Quantitative radiobiology for treatment planning

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Aim of Radiotherapy

- **Lethal dose in tumor - Kill all the cancer cells**
- **Sparing Normal tissue and OAR**
- **Manageable comorbidity**

Determinants of Tumor Cure

Heterogeneity:

- Biological
  - Number of clonogenic “stem cells”
    - Intrinsic radio sensitivity
    - Proliferative potential
    - pro-apoptotic tendency
    - Repair- T1/2- fast and slow repair
- Rate of repopulation/regeneration during therapy
  - Tpot – doubling time, Reoxygenation (extent of hypoxia)
  - PO_2 (dependence on tissue type, vascularity?)
- Redistribution
  - Growth fraction (dependence on cell type, growth factors
  - Tumor microenvironment
    - Hypoxia, Metabolism
    - Host cell infiltrates, Interstitial pressure
  - Genetic
    - Oncogenes, Tumor suppressor genes
- Physical
  - Dose heterogeneity
  - Geographic miss

Tumor Growth and Regression

The **kinetics** of tumor growth and regression depend upon

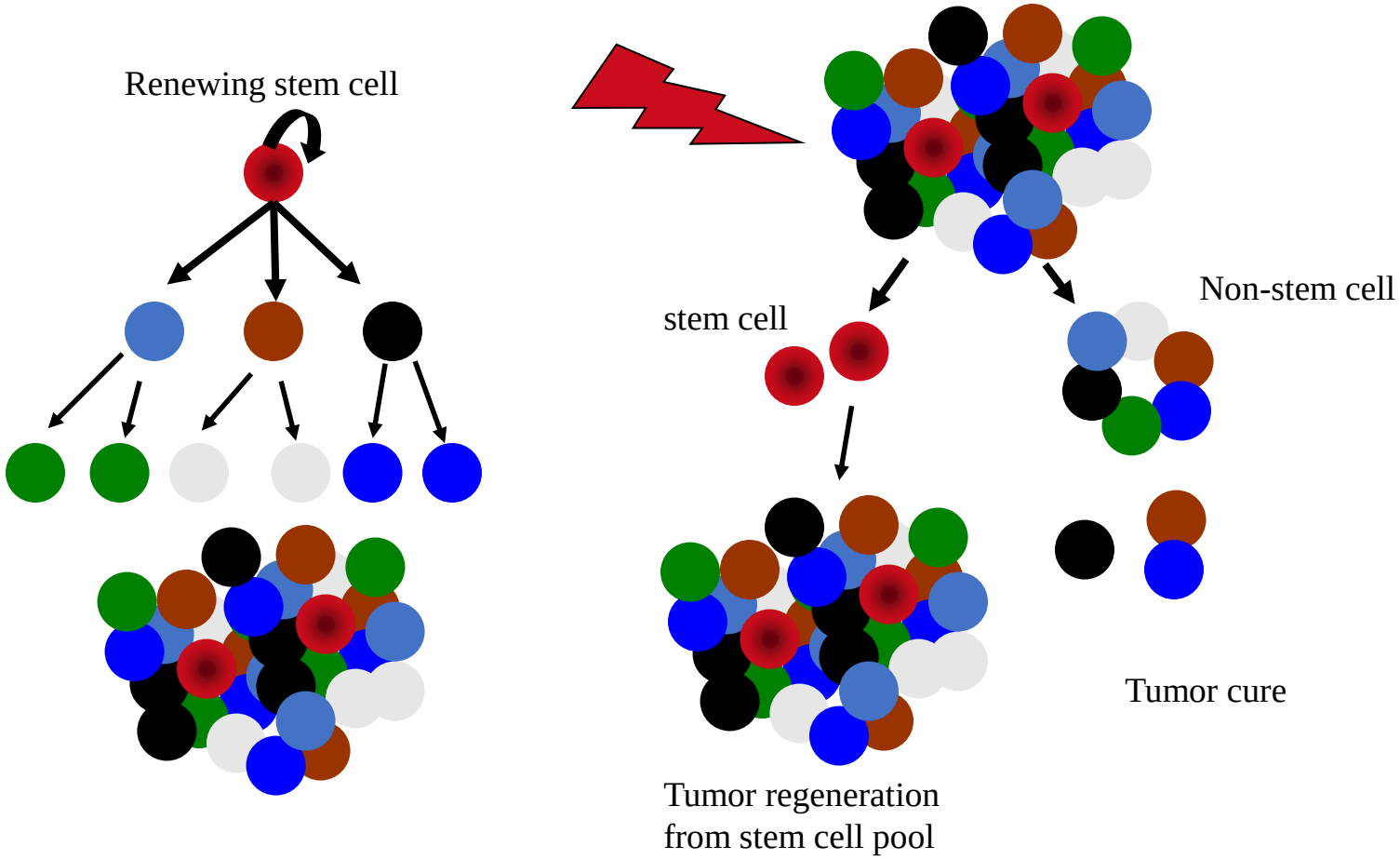
- Cell cycle
- Growth fraction (G.F.)
  - G.F. is the proportion of proliferating cells
  - G.F. = P / (P + Q) where P = proliferating cells and Q = non-proliferating cells (quiescent/senescent/differentiated cells)
- Cell loss factor
  - Cell Loss Factor (Φ) measures loss of cells from a tissue
  - If $\Phi = 0$, Td = Tpot where Td is the actual volume doubling time and Tpot is potential volume doubling time
  - $\Phi = 1 - Tpot / Td$
  - if G.F. = 1 then Tpot = Tc
  - Under steady state conditions, constant cell number is maintained by the balance between cell proliferation and cell loss i.e. $\Phi = 1.0$. In tumors (and embryos) $\Phi < 1.0$

  - EVIDENCE BASED TREATMENT- FLOW CYTOMETRY, FISH, PCR
  - PET, DTI- MRI - MOLECULAR IMAGIMNG - BIOLOGY OF TUMOR- TAILOR MADE TREATMENT

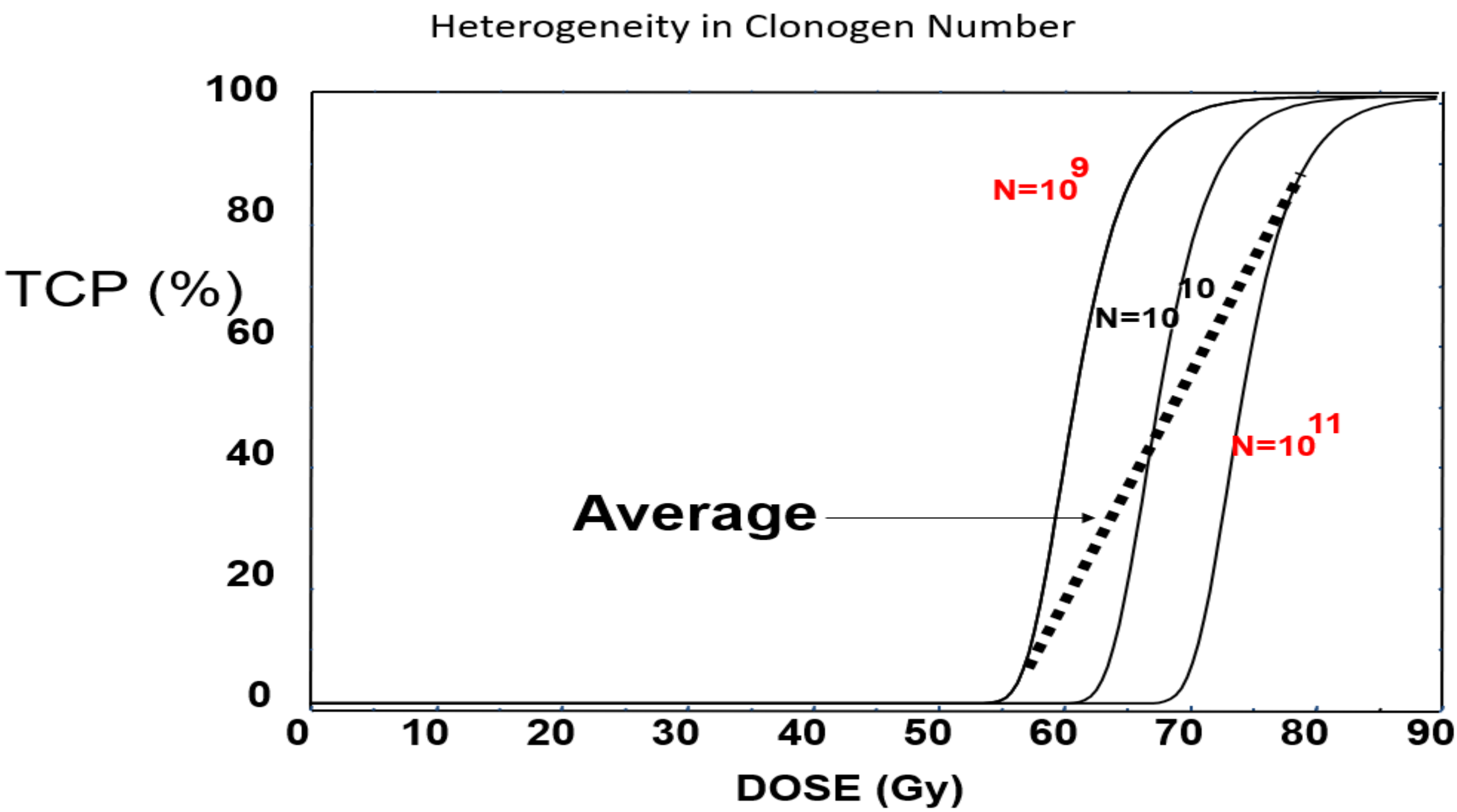
Tumor Kinetics

		Human SCC	
Tc	Cell cycle time	36 hrs	
G.F.	Growth fraction	0.25	
Tpot	Pot. doubling time	6 days	(36hr x 4)
Td	Actual doubling time	60 days	
Φ	Cell loss factor	0.9	(1-6/60)

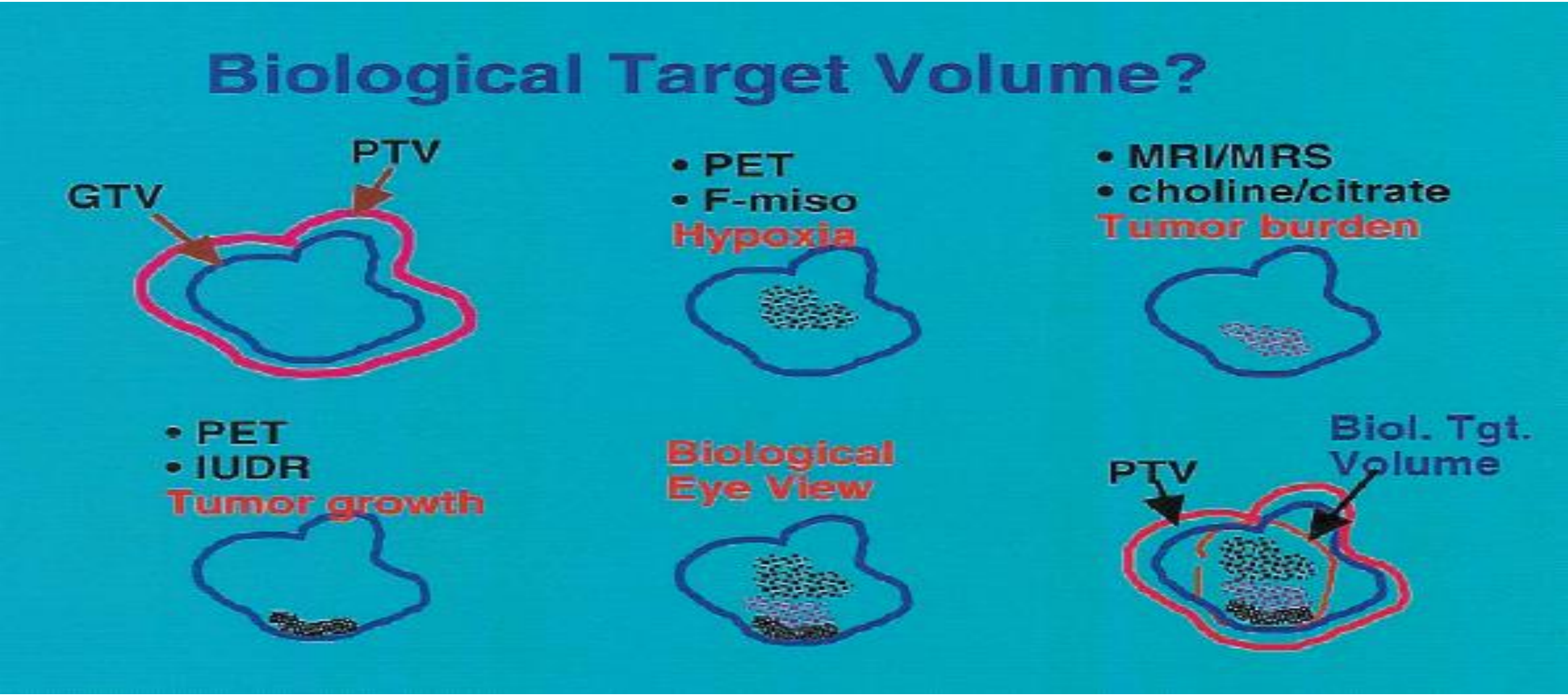
Rate of tumor growth and rate of tumor regression after therapy are determined largely by the cell loss factor, that varies greatly from tumor to tumor



The cancer stem cell hypothesis suggests that there are a **small number of clonogenic stem cells in a tumor and that, if they are therapy-resistant, they are responsible for recurrences**, and accelerated tumor repopulation during therapy.


Heterogeneity in Clonogen Number
TCP (%)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
DOSE (Gy)
N=10^9
N=10^10
N=10^11
Average

Concept of biological target volume (BTV): C. Ling



IJROBP Vol. 47, **2000**

The **complete prescription** of radiation treatment must include:

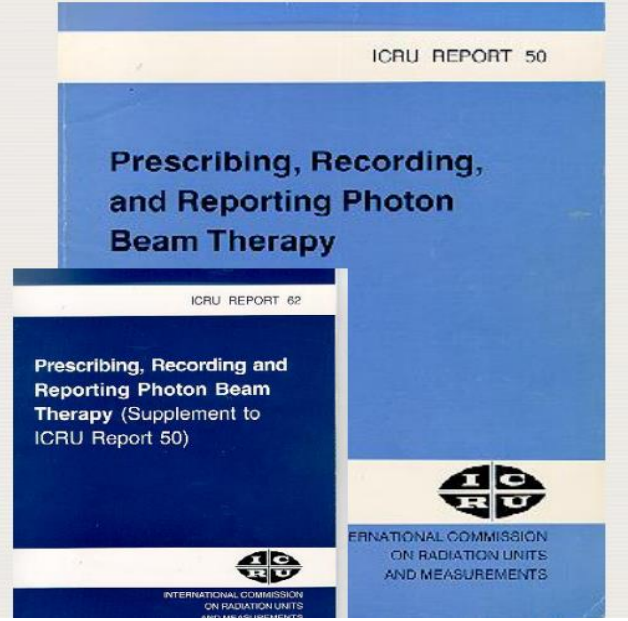
- Definition of the **aim** of therapy
- **Volumes** to be considered
- **Prescription** of **dose** and **fractionation.**

Only detailed information regarding total dose, fractional dose and total elapsed treatment days allows for proper comparison of outcome results.

Different concepts have been developed for this requirement.

The **ICRU 50 and 62 Reports** define and describe several target and critical structure volumes that:

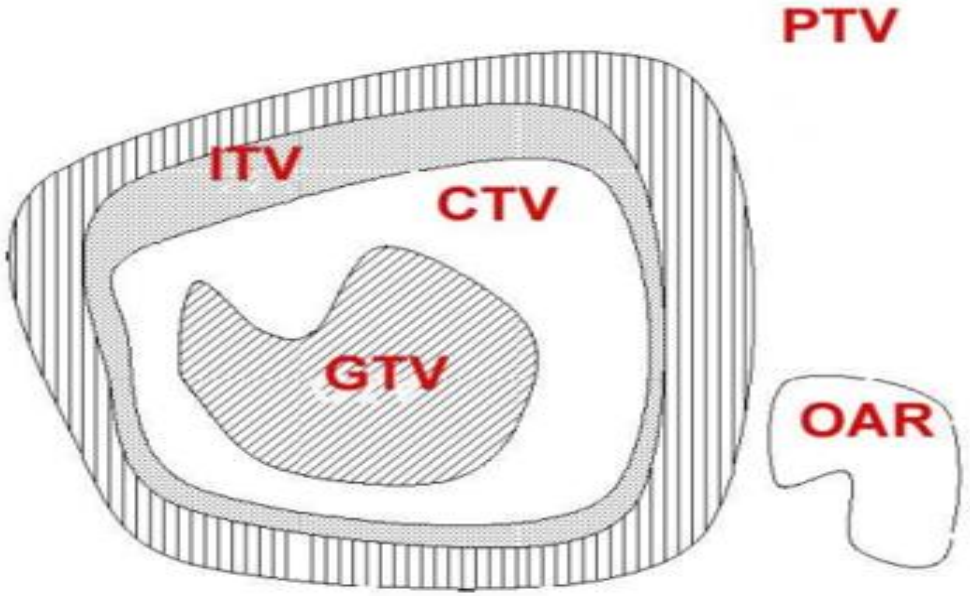
- Aid in the treatment planning process
- Provide a basis for comparison of treat-ment outcomes.



The ICRU report 50 recommends a target dose uniformity **within +7 % and –5 %** relative to the dose delivered to a well defined prescription point within the target.

Since some dose heterogeneity is always present, a method to describe this dose heterogeneity within the defined volumes is required.

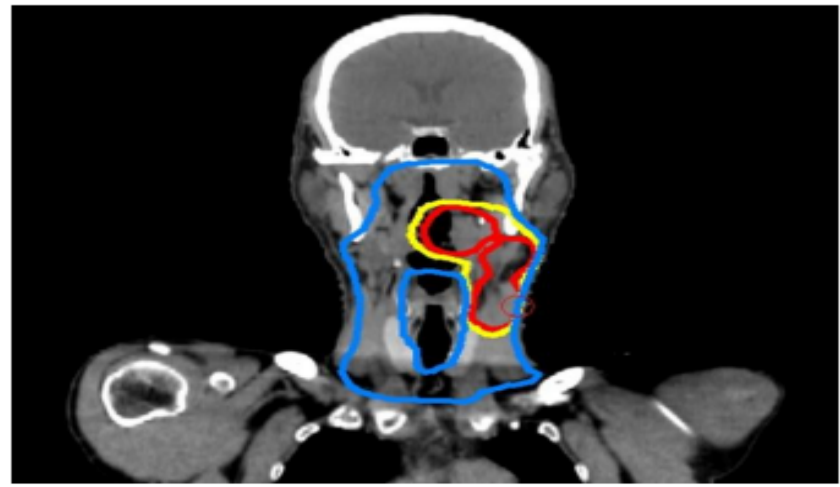
ICRU Report 50 is suggesting several methods for the **representation** of a spatial dose distribution.

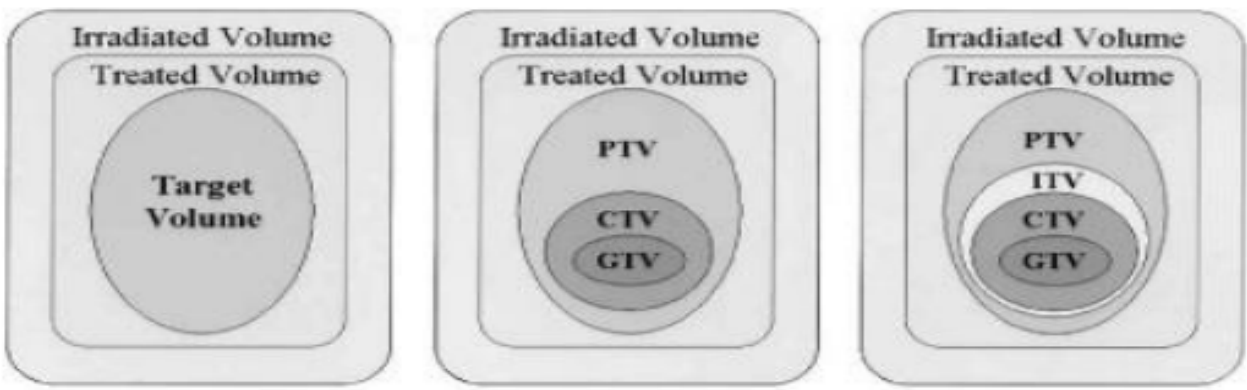


ITV Internal margin, GTV- Gross tumour volume, PTV- planned tumour volume, CTV- clinical tumour volume

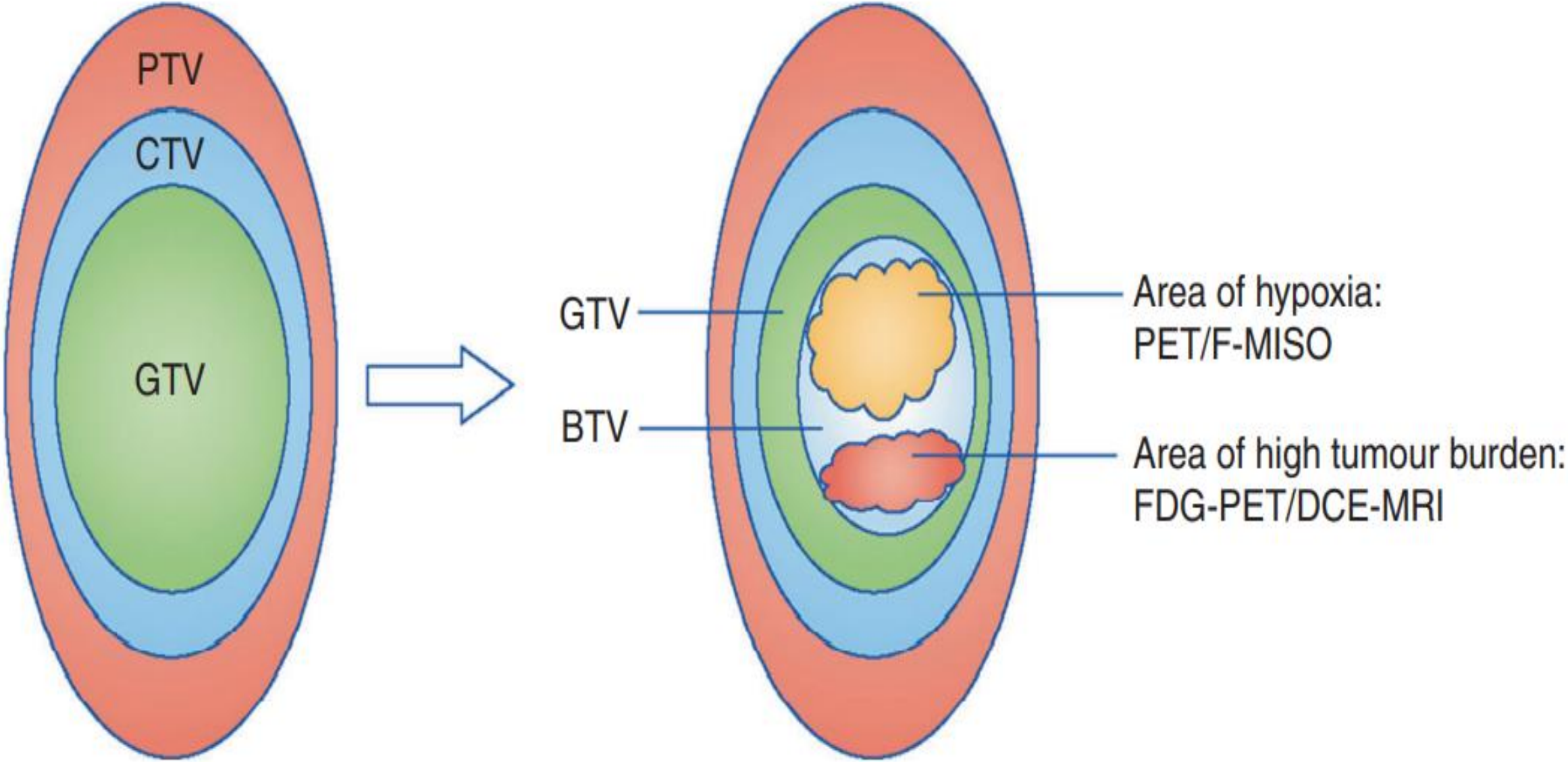
New Issues about Volumes

- Multiple GTV : anatomic vs functional imaging; before and during treatment....
- GTV to CTV margins: clinical probability
- CTV to PTV margins: geometric probability, overlapping volumes...
- ITV : Internal Margin???
- OAR: open vs closed?
- Remaining normal tissues?
- PRV: serial vs parallel OAR





(A) ICRU 29 (B) ICRU 50 (C) ICRU 62



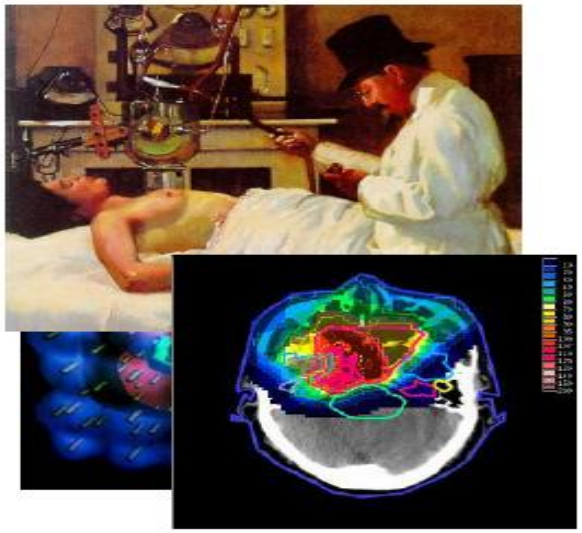
Target volume definitions and the concept of the biological target volume

British Journal of Cancer (2019) 120:779–790; https://doi.org/10.1038/s41416-019-0412-y

Towards Personalized Radiation Oncology

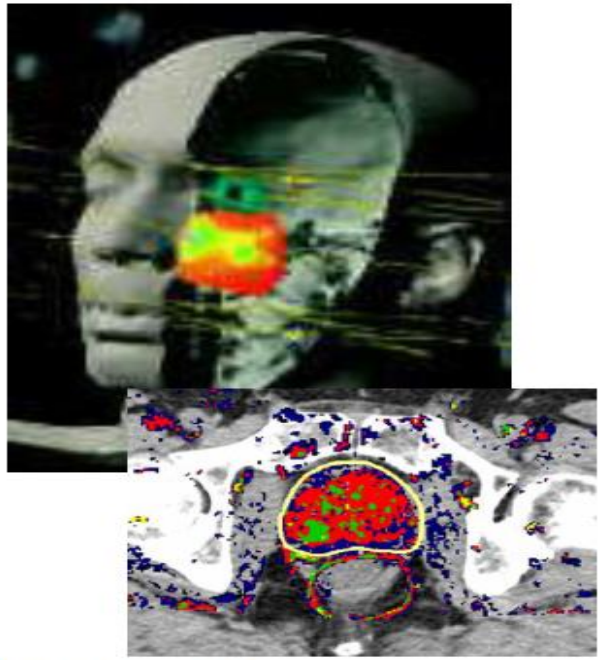
Integration of radiation technologies, imaging and biology

Radiation Technologies



Enhancing conformity

Imaging



Anatomy

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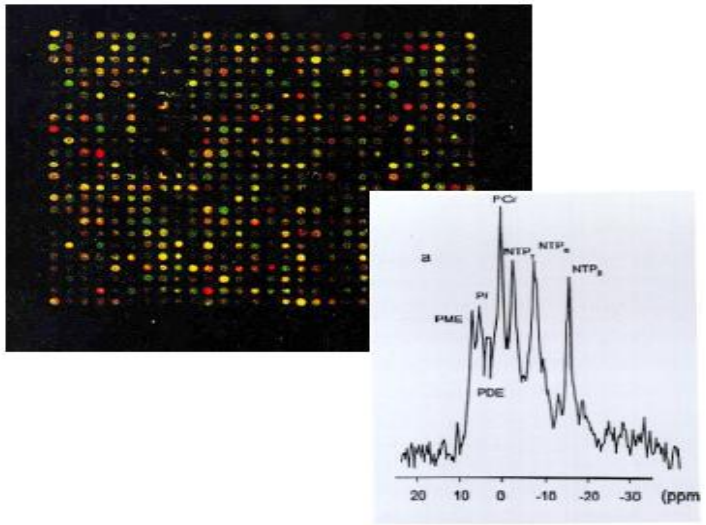
Functional & biol inform
(metabolism, proliferation, hypoxia, angiogenesis)

Tumor biology



Genomics

↓

Proteomics

↓

Metabolomics

- ***The first step in being able to deliver precision radiotherapy is accurate target delineation during the radiotherapy planning process.***

- *Advanced multi-modality diagnostic imaging such as*

  - computed tomography (CT),
  - high-resolution magnetic resonance imaging (MRI)
  - 18-F-fluorodeoxyglucose positron emission tomography
  - FDG-PET/CT imaging now is part of the routine staging process
  - Functional imaging-individual tumor biology, areas of radio-resistance within a tumor

  CT - imaging modality for radiotherapy planning, provide a three-dimensional (3D) view of the tumor as well as data regarding electron density, required for dose calculations.

•**Functional imaging map tumor characteristics**, such as

• - hypoxia,

• - vascularity

• - cellular proliferation,

Understanding of tumor biology, the concept of a '***biological target volume' (BTV)*** '

Delineating a BTV take into account

- The metabolic,
- biochemical,
- physiological
- functional changes within a tumor,

- 'imaging biomarkers'—qualitative or quantitative measurements from imaging modalities mapping spatial heterogeneity within the tumor focused biological dose escalation.

FDG-PET imaging is currently the most widely used functional imaging technique for BTV delineation,

Functional imaging techniques provides

- prognostic information on a tumor prior to radiotherapy treatment,
- **identify sub volumes of a tumor representing areas of radio-resistance–the biological target volume—and receive an extra dose of radiation with high precision without increasing the dose to the whole tumor.**

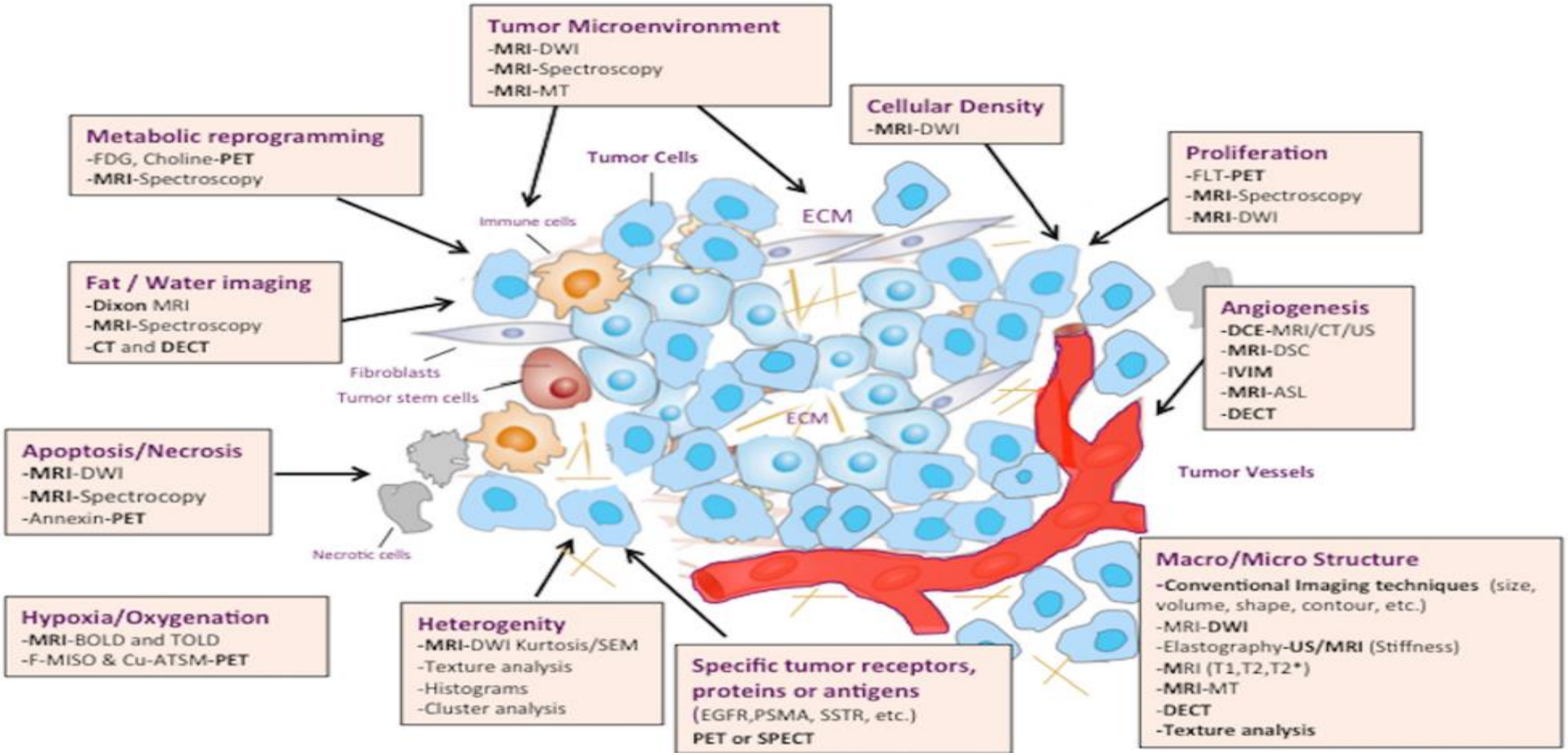
On-board imaging systems -cone beam CT (CBCT) scans prior to treatment provide accurate information

- tumor location ,
- daily changes in tumor position
- bladder and bowel filling

The implantation of fiducial markers, either within or near to the tumor, prior to the start of treatment helps in - safe delivery of radiotherapy by IMRT and IMAT

Accurate imaging is essential for the planning, delivery and evaluation of precision radiotherapy.

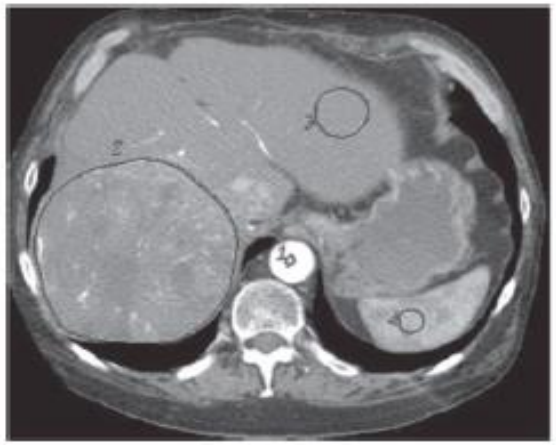
Imaging Biomarker for Tumor Microenvironment Response

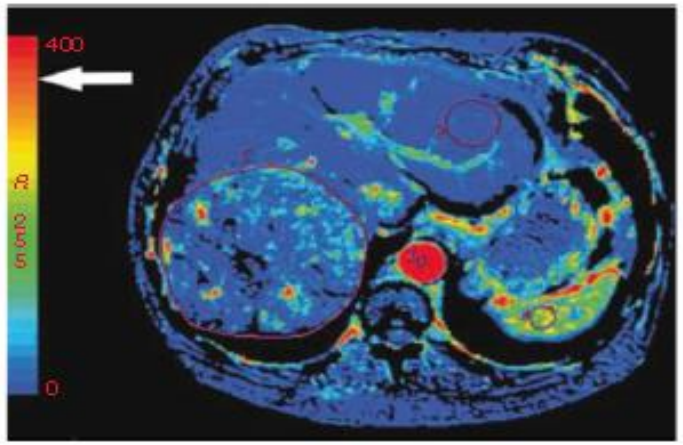


Garcia-Figueiras et al. Insights into imaging 2019 10:28

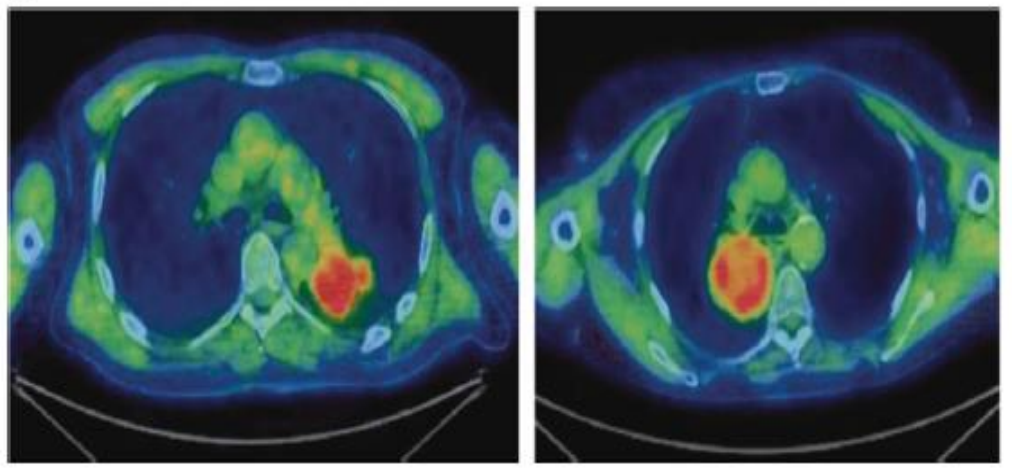
Biological Imaging for Precision Radiation Oncology

Definition of regions of interest (ROI)

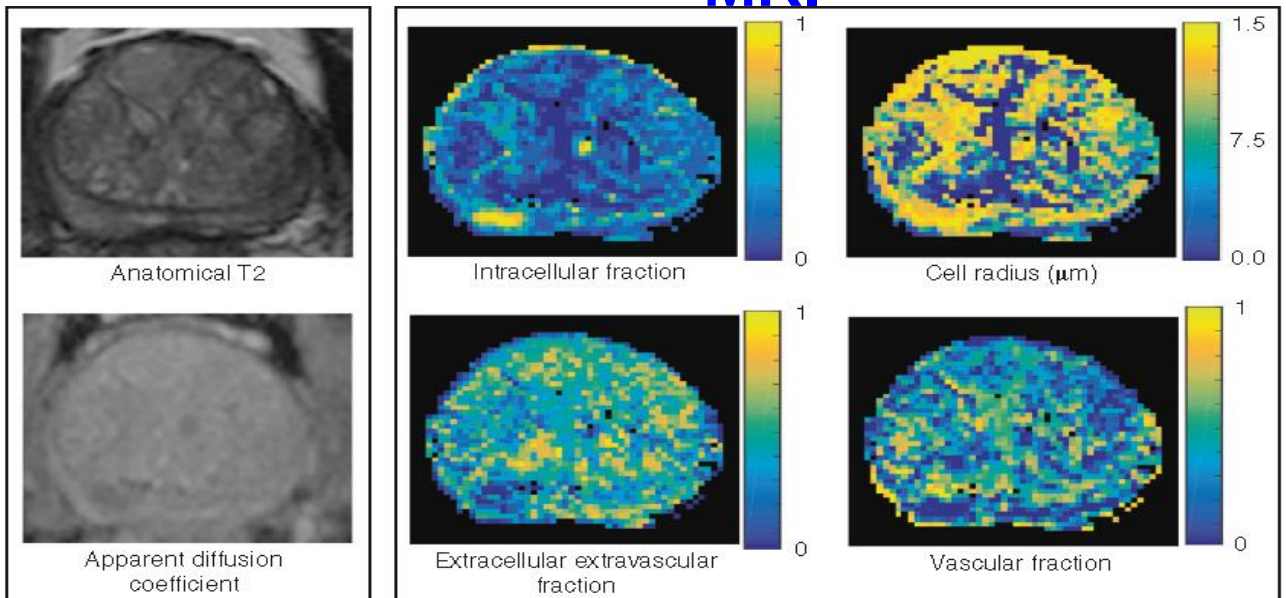


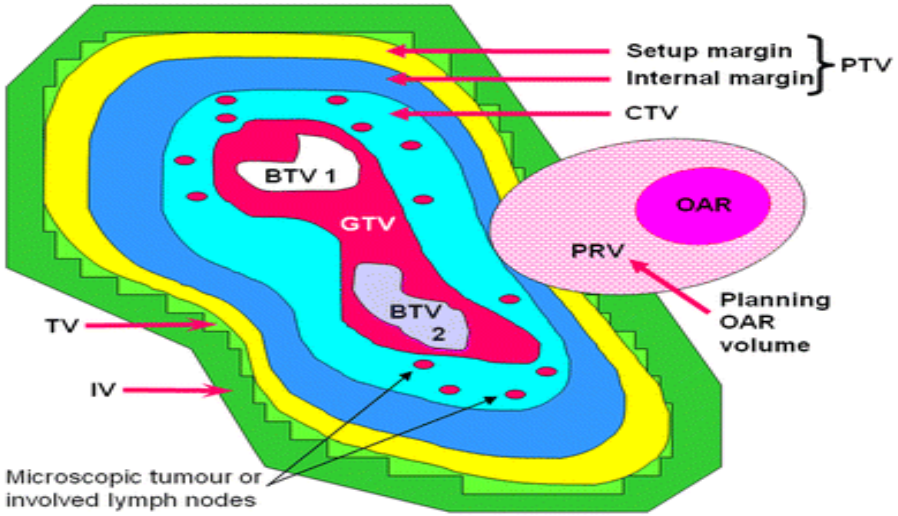


Colour maps of perfusion parameters

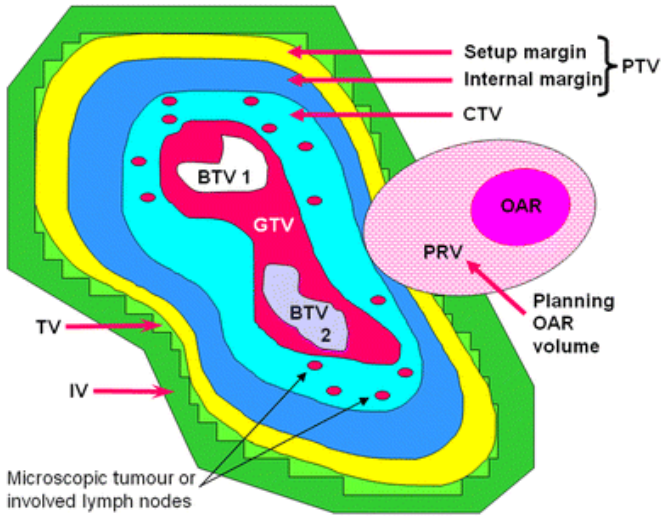


MRI





L Beaton et al. BJC (2019) 120:779-790.



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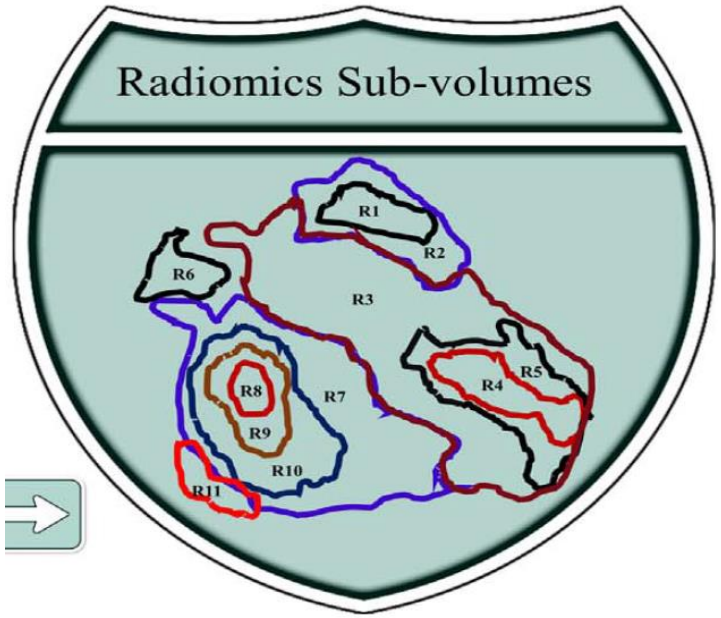


H Addollahi et al. Phys.Med.Biol.67 (2022) 12TR02

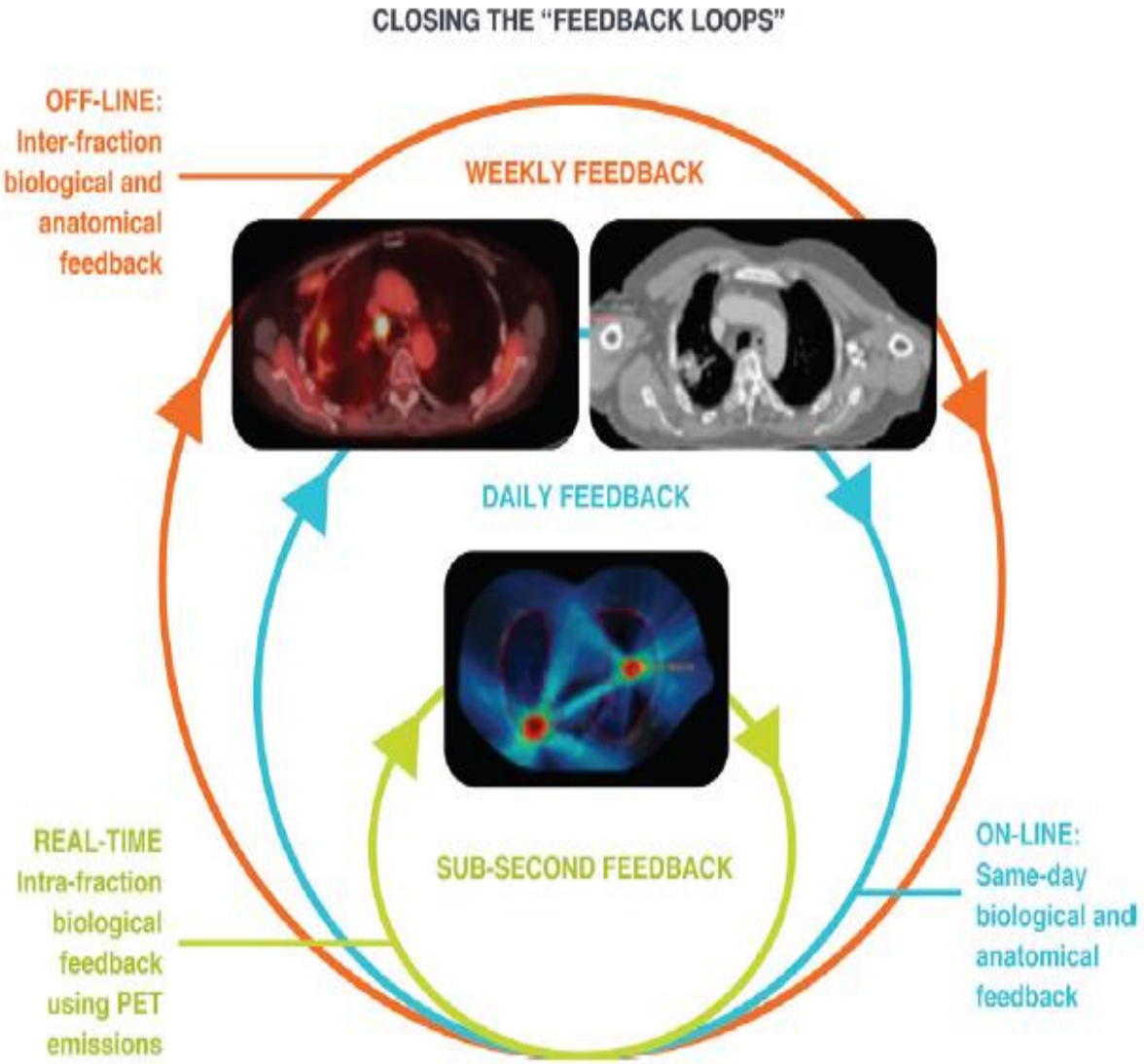
- Evidence-based cause for RT failure is due to hypoxia, radiodensity, tumour cell proliferation and tumour heterogeneity etc.
- Molecular, functional, metabolic and genomic information are now available.
- The success of the treatment depends on the ability to chose the right treatment regimens (precision) for the right patient (personalized).
- One-size-fit-one approach – Personalized Radiation Therapy.

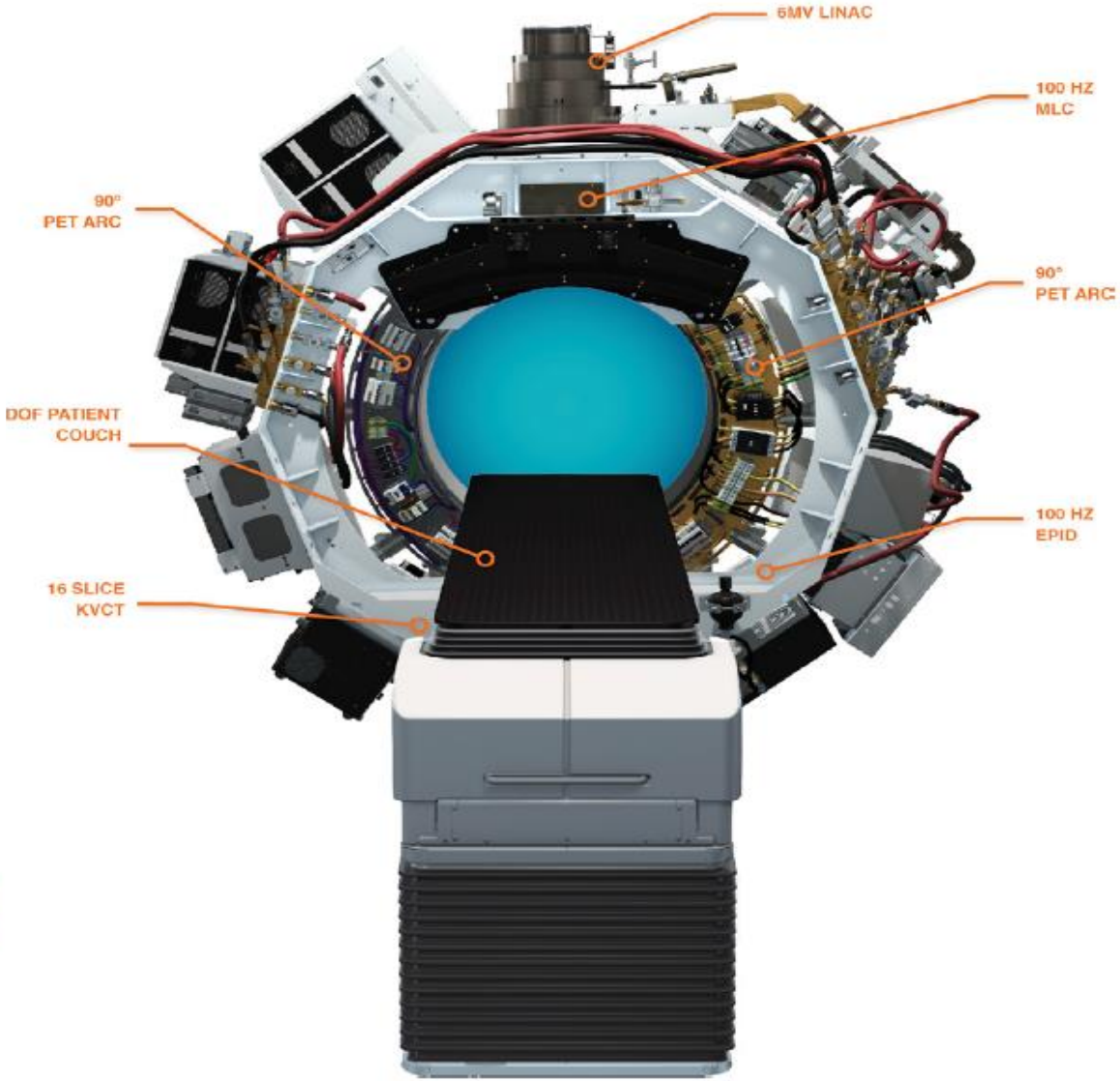
- Biological Imaging (Functional and Molecular Imaging)-BTV

- Quantitative Imaging and/or Genomic Biomarker
  - Radiomics, Genomics and Radiogenomics

- Integrating Imaging and Therapy Systems
  - **-MR-Guided Radiotherapy- MR-Linac system**
  - **- PET-Guided Radiotherapy- PET-Linac system**

BGRT PET-Linac System: Reflexion





Precision Medicine-Radiation Oncology

1. Technology-driven Precision Radiation Oncology
   -IMRT, SRS/SBRT, 4D /ART, Particle Therapy, Image-Guided BT
2. Biology-driven Precision Radiation Oncology
   - Quantitative Imaging or Imaging Biomarker
     - Radiomics, Genomics and Radiogenomics

RADIOMICS- radiomics is **a method that extracts a large number of features from medical images using data- characterization algorithms**. tumoral patterns and characteristics, the spatial distribution of signal intensities and pixel interrelationships, radiomics quantifies textural information by using analysis methods from the field of AI.
Radiomics enhances clinical decision making.

GENOMICS- **The study of the complete set of DNA (including all of its genes) in a person or other organism.** Genomics, is **making it possible to predict, diagnose, and treat diseases more precisely and personally, than ever**.

RADIOGENOMICS- the relationship between the imaging characteristics of a disease (i.e., the imaging phenotype or radiophenotype), and its gene expression patterns, gene mutations, and another genome related characteristics. **The relationship between the imaging features of a particular disease and various genetic or molecular features** helps improved decision making, and as a result, improved

patient outcomes.

Current Practice of Radiation Oncology-Medical Physics

Multi-Modal Imaging

- Accuracy in tumor & normal tissue definition
- Tighter safety margin
- Higher prescription dose

Radiation Treatment Planning

- Image registration (rigid & deformable)
- Autosegmentation
- Advanced dose calculation algorithms (MC)
- Optimization methods (physical & biological)

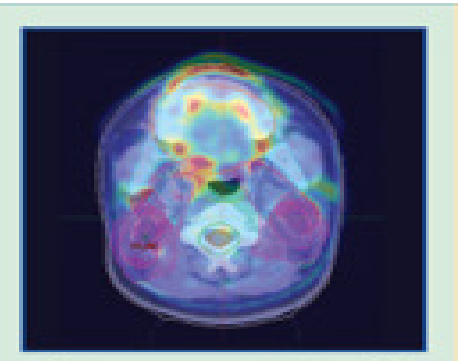
Treatment Verification (pre, during, post)

- Geometric Accuracy (2D/3D and 4D/real-time)
- Dosimetric Accuracy (2D and 3D)

Computer-controlled Treatment delivery

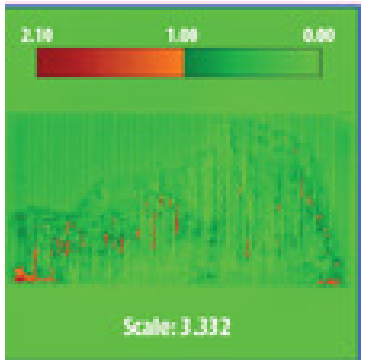
- Focused, smaller beams (SRS,SRT & SBRT)
- Intensity modulated beams (IMRT)
  - Real-time, dynamic beams (4DRT & ART)
  - Unflattened beams (FFF Linac), proton, C-ion

Image Acquisition



Tumor & OAR definition

Treatment planning



Treatment verification

Treatment delivery

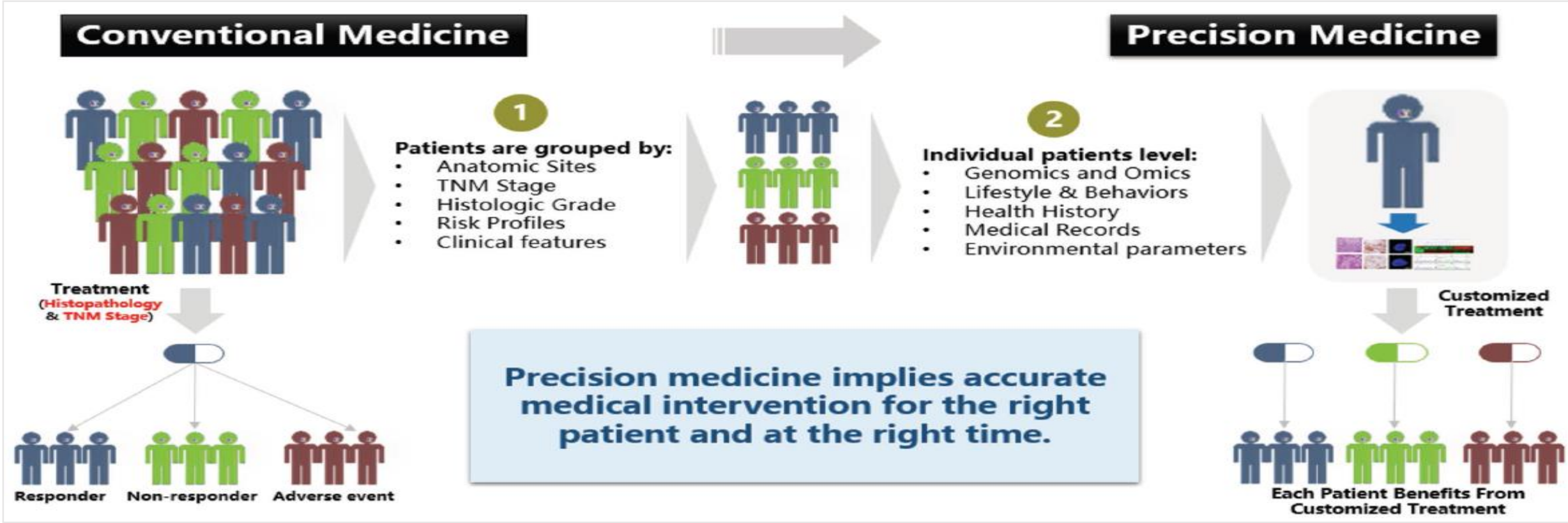
Precision Medicine & Personalized Radiotherapy

Precision Medicine

Is "a form medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease"

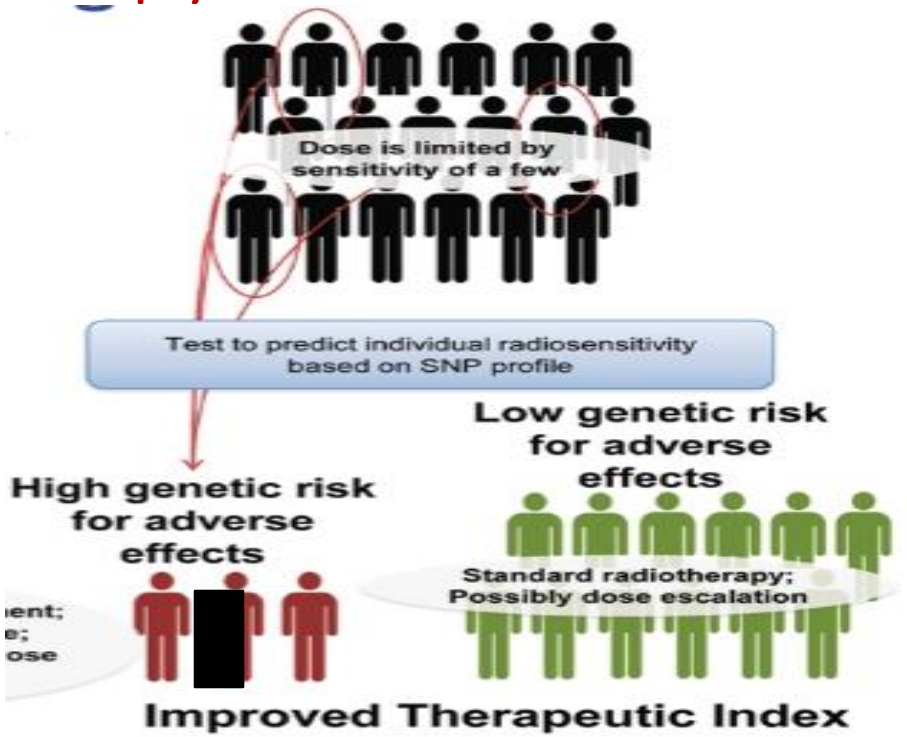
Personalized Radiotherapy

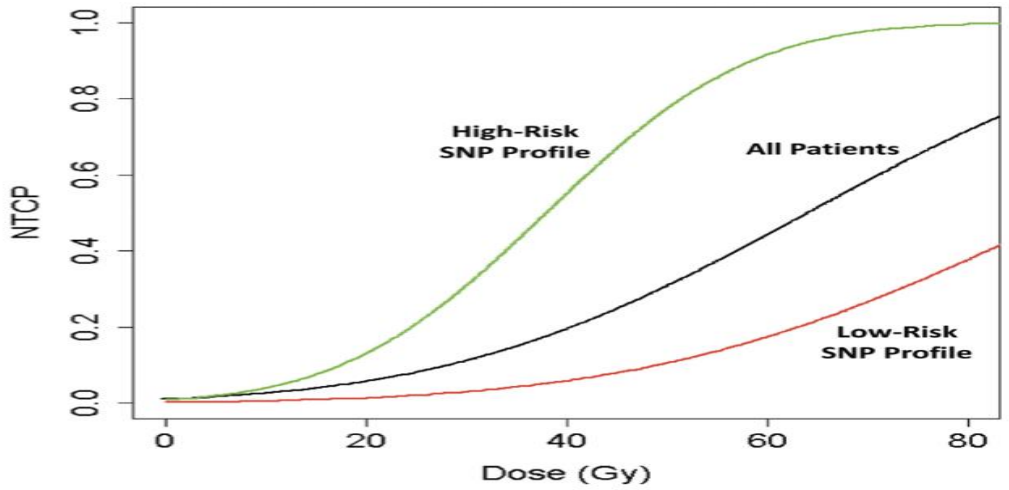
When cancer radiation treatment move from one-size-fits-all to individualized treatment, which is tailored based on the individual patient's genomic profile in addition to image based profile, is known as "personalized radiation therapy'



Genomically-Guided Radiotherapy

- Incorporating tumor molecular/genetic information into RT process
- Molecularly/genetically-defined Individualized prescription dose based on genetic make-up
- **Genomically-Adjusted Radiation Dose (GARD)** - Radiation Sensitivity Index (RSI)
- Increase the dose more to resistant tumor
- Lowering dose to more sensitive tumors





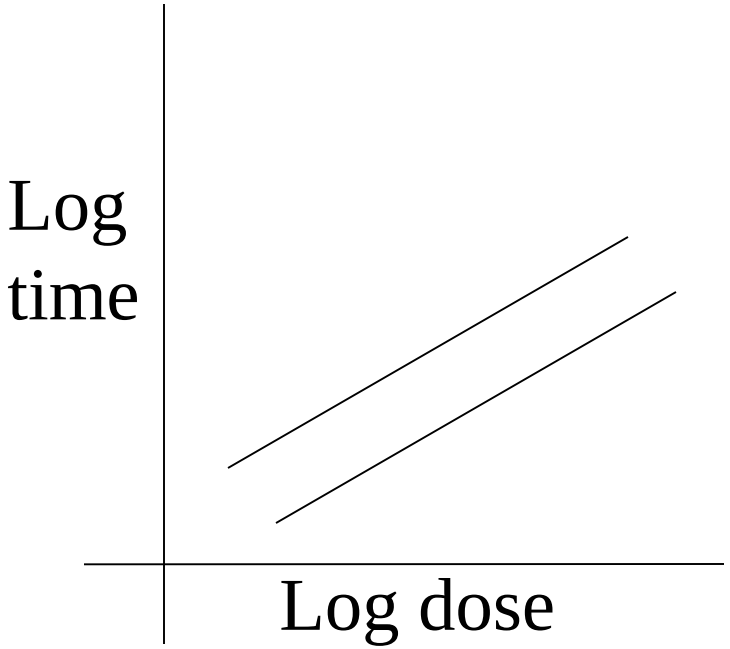
P4 Medicine in Cancer treatment

1. Prediction of tumor response
2. Prevention of normal tissue toxicity
3. Personalized radiotherapy
4. Participatory, or patient-centered treatment

RADIOBIOLOGICAL MODELS FOR RADIOTHERAPY

- **Over the years the knowledge of cell kinetics and factors influencing the effect of radiation at cellular level has increased**
- *Since treatment schedules are numerous and different from each other ,it is rather difficult to intercompare them unless they can be reduced to preferably single number. If a model is desired, how complex need it be ? How many parameters are needed and how important are their exact numerical value?*
- Radiobiological effectiveness of various dose fractionation schedules on normal and tumor- radiobiology is understood with increasing clinical experience.
- Various concepts of time ,dose, fractionation were introduced in 1950's to correlate biological effectiveness .

❖Strandqvist (1944)-first scientific approach - *related dose with overall treatment time for equivalent biological effect.*



❖Cohen (1949)-analyzed data of Reisner (1933), Quimby (1937) and Strandqvist (1944).

$$\text{Dose} \propto (\text{Time})^n$$

$$D = KT^n$$

D = Total dose for specific effect in T days.

Cohen (1952) showed that

$n = 0.33$ for normal tissue

$n = 0.22$ for malignant tissue

therefore, $D = KT^n$

becomes $D = KT^{0.33}$ ——— (1) for normal tissue

$D = KT^{0.22}$ ——— (2)for malignant tissue

Equation (1) rewritten as

$D = KT^{0.22} \quad T^{0.11}$ ——— (3)

- Intracellular Elkind type recovery " $T^{0.22}$ "
- Homeostatic recovery $T^{0.33-0.22} = T^{0.11}$

Ellis (1969)

❖ Elkind type recovery representing number of fractions (N)

Standard treatment is 30F , 5F/wk , 42 days

therefore $30^{0.24} = 42^{0.22}$

(N) (T)

Therefore ,for normal tissue

$$D = KT^{0.22} \quad T^{0.11}$$

changed to

$$D = KN^{0.24} \quad T^{0.11}$$

Ellis termed the constant ‘k’ as

Nominal standard dose (NSD)

$$NSD = D\, N^{-0.24}\, T^{-0.11}$$

But $D = N \cdot d$ D = total dose

N = number of fractions

d = dose/fraction (cGy/F)

$$NSD = d\, N^{0.65}\, X^{-0.11}$$

Where X = Time (T)/ Number of Fractions (N)

For standard treatment NSD ≈ 1800 rets [radi. Equ. Therapy]

Concept of Cumulative Radiation Effect (CRE)

Kirk (1971) - NSD for tolerance dose, not for sub tolerance level . For sub tolerance level

$$D \propto n^{0.24}\ t^{0.11}$$

$$D = CRE\ n^{0.24}\ t^{0.11}$$

$$CRE = D\ n^{-0.24}\ t^{-0.11}$$

$$CRE = d\ n^{0.65}\ x^{-0.11}$$

CRE – reu (radiation effect unit)

CRE for brachytherapy- $D = KT^{-v}$

$CRE_c = 0.53\ RT^{0.71}$ R = dose rate $_{[cGy]/}$hr T = treatment time hours

Concept of Time Dose Fractionation – TDF

Orton and Ellis (1973) developed the time, dose and fractionation concept which is additive for fractionation treatment.

$$TDF = d^{1.538} . n. X^{-0169} . 10^{-3}$$

$$\mathbf{TDF_c = 3.864\ R.\ t^{1.408}}$$

Where 'R' is dose rate cGy/hr and 't' treatment time in hours

Gap correction = [T/ (T + G)] $^{0.169}$

TDF is additive, for standard treatment TDF= 100, Tables for 1- 6 fraction/wk available. Very easy to compare different fractionation schedules

Limitations of NSD, CRE, TSD and TDF concepts

- *These biological models do not take into account the complex biological processes – too simplification*
- *NSD is not the same for different kind of tissue and the exponent of N ranges from 0.2 – 0.3*
- *Only early effects are considered , no model takes into account the late effects which are different from early effects*
- *Radio sensitivity – depends upon many intrinsic factors , cell phase, mitotic rate, blood/oxygen/nutrient supply and the tissue microenvironment*

Linear Quadratic (LQ) Model

The model is originally proposed by Kellerer and Rossi (1972)

Barendsen (1982) applied to radiotherapy data

LQ model in mathematical form is

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

Where ‘α’ and ‘β’ are tissue specific constants. ‘D’ total dose in Gy.

First term is linear – effect is linearly proportional to dose- direct hit

Second term is quadratic– effect is proportional to square of dose- indirect hit

Individual values of α and β are not required but the ratio α/ β

Barendsen [1982] modified the formula as

$$(E/\alpha) = D\,[\,1 + D/(\alpha/\beta)]$$

term in bracket is called as relative effectiveness per unit dose

$$RE = 1 + D/(\alpha/\beta)$$

Cell survival curves and the linear-quadratic model

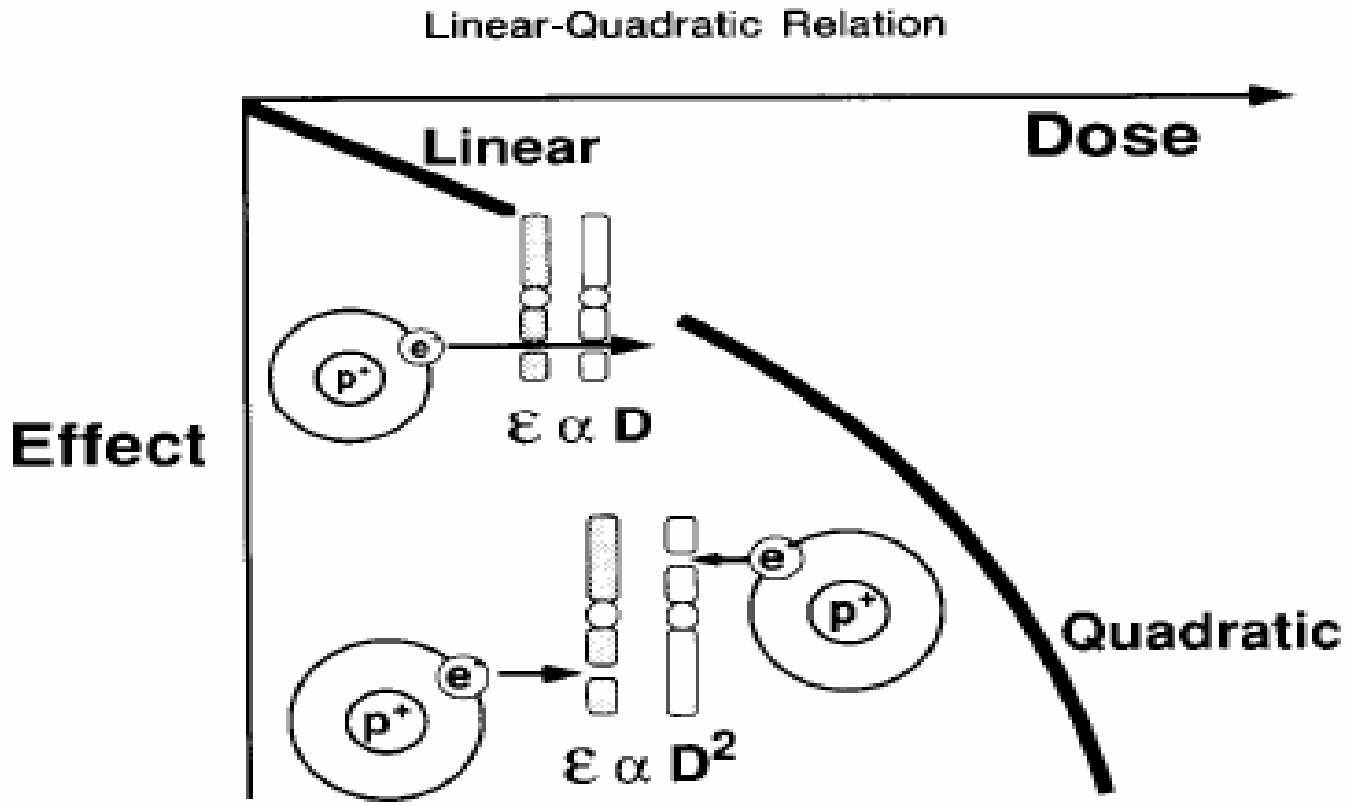


Figure 3-4. Relationship between chromosome aberrations and cell survival. Cells that suffer exchange-type chromosome aberrations (such as a dicentric) are unable to survive and continue to divide indefinitely. At low doses, the two chromosome breaks are the consequence of a single electron set in motion by the absorption of x- or γ-rays. The probability of an interaction between the breaks is proportional to dose; this is the linear portion of the survival curve. At higher doses, the two chromosome breaks may result also from two separate electrons. The probability of an interaction is then proportional to (dose)^2. The survival curve bends when the quadratic component dominates.

$$P_{\text{survival}} = e^{-\alpha D - \beta D^2}.$$

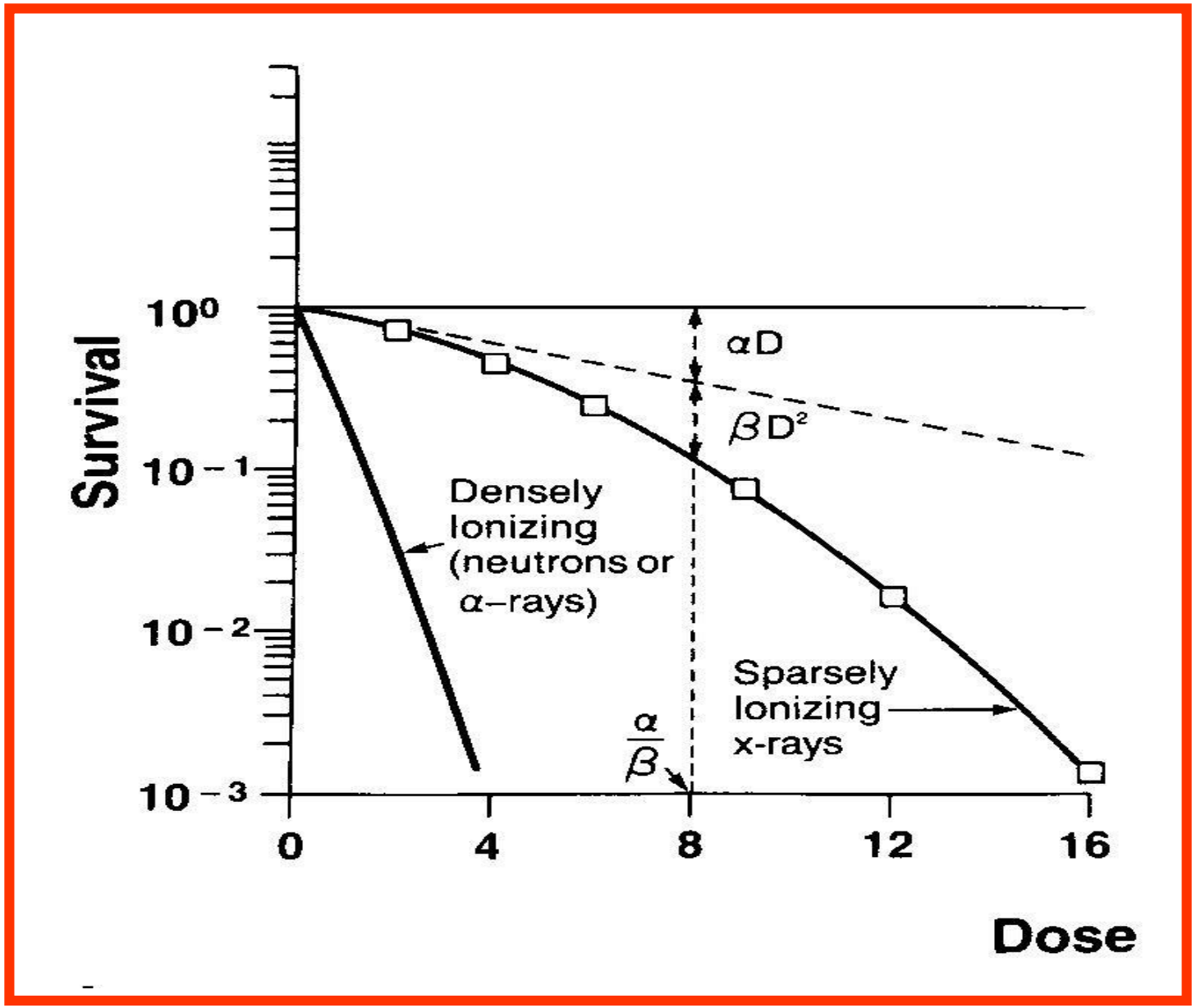
Cell survival curves and the linear-quadratic model

α component

- **Linear variation with dose (Gy^{-1})**
- **Lethal damage**
- **DSB**
- **Predominant for high LET radiation**

β component

- **Quadratic variation with dose (Gy^{-2})**
- **Damage can be repaired**
- **SSB**



For fractionated radiotherapy D = n. d

$$E/\alpha = n.\ d\ [\ 1 + d/\ (\alpha/\ \beta)]$$

The (E/α) term is called
'Extrapolated tolerance dose' [ETD] or
'Extrapolated response dose '[ERD] or
'Biological effective dose ' BED'

Therefore **ERD= BED= ETD** $= n.\ d\ [\ 1 + d/\ (\alpha/\ \beta)]$

Generally, for

a. Acute epithelial tissue reactions in radiotherapy – normal tissue reaction $\alpha/\ \beta$ is 8 – 13 Gy with average of 10 Gy [Fowler 1984]

b. Late tissue reactions $\alpha/\ \beta$ is about 2 – 6 Gy

c. Tumor tends to be characterized by high $\alpha/\ \beta$ typically 10 – 25 Gy

d. Slow growing tumours prostate – 1.5- 2.0 Gy, Breast ~4.0- 5.0 Gy

For standard treatment of 2 Gy/F, 5 F/wk to total dose of 60 Gy

ERD for tumor = 30 x 2 [1 + 2 /10] α/β = 10 Gy for tumor

= 72 Gy

ERD for late reaction = 30 x 2 [1 + 2/2.5] for α/β for late effect = 2.5 Gy

= 108 Gy

Similarly, ERD for acute normal tissue damage with α/β = 8 Gy is

ERD = 75 Gy

What is the equivalent dose with 3 Gy/F , 5F/wk

For standard treatment ERD late effect = 108 Gy to keep the dose in tolerance limit

108 = n x 3 [1 + 3/2.5]

Therefore n = 108/6.6 = 16.36 ~ 16 fractions of 3 Gy [D= 48 Gy] equivalent to 30 fractions of 2 Gy [60 Gy]

Similarly, 10 Gy single fraction will be equivalent to 28 Gy by 2Gy/F

ERD late = 1 x 10 [1 + 10/2.5] = 50 Gy

50 = n x 2 [1 + 2/2.5] n = 50/3.6 = 13.88 ~ 14 D = 14x2= 28 Gy

Dale [1986] gave ERD equations for 2, 3 and 4 fractions/day

For 2 fractions/ day with ‘X’ hours as inter fraction period and ‘ μ’ as repair constant

$$ERD = n \times d\{1+ [d /2(\alpha/ \beta)][2 + 2 e^{- \mu x}]\}$$

ERD for 3 fractions/day is

$$ERD = n \times d\{1+ [d /3(\alpha/ \beta)][3 + 4 e^{- \mu x} + 2 e^{- 2\mu x}]\}$$

ERD for 4 fractions/day is

$$ERD = n \times d\{1+ [d /4(\alpha/ \beta)][4 + 6 e^{- \mu x} +4 e^{- 2\mu x} + 2 e^{- 3\mu x}]\}$$

ERD for brachytherapy ‘ R’ dose in Gy/hr, ‘ T’ treatment time in hours

$$ERD = D [1+2R(\alpha/ \beta)/ \mu][1- 1/ \mu T][1- e^{- \mu t}]\}$$

LQ model with time constant

Travis and tucker [1987,1990] added time constant to take care repopulation during prolonged overall treatment time

$$(E/\beta) = TE = n \,.\, D\,[\,(\alpha/\beta) = d\,] - (\gamma/\beta)\,.\,T$$

Where 'TE' is total effect and 'γ/β' is repopulation constant

Geijn [1989] gave ERD with time as

$$ERD = n \,.\, \alpha \,.\, d + n \,.\, \beta.\, d^2 - (\gamma/\beta)\,[T - T_k]$$

Where ' T_k ' is kick of time of proliferation, ' T' is total treatment time

BED - Biological effective Dose

ETD - Extrapolated tolerance dose

ERD- Extrapolated response dose

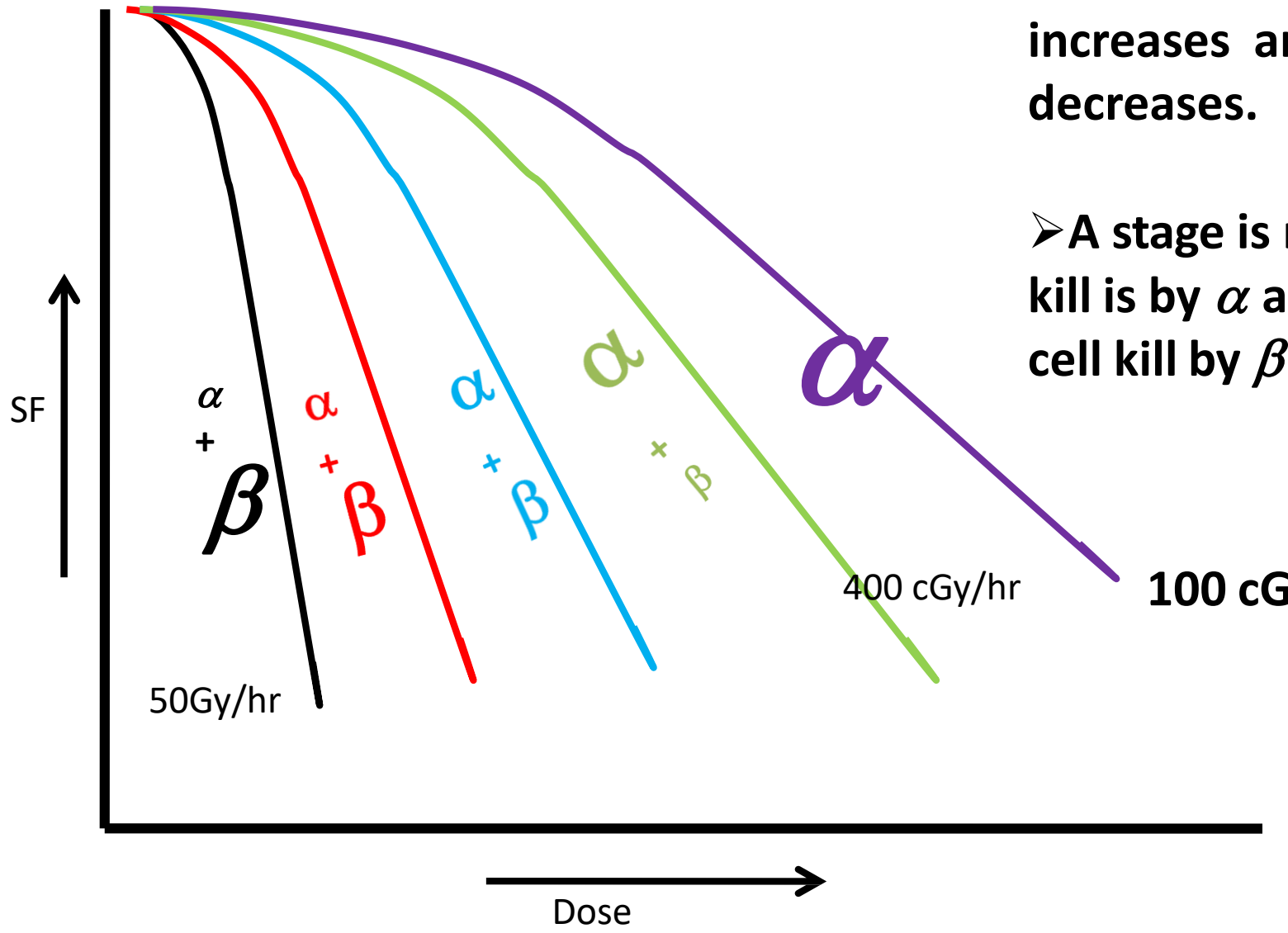
Applied to all types of biological effects on all types of tissue including normal tissue.

Radiobiological basis of fractionation

Small dose/fraction protects tumors with low α/β ratio compared to tumors with high α/β ratio

Large dose/fraction more toxic to tumors with low α/β ratio compared to tumors with high α/β ratio

Dose Rate Effect

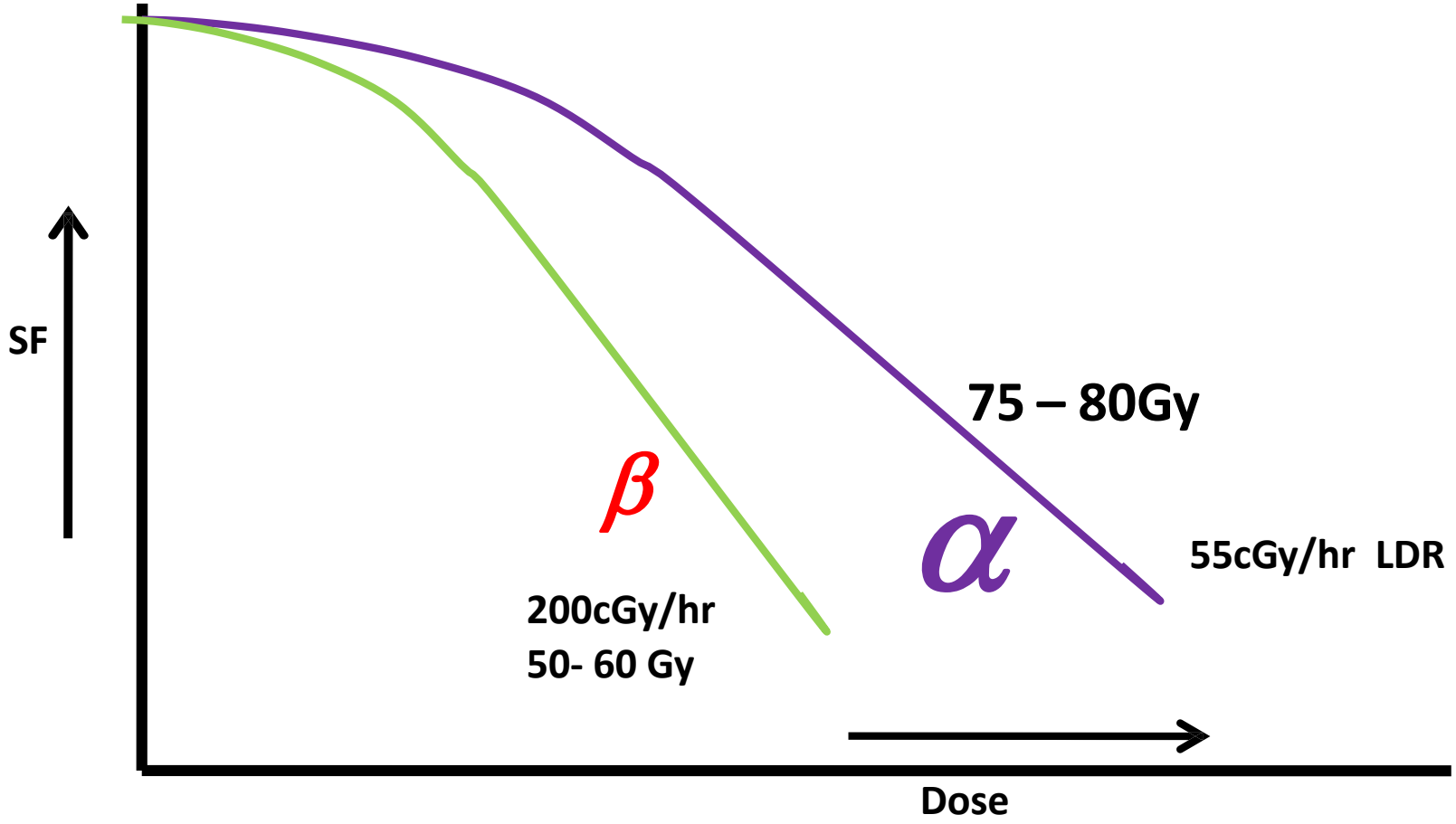


- **Relative contribution by α cell kill increases and by β cell kill decreases.**
- **A stage is reached when all cell kill is by α and no contribution in cell kill by β**

Dose Rate Effect Clinical Application

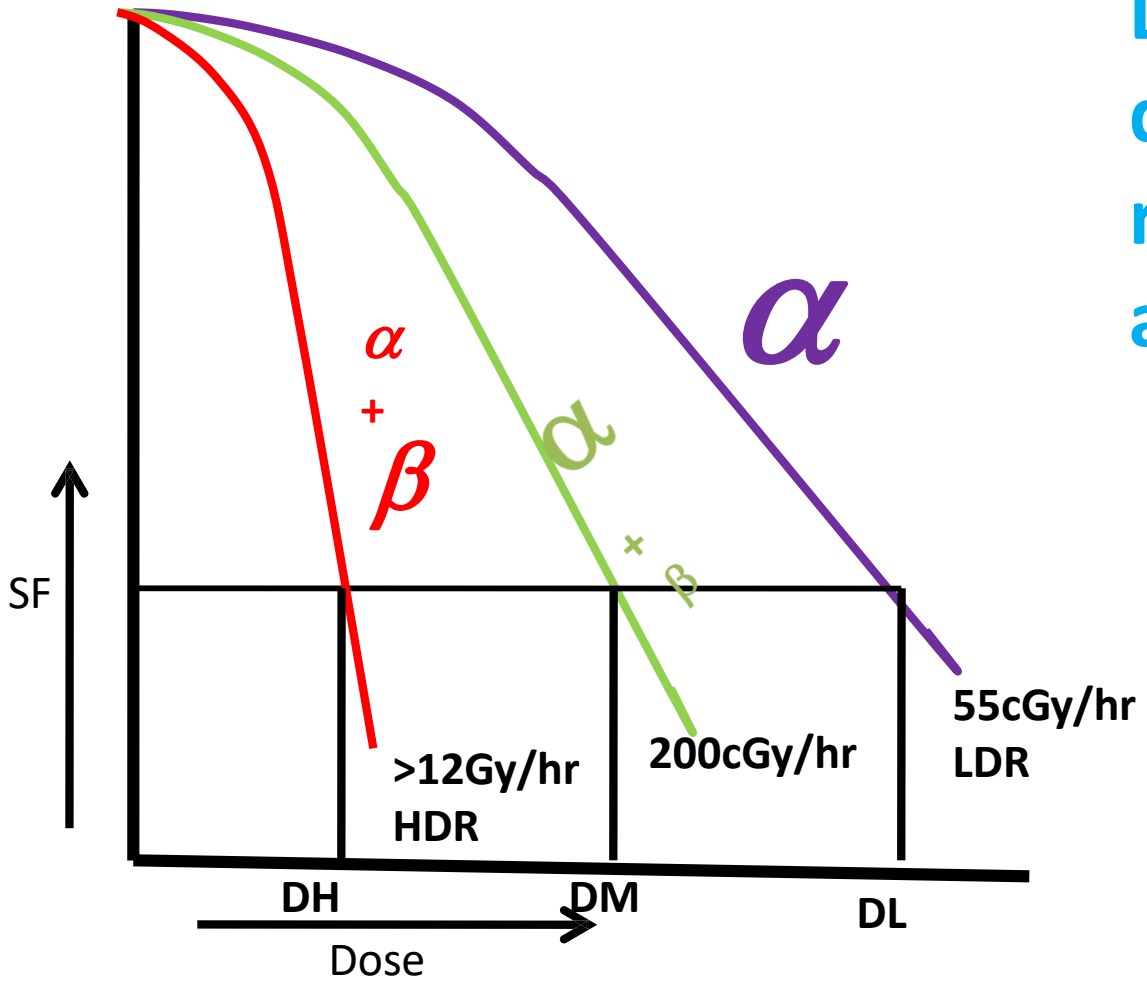
Carcinoma Cervix

- **LDR 55 cGy/hr. [preloaded system with Ra226] , treatment time of about 140 – 160 hrs [6 – 7 days] and total dose delivered was 75- 80 Gy [7000- 8000 R] at point A**
- **At this dose rate all the cell kill is by α kill (<100cGy/hr).**
- **MDR dose rate 200- 250 cGy/hr- total dose 50 – 60 Gy in 20- 30 hrs**



Dose Rate Effect Clinical Application

LDR to HDR



When we shift form LDR to HDR, total dose is to be reduced roughly by a factor of 30 – 40%

Total Dose for ca cervix after EBRT is 21 to 24 Gy which is equivalent to 35 Gy by LDR

LDR- MDR - BED for brachytherapy

‘ R’ dose in Gy/hr, ‘ T’ treatment time in hours

$$BED = D\,[1+2R(\alpha/\beta)/\mu][1-1/\mu T][1-e^{-\mu t}]\}$$

where μ is a constant, which is dependent on the half time of recovery:

$\mu = \text{Log}_e\ 2/T_{1/2} = 0.693/T_{1/2}$

$T_{1/2}$ = 30 min to 1 h for early-reacting normal tissues and tumors.

$T_{1/2}$ = 1.5 h for late-reacting normal tissues

The radiobiological processes involved in HDR BT are in all respects similar to those involved in fractionated external beam radiation therapy, except for the volume effect and the non-uniform dose distribution

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Early reactions				
Skin	Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
	Erythema	12.3	1.8; 22.8	Bentzen *et al.* (1988)
	Dry desquamation	~8	N/A	Chogule and Supe (1993)
	Desquamation	11.2	8.5; 17.6	Turesson and Thames (1989)
Oral mucosa	Mucositis	9.3	5.8; 17.9	Denham *et al.* (1995)
	Mucositis	15	−15; 45	Rezvani *et al.* (1991)
	Mucositis	~8	N/A	Chogule and Supe (1993)

From Basic Clinical Radiobiology- Ed. Michael Joiner and Albert van der Kogel

Late reactions				
Skin/vasculature	Telangiectasia	2.8	1.7; 3.8	Turesson and Thames (1989)
	Telangiectasia	2.6	2.2; 3.3	Bentzen *et al.* (1990)
	Telangiectasia	2.8	−0.1; 8.1	Bentzen and Overgaard (1991)
Subcutis	Fibrosis	1.7	0.6; 2.6	Bentzen and Overgaard (1991)
Breast	Cosmetic change in appearance	3.4	2.3; 4.5	START Trialists Group (2008)
	Induration (fibrosis)	3.1	1.8; 4.4	Yarnold *et al.* (2005)
Muscle/vasculature/ cartilage	Impaired shoulder movement	3.5	0.7; 6.2	Bentzen *et al.* (1989)
Nerve	Brachial plexopathy	<3.5*	N/A	Olsen *et al.* (1990)
	Brachial plexopathy	~2	N/A	Powell *et al.* (1990)
	Optic neuropathy	1.6	−7; 10	Jiang *et al.* (1994)
Spinal cord	Myelopathy	<3.3	N/A	Dische *et al.* (1981)
Eye	Corneal injury	2.9	−4; 10	Jiang *et al.* (1994)
Bowel	Stricture/perforation	3.9	2.5; 5.3	Deore *et al.* (1993)
Bowel	Various late effects	4.3	2.2; 9.6	Dische *et al.* (1999)
Lung	Pneumonitis	4.0	2.2; 5.8	Bentzen *et al.* (2000)
	Lung fibrosis	3.1	−0.2; 8.5	Dubray *et al.* (1995)

Tissue	Endpoint	D_{prolif} (Gy/day)	95% CL (Gy/day)	T_k^+ (days)	Source
Early reactions					
Skin	Erythema	0.12	−0.12; 0.22	<12	Bentzen *et al.* (2001)
Mucosa	Mucositis	0.8	0.7; 1.1	<12	Bentzen *et al.* (2001)
Lung	Pneumonitis	0.54	0.13; 0.95		Bentzen *et al.* (2000)*
Tumours					
Head and neck					
Larynx		0.74	0.30; 1.2		Robertson *et al.* (1998)
Tonsils		0.73	30		Withers *et al.* (1995)
Various		0.8	0.5; 1.1	21	Robers *et al.* (1994)
Various		0.64	0.42; 0.86		Hendry *et al.* (1996)*
Esophagus		0.59	0.18; 0.99		Geh *et al.* (2005)
Non-small cell lung cancer		0.45	N/A		Koukourakis *et al.* (1996)
Medulloblastoma		0.52	0.29; 0.75	0 or 21	Hinata *et al.* (2001)

Cancer Cervix α/β for tumor is 10 and for late reaction α/β is 2.5

ERD= BED= ETD = n. d [1 + d/ (α/β)]

2 Gy x 22 F = 44 Gy- **EBRT**

BED_t = 22 x 2 [1 + 2/10] = 52.8 Gy

BED_{ln} = 22 x 2 [1 + 2/2.5] = 79.2 Gy

For HDR brachytherapy, 7.5 Gy/F, 3F, one week apart

BED_t = 3x 7.5 [1 + 7.5/10] = 39.4 Gy

BED_{ln} = 3 x 4.5 [1 + 4.5/2.5] = 37.8 Gy [dose to rectum is taken as 60 % of prescribed dose i. e. 7.5 x 0.6 = 4.5 Gy]

For HDR brachytherapy, 9.0 Gy/F, 2F, one week apart

BED_t = 2x 9.0 [1 + 9.0/10] = 34.2 Gy

BED_{ln} = 3 x 5.4 [1 + 5.4/2.5] = 51.2 Gy [dose to rectum is taken as 60 % of prescribed dose i. e. 9 x).6 = 5.4 Gy]

For HDR brachytherapy, 7.0 Gy/F, 2F, + 5 Gy/F one fraction - one week apart

BED_t = 2x 7.0 [1 + 7.0/10] = 23.8 Gy

BED_t = 1x 5.0 [1 + 5.0/10] = 7.5 Gy Total 31.3 Gy

BED_{ln} = 2 x 4.2 [1 + 4.2/2.5] = 22.5 Gy

BED_{ln} = 1x 3.0 [1 + 3.0/2.5] = 6.6 Gy Total 29.1 Gy

Patient Ca. Cx receives EBRT 22 F of 2Gy/F and then I/C brachytherapy of 7.5 Gy in 3 fractions, what is ERD and equivalent EBRT dose?

$ERD_{EBRT} = n.\ d\ [\ 1 + d/\ (\alpha/\ \beta)]$

$= 22 \times 2\ [\ 1 + 2/10]$

$= 44 \times 1.2$

$= 52.8$ Gy

$ERD_{[I/C]} = 3 \times 7.5\ [1 + 7.5/10] = 22.5 \times 1.75 = 39.375$ Gy

Total [EBRT + I/C] = 52.8 + 39.375 = 92.175 Gy

Equivalent to $92.175 = n \times 2\ [\ 1 + 2/10]$

n = 38.41 ~ 77 Gy with 2 Gy/F EBRT

Justification of Hypofractionation for Prostate cancer based on Radiobiology

Prostate is a slow-growing tumor with a potential T doubling time of around 45 days [ranges 30 - 70 days] and also the Tk [kick time] is of 6 - 8 weeks therefore for tumor effect its 1 F/week, or 5 F/wk as far total time is less than 5 weeks has no substantial effect.

Based on alpha/beta of 2 Gy for prostate tumor and 10 Gy for early normal tissue reactions compare the BED's

Schedule : 2 Gy x 35 F = 70 Gy, 5F/wk

BEDt = 2 x 35 [1 + 2/2] = 140.0 Gy

BEDn = 2 x 35 [1 + 2/10] = 84.0 Gy

BEDnl = 2 x 35 [1 + 2/2.5] = 126.0 Gy

Schedule II : 3.0 Gy x 20 F = 60 Gy

BEDt = 3 x 20 [1 + 3/2] = 150.0 Gy

BEDn = 3 x 20 [1 + 3/10] = 78.0 Gy

BEDnl = 3 x 20 [1 + 3/2.5] = 132.0 Gy

Schedule III : 7.0 Gy x 5 F = 36.25 Gy

BEDt = 7 x 5 [1 + 7.25/2] = 157.5 Gy157.5

BEDn = 7 x 5 [1 + 7.25/10] = 60.4 Gy

BEDnl = 7 x 5 [1 + 7.25/2.5] = 133 Gy

Comparison of BED for Low LET Radiation and High LET Radiation

For Low LET $BED = N_L\, d_L\, [\, 1 + d_L / (\alpha/\beta)_L]$

For High LET $BED = N_H\, d_H\, [RBE_{max} + d_H / (\alpha/\beta)_L]$

For low LET radiation 2 Gy/F 30 F 60 Gy

BED_T = 30 x 2 [1 + 2/10] = 60 x 1.2 = 72 Gy

BED_{late} = 30 x 2 [1 + 2/2.5] = 60 x 1.8 = 108 Gy

For high LET Radiation - Carbon particle RBE = 3 [Bragg Peak region] RBE = 1

4Gy/ F 6 F 24 Gy [72 GyE]

BED_T = 6 x 4 [3 + 4/10] = 24 x 3.4 = 81.6 Gy

BED_{late} = 6 x 4 [3 + 4/2.5] = 24 x 4.6 = 110.4Gy [within Brag peak area]

BED_{late} = 6 x 4/2 [1 + 2/2.5] = 12 x 1.8 = 21.6 Gy [Outside Bragg peak area]

ERD correction for gap

ERD= BED= ETD $= n.\ d\ [\ 1 + d/\ (\alpha/\ \beta)] - k\ [\ T - T_k\ ]$

For cancer cervix treated with 2 Gy/F, 30 F to 60 Gy

ERD= BED= ETD $= n.\ d\ [\ 1 + d/\ (\alpha/\ \beta)] = 30\ x2\ [1+\ 2/10] = 72$ Gy

Effective ERD after one year [365 days] of completion of treatment, $T_k = 28$ days, $k = 0.2$

$ERD = n.\ d\ [\ 1 + d/\ (\alpha/\ \beta)] - k\ [\ T - T_k\ ] = \ 72 - 0.2\ [\ 365\text{-}28] = 72\text{-}\ 67.4 = 4.6$ Gy

For very slow growing tumour like prostate, Effective ERD after one year [365 days] of completion of treatment, $T_k = 80$ days, $k = 0.1$

$ERD = n.\ d\ [\ 1 + d/\ (\alpha/\ \beta)] - k\ [\ T - T_k\ ] = \ 72 - 0.1\ [\ 365\text{-}80] = 72\text{-}\ 28.5 = 43.5$ Gy

Growth rate of tumor	*k* (BED units/day)
slow	about 0.1
average	about 0.3
rapid	about 0.6

Total doses for radiotherapy schedules calculated to keep late effects constant, as a function of dose per fraction. Standardized to 200 cGy per fraction.

Dose per fraction (cGy)	Total doses for equivalent late effects 30F X 200=6000 cGy			35F X 200 = 7000 cGy		
	α/β = 2 Gy	3Gy	4 Gy	2Gy	3 Gy	4Gy
120	7500	7143	6923	8750	8333	8080
140	7059	6818	6667	8235	7955	7778
160	6667	6522	6429	7778	7609	7500
180	6316	6250	6207	7368	7292	7241
200	6000	6000	6000	7000	7000	7000
220	5714	5769	5807	6667	6731	6774
240	5455	5556	5625	6364	6482	6563
260	5217	5357	5455	6087	6250	6364
280	5000	5172	5294	5833	6035	6177
300	4800	5000	5143	5600	5833	6000
350	4364	4615	4800	5091	5385	5600
400	4000	4286	4500	4667	5000	5250
450	3629	4000	4235	4308	4667	4941
500	3429	3750	4000	4000	4375	4667
600	3000	3333	3600	3500	3889	4200
700	2667	3000	3273	3111	3500	3818
800	2400	2727	3000	2800	3818	3500

This table is only a guide. It should not be used to pre-empt clinical judgments. Calculated from $E/\alpha = nd(1+d(\beta/\alpha)$ = constant: 100 for 30 F X 2Gy; 116.7 for 35F X 2 Gy

Radiobiological basis of fractionation

Large dose/fraction [Hypofractionation] more toxic to tissues with low α/β ratio compared to tissues with high α/β ratio

Small dose/fraction [Hyperfractionation]protects tissues with low α/β ratio compared to tissues with high α/β ratio

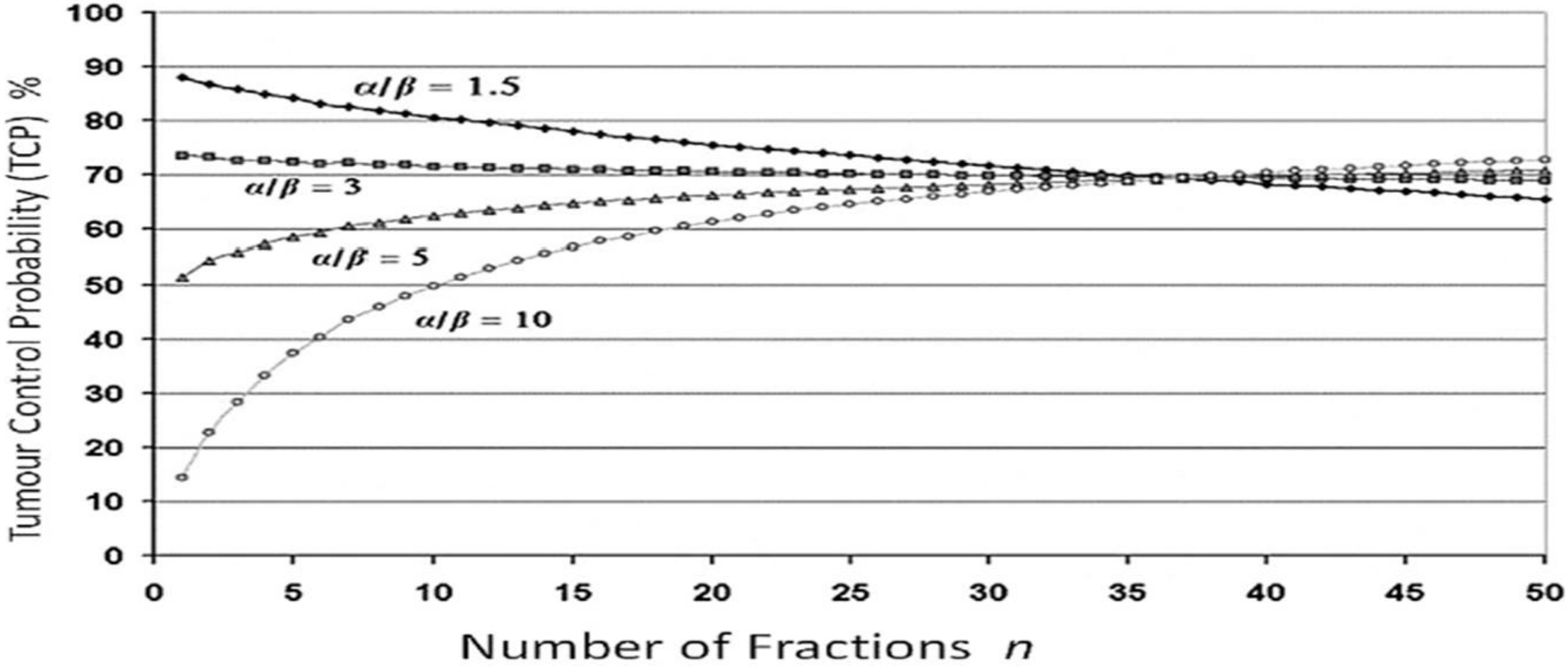
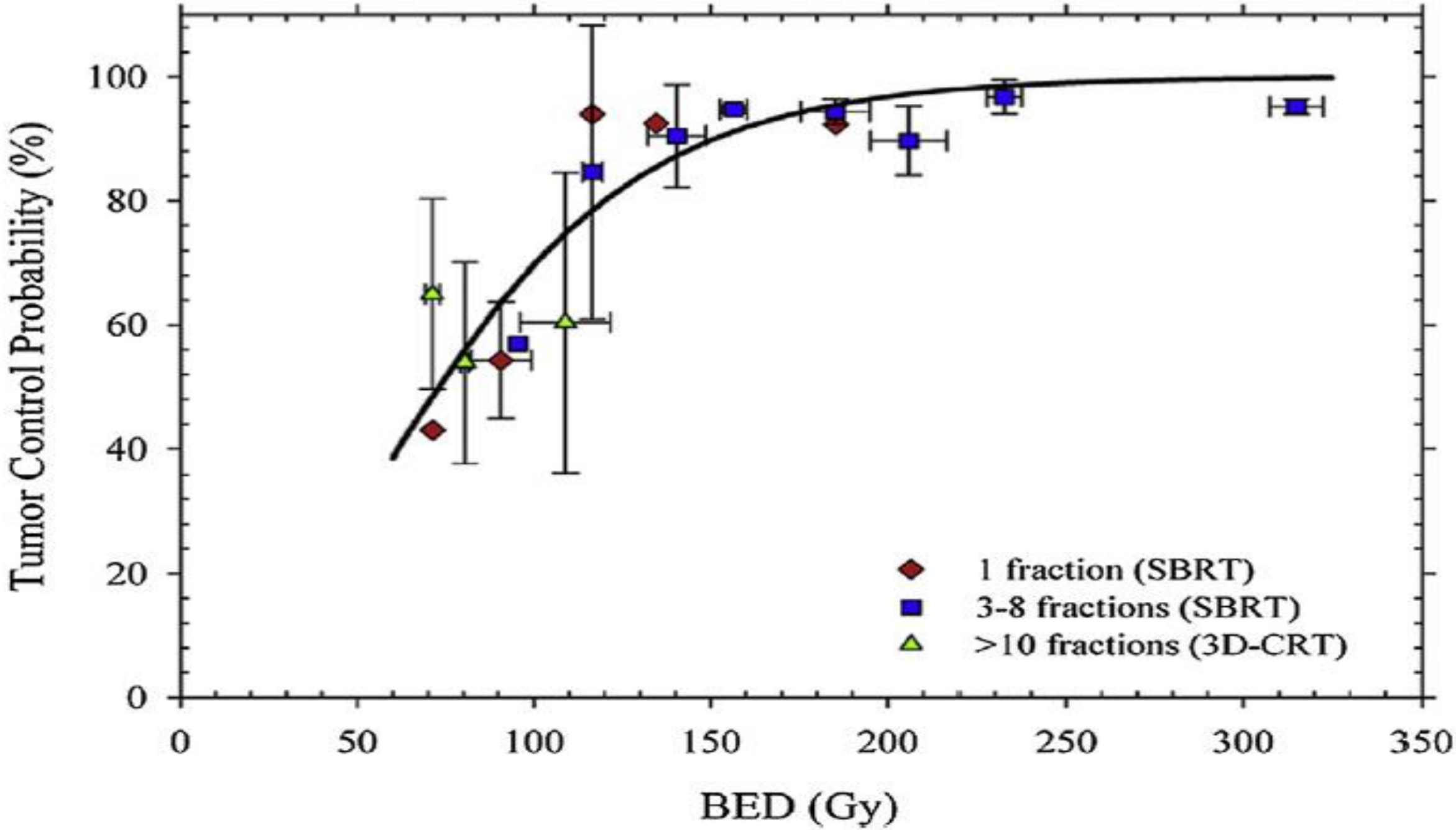
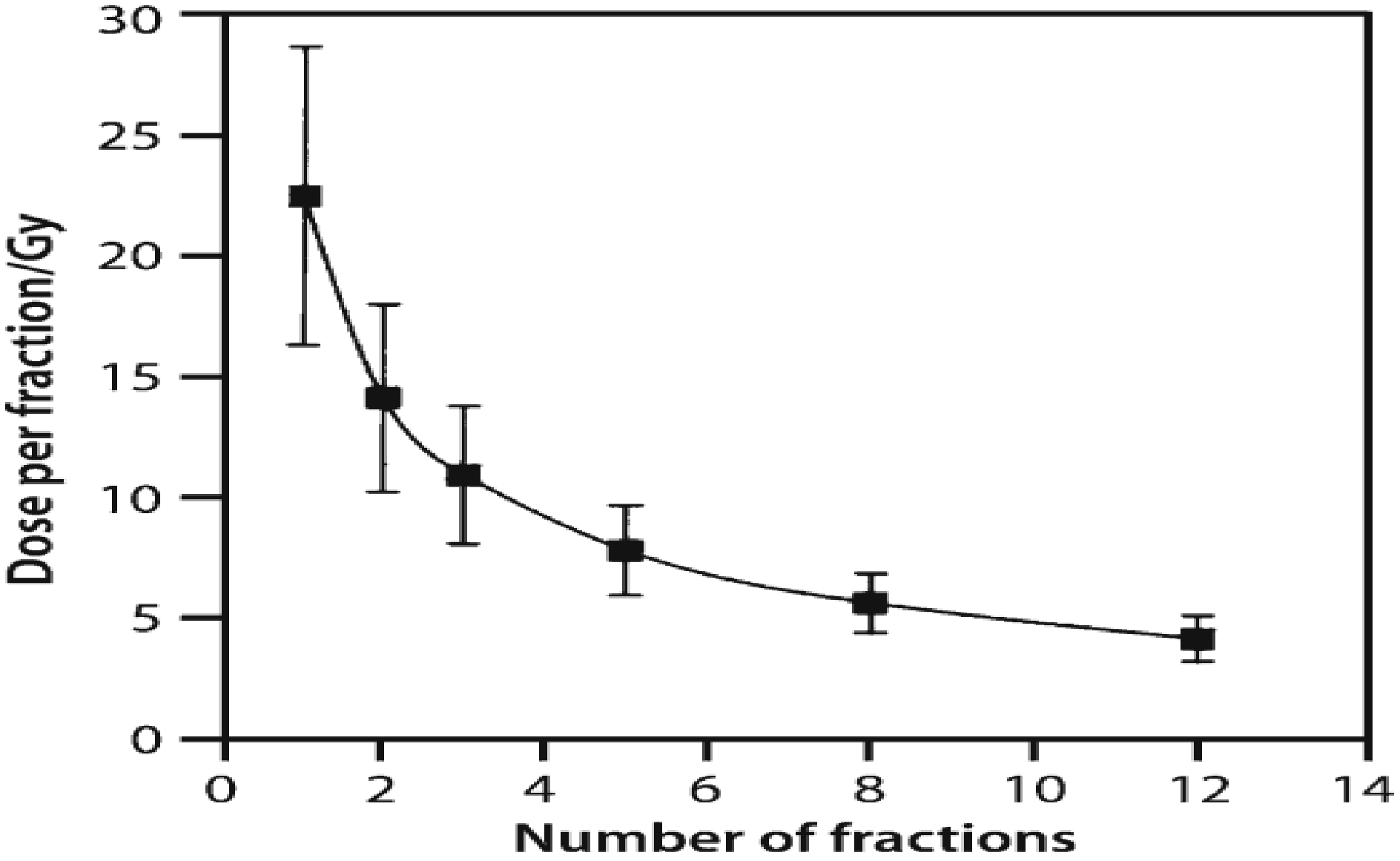


Fig 1. Tumour control probability (TCP) for a target volume (receiving a homogenous dose) over a range of fraction numbers (1–50) for different tumour α/β. All curves are for the same normal tissue complication probability (NTCP), i.e. 'isotoxic', here for rectal bleeding (4.3%) for which $\alpha/\beta = 3$ Gy has been used. Open circles, $\alpha/\beta = 10$ Gy; triangles, $\alpha/\beta = 5$ Gy; squares, $\alpha/\beta = 3$ Gy; diamonds, $\alpha/\beta = 1.5$ Gy


Tumor Control Probability (%)
100
80
60
40
20
0
0
50
100
150
200
250
300
350
BED (Gy)
1 fraction (SBRT)
3-8 fractions (SBRT)
>10 fractions (3D-CRT)



Dose/fraction as a function of the number of HDR treatments to achieve equal biological effect

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The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction

David J. Brenner, PhD, DSc

The tool most commonly used for quantitative predictions of dose/fractionation dependencies in radiotherapy is the mechanistically based linear-quadratic (LQ) model. The LQ formalism is now almost universally used for calculating radiotherapeutic isoeffect doses for different fractionation/protraction schemes. In summary, the LQ model has the following useful properties for predicting isoeffect doses: (1) it is a mechanistic, biologically based model; (2) it has sufficiently few parameters to be practical; (3) most other mechanistic models of cell killing predict the same fractionation dependencies as does the LQ model; (4) it has well-documented predictive properties for fractionation/dose-rate effects in the laboratory; and (5) it is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction. To date, there is no evidence of problems when the LQ model has been applied in the clinic.
Semin Radiat Oncol 18:234-239

Critical Review

The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?

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"…..we conclude that the available preclinical and clinical data do not support a need to change the LQ model"

Any Questions?