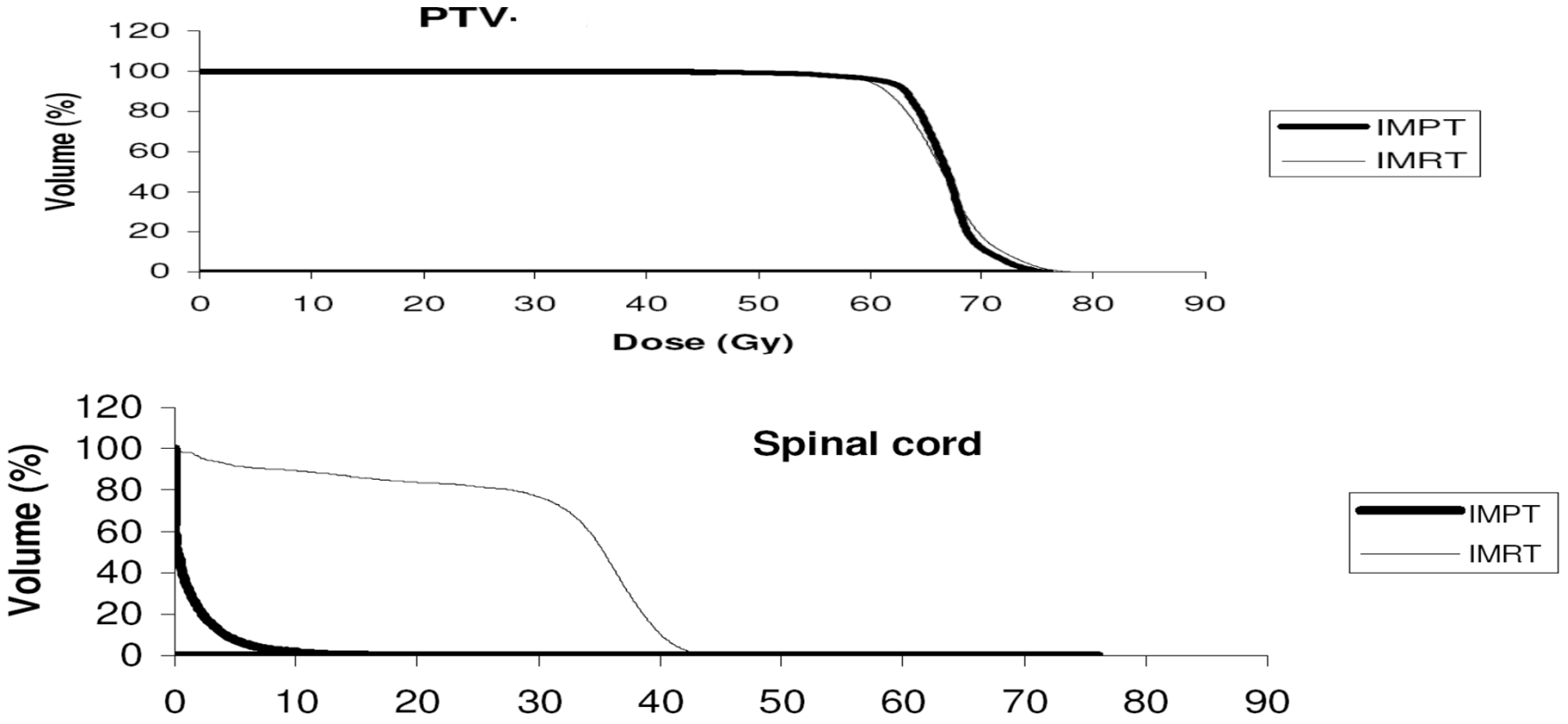


Photon beam displaying exit dose



Proton beam displaying how dose stops

Example of DVH in Ca NPX



Zahra Taheri-Kadkhoda
Radiation Oncology 2008, **3**:4

Tumors considered for proton therapy

- High doses of radiations for control
- Located near sensitive normal tissues

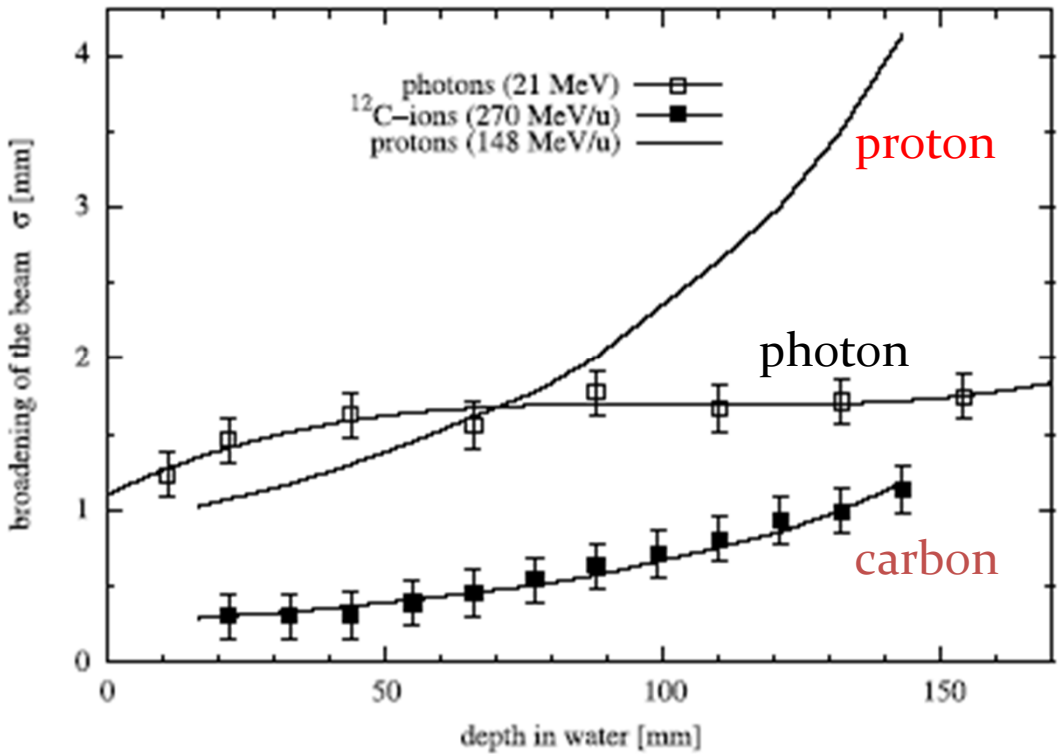
Heavy Ion therapy

Biological aspects-carbon

- Major advantage - increased biological effectiveness in the Bragg peak region so in the tumor volume
- Increased effectiveness →specific microscopic dose deposition pattern
- Photons deposit energy →randomly and homogeneously
- Charged particles →narrow region around the particle trajectory
- Very localized & concentrated energy →Increased effectiveness

Lateral Scattering

- Lateral scattering more important than longitudinal straggling
- carbon → broadening is < 1 mm up to depth 20 cm
- Protons → 2 mm depth > 7 cm.
- Lateral scattering for protons > photons
- Deep-seated tumors precisely with carbon ions
- Superficial tumors (eye) satisfactory with protons



Comparison of the lateral scattering of photon, proton and carbon beams as function of the penetration depth

Weyrather *Clinical Oncology* (2003) **15**: S23–S28

Clinical Evidence

- Protons
- Ions as Carbon, He
- Neutrons

Proton Beam Therapy

Proton Beam: Clinical Implications

- Uveal (choroidal) melanoma.
- Skull base tumors
- Spinal cord tumors – Chordoma.
- Prostate cancer.
- Pituitary tumor.
- Acoustic neuromas.
- Paranasal sinus & Nasopharynx.
- Others – AVM.

Summary of Clinical Evidence

Table 1
Results literature review in comparison with conventional therapy classified by tumour site

Tumour site	Protons		Ions	
	n studies/*N*	Result	*n* studies/*N*	Result
Head and neck	2/62	No firm conclusions	2/65	Similar to protons
ACC (locally advanced)	–	–	1/29	Superior
Prostate cancer	3/1751	Similar	4/201	No firm conclusions
Ocular tumours	10/7708	Superior	2/1343	Similar to protons
Gastro-intestinal cancer	5/369	No firm conclusions	2/73	No firm conclusions
Lung cancer (non-small cell)	3/156	No firm conclusions	3/205	Similar to SRT
CNS[a]	10/839	Similar	3/405	Similar to protons
Chordomas of skull base	3/302	Superior	2/107	Similar to protons
Sarcoma's	1/47	No firm conclusions	1/57	No firm conclusions
Pelvic tumours	3/80	No firm conclusions	2/49	No firm conclusions

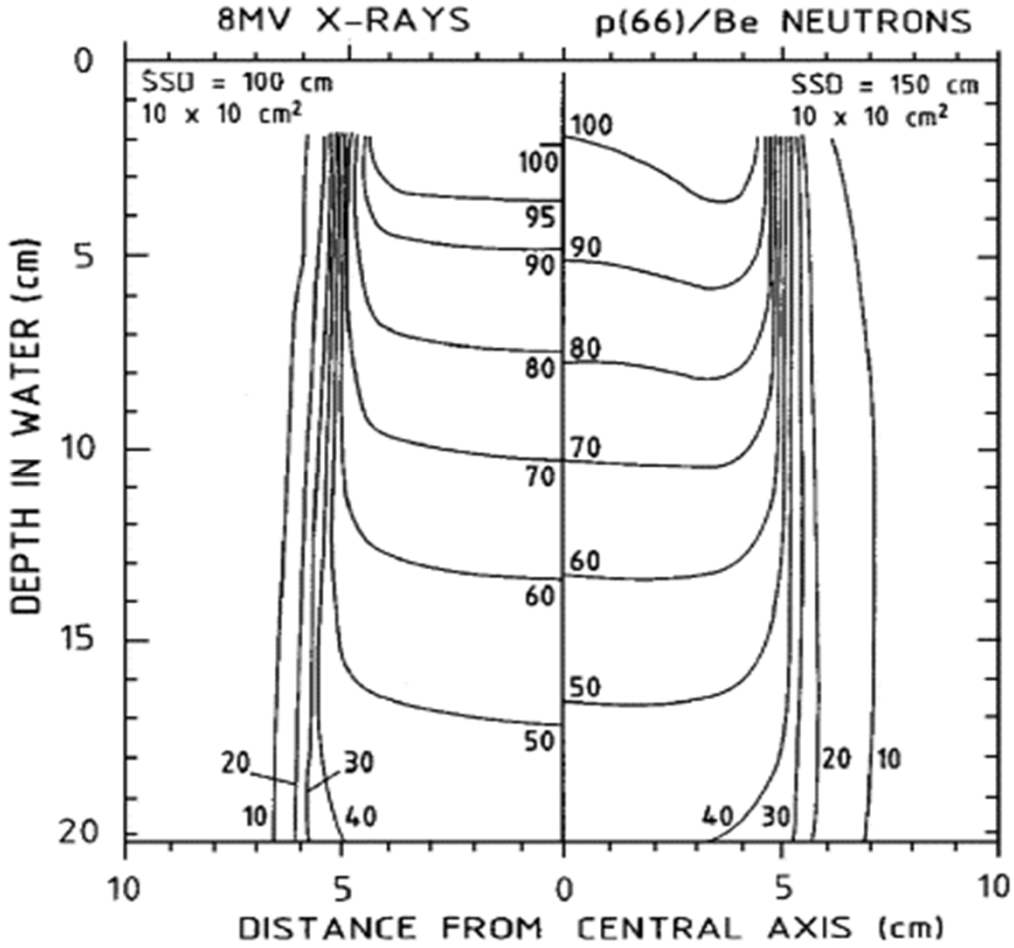
Abbreviations: *N*, number of patients; ACC, adenoid cystic carcinomas; SRT, stereotactic radiotherapy.
[a] CNS, central nerve system tumours; inclusive skull base, spinal cord chondroma and chondrosarcomas.

M. Lodge et al. / Radiotherapy and Oncology 83 (2007) 110–122

Neutron Therapy

Neutron Therapy

- Neutrons first were introduced without proper experimental data on sole basis that lower OER
- Since biological effect not taken into consideration major set back due very severe late reaction.
- Later on RBE concept taken into consideration
- Production –
  -Deuterium Tritium generators.
  -Paricle Accelerators
- Bombarding particles – Deuterons, proton.
- Target material – Usually beryllium.
- Depth dose data same as photons



Isodose distributions for 8 MV X-ray and p(66)/Be neutron

Interactions

- No charge but with high LET, RBE value.
- Indirectly ionizing.
- Two mechanism

  - Recoiling with hydrogen or heavy nucleus of element.

  - Nuclear disintegration.

Indications for fast neutron therapy

Region	Tumour
Base of skull	Chordomas
	Chondrosarcomas
Head and neck	Salivary gland tumours
	Paranasal sinus tumours
Chest and abdomen	Breast tumours
Pelvis	Prostate tumours (T3, T4)
	Uterine sarcomas
	Chordomas
	Chondrosarcomas
Trunk and extremities	Osteosarcomas
	Malignant melamonas STS
	Soft tissue sarcomas

D.T.L. Jones, A. Wambersie / Nuclear Instruments and Methods in Physics Research A 580 (2007) 522–525

Neutrons: Advantage only in few selected tumors

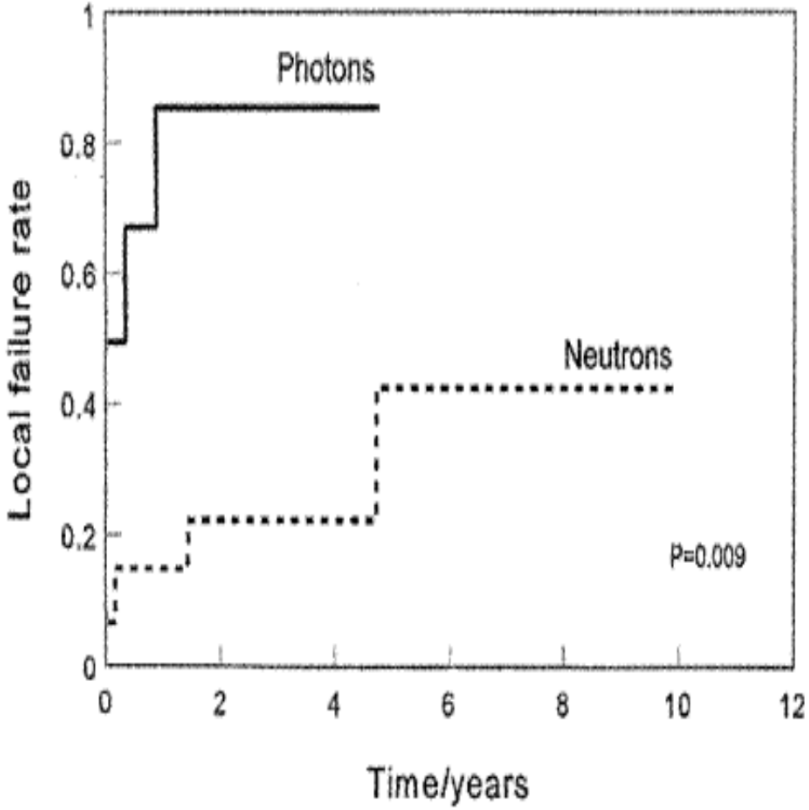
- Salivary gland.
- Prostate cancer.
- STS.
- Head and neck malignancies (Advanced).
- NSCLC.
- Breast

Salivary gland

- Based on strong radiobiological rationale given by Batterman et al
- Salivary gland tumor has RBE ~ 8 as compare to other late effect (3 - 3.5)
- 20Gy of neutrons are equivalent to 160Gy at tumor site, 60Gy at normal tissue level
- Therapeutic gain factor for salivary gland tumor is 2.3-2.6

RTOG/MRC trial

- RCT
- Accrual stopped as 2 year data showed strong trend towards neutron
- Followed up 10 yr
- Improved local control in neutron arm 56% Vs 17%. P=0.009
- No difference in long term survival due to distant mets.



Prostate cancer

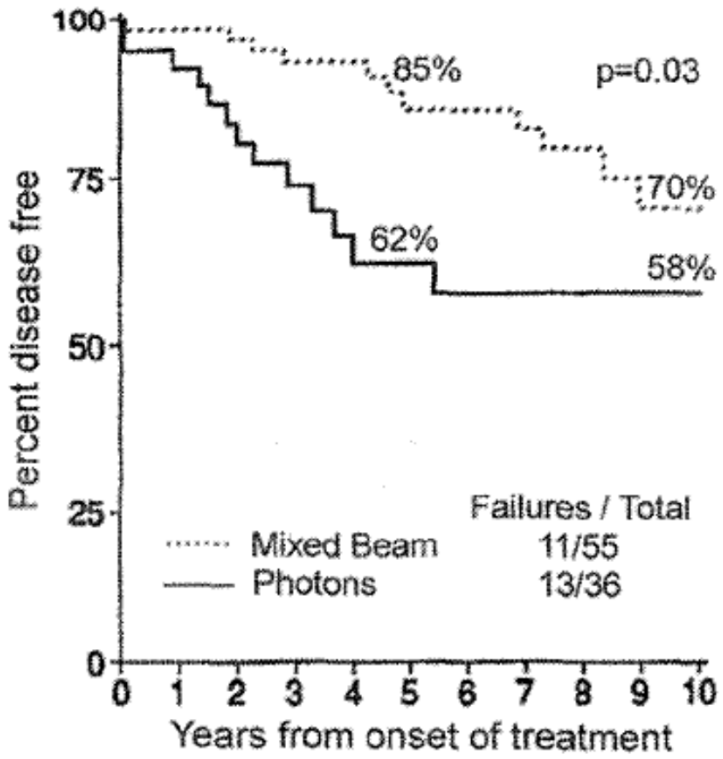
- 2 RCT.

- RTOG* – compared mixed beam with photon alone in locally advanced cases.

  -91 pt..
  -At 10 yr F/U

LRC *70%* vs 58%(p=0.03),
survival *46%* vs 29% (p=0.04).

  -*No difference in toxicity!*



*Am J Cli onco 1993,16,164

- 2nd RCT
- NTCWG Russell et al.*
- 172 pt.
- Fast Neutron vs photon.
- No difference in survival.

*IJROBP 1993,28,47

Drawbacks

- Enormous cost involved. (~US $100m)
- More complex and bulky equipment necessary to accelerate particles.
- Stringent quality assurance needed.
- No long term data available to consider late effects of treatment.
- Dose tolerance for various organs are not available.

Conclusions

- Advances in radiation physics and better understanding of tumour biology allows us to plan more complex yet safe radiation therapy.

- This will lead to better tumour control and reduction in normal tissue toxicity thus improving the therapeutic ratio.

- Young Generation - :
  - Undertake clinical trials to validate the radiobiological concepts.
  - Develop models to individualize Radiotherapy based on tumour kinetics.


Thank You