SBRT: RADIOBIOLOGY RATIONALE

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LEARNING OBJECTIVES

- What is the rationale of SBRT?
- Dose-effect relationships
  - What effect does occur increasingly at higher doses per fraction?
  - Are “Rs” of radiotherapy still relevant to SRS/ SBRT regimens?
- LQ models for SBRT
  - Rational of prescription schemes
  - Does the LQ model work at high doses?
- Proposed radiobiological models for SBRT
- Radiobiology of SBRT in practice
- Latest trends

RATIONALE OF SBRT

"Technology that uses elements of 3D conformal therapy in addition to stereotactic targeting while incorporating systems for decreasing the effects of lung and other organ movements that would otherwise translate into target motion."

- The Rationale
  - Highly **ablative** dose in a few fractions (typically < 5 fractions)
  - Promotes cell death, while allowing time for repair and repopulation of normal tissues.

(Timmerman R., et al. Journal of Clinical Oncology, Vol 24, No 30, 2006, pp4833-4839)

SBRT

Began as an extension of SRS and shares some of the same characteristics.

– Hypofractionation with markedly **increased dose** per fraction.

– Significantly reduced elapsed treatment **time** (Timmerman et al. 2006)

– Dramatic reduction in size of the **treatment volume**.

– Effective **immobilization** and tumor **motion management**.

– A high level of confidence in the **accuracy and precision** of treatment delivery practices. (AAPM Task Group Report 101: Stereotactic body radiation therapy)

SBRT

Attempts to mimic the **dose distribution** of SRS.

- Prescribed to an isodose line with 70 –90% (usually 80%)
- High dose/fx
- Conformal to PTV

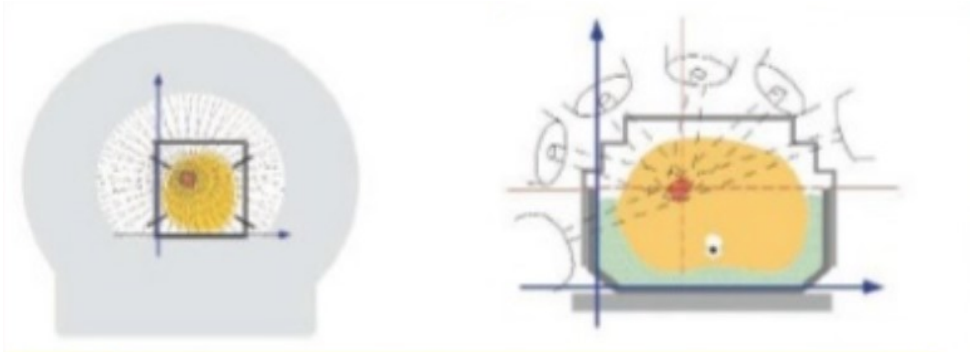
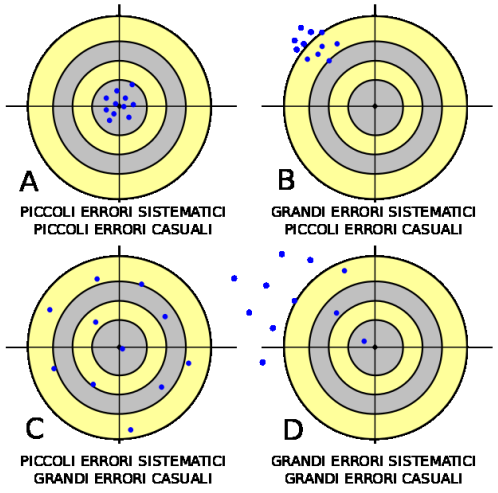


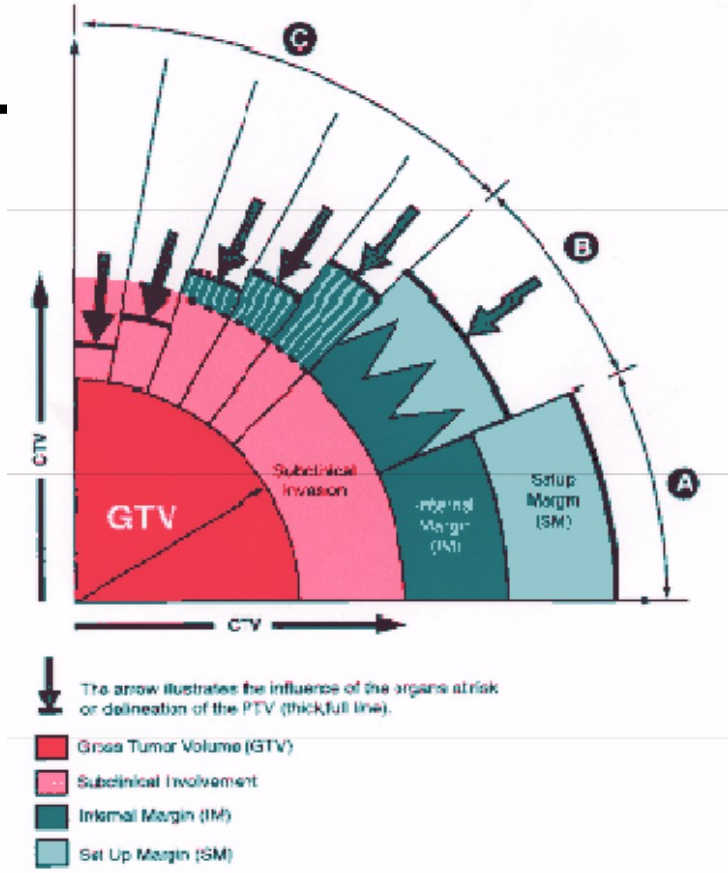
FIGURE 1. The left panel shows a schematic drawing of intracranial stereotactic radiosurgery with the Gamma Knife (Elekta, Norcross, GA). The stereotactic frame is fixed with screws into the skull. The right panel shows a schematic drawing of extracranial stereotactic radiation therapy with linear accelerator. The patient is fixed in the stereotactic body frame.

- High **precision**
- High **accuracy**



THE TARGET IN RADIOTHERAPY

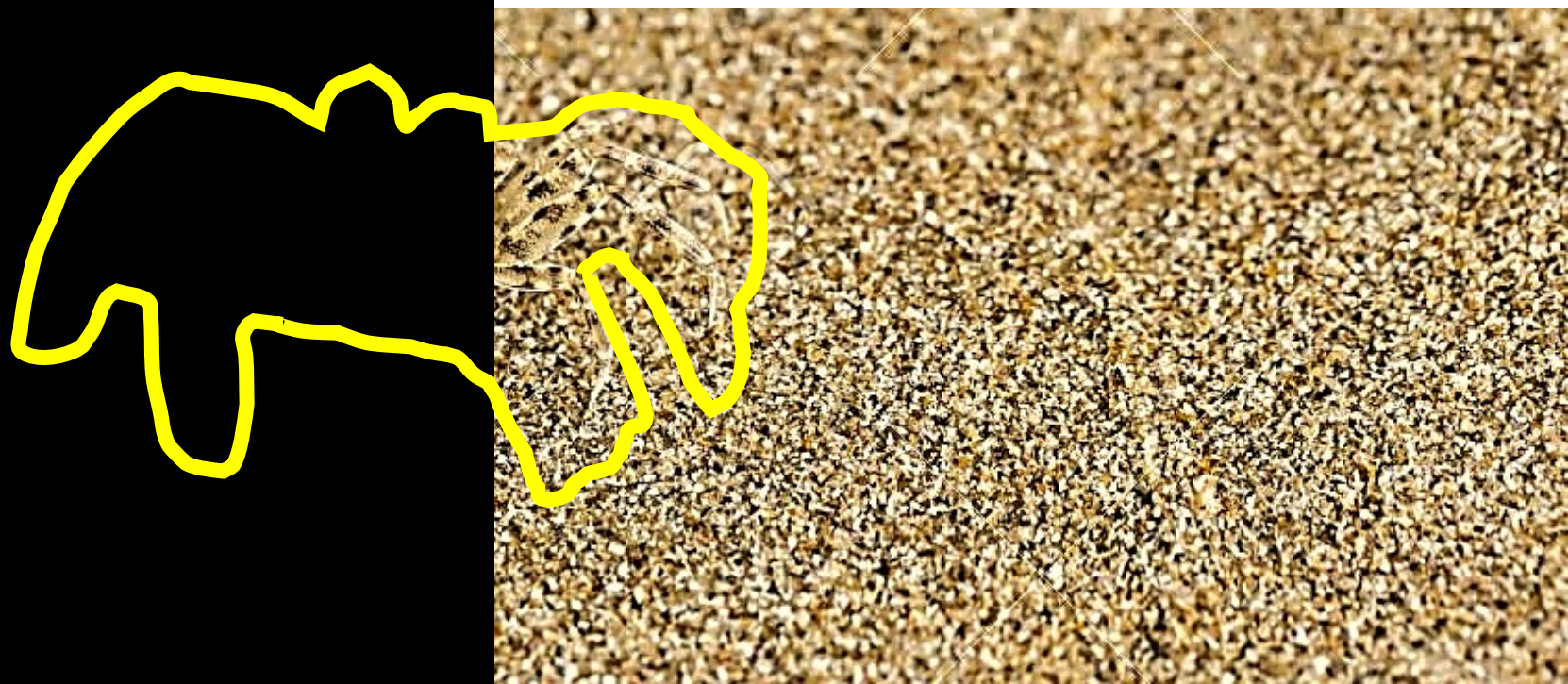
- The bulk tumour
  - may be able to distinguish different parts of the tumour in terms of radiosensitivity and clonogenic activity
- Confirmed tumour spread
- Potential tumour spread



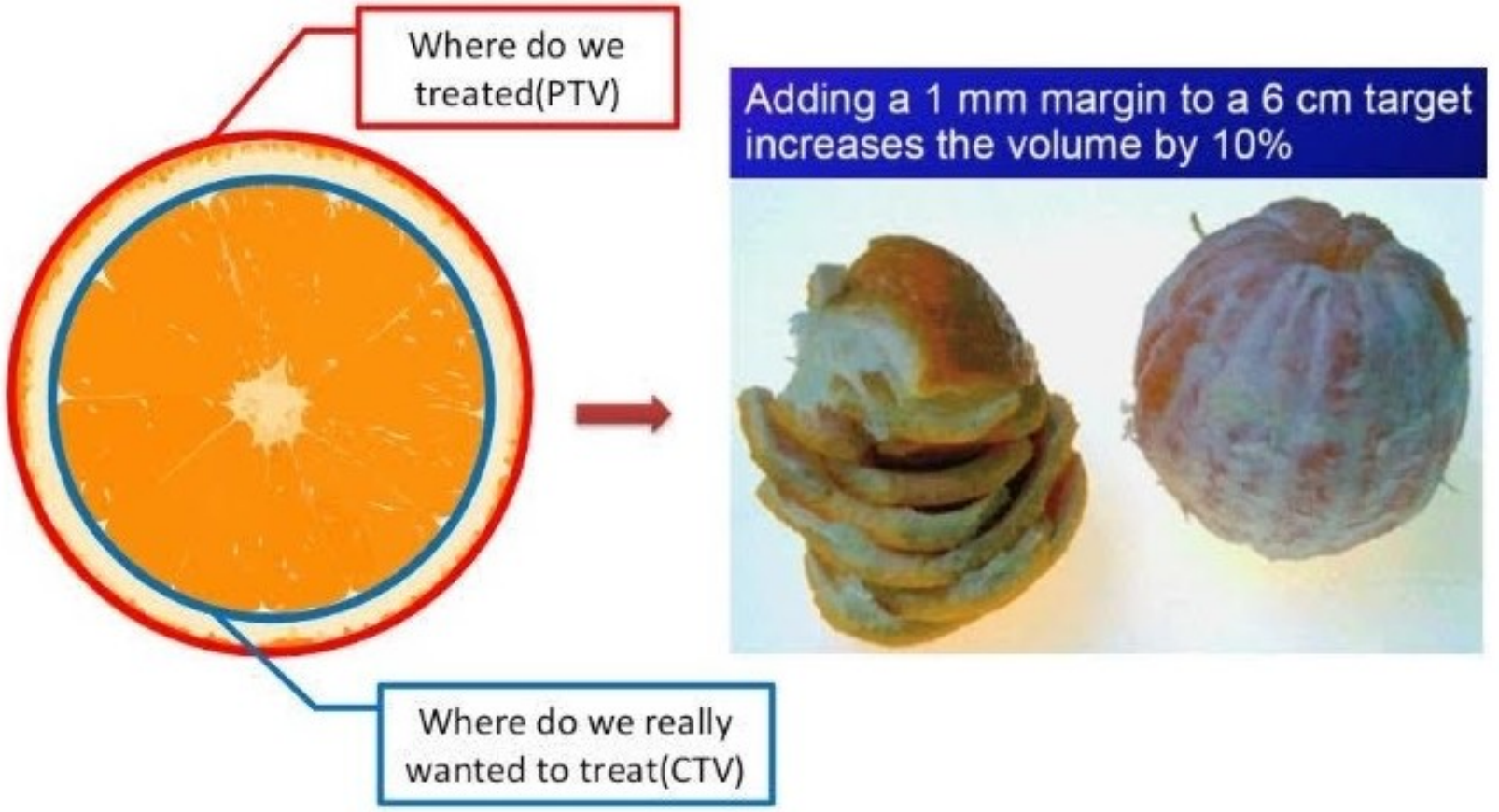
- Large mass (1kg) = 10^{12} cells - need three orders of magnitude → more cell kill
- Palpable tumour ($1cm^3$) = 10^9cells !!!
- Microscopic tumour, micrometastasis = around 10^6 cell - need less dose

❑ Rationale of SBRT

**“IF YOU CAN'T SEE IT,
YOU CAN'T HIT IT,
AND IF YOU CAN'T HIT IT,
YOU CAN'T CURE IT”**



PTV MARGINS IN SBRT



ttps://www.umcutrecht.nl/en/Research/Research-centers/UMC-Utrecht-Center-for-Image-Sciences/Research-programs/MR-Radiotherapy/MRI-guided-Radiotherapy/MRI-guided-proton-therapy

- GTV

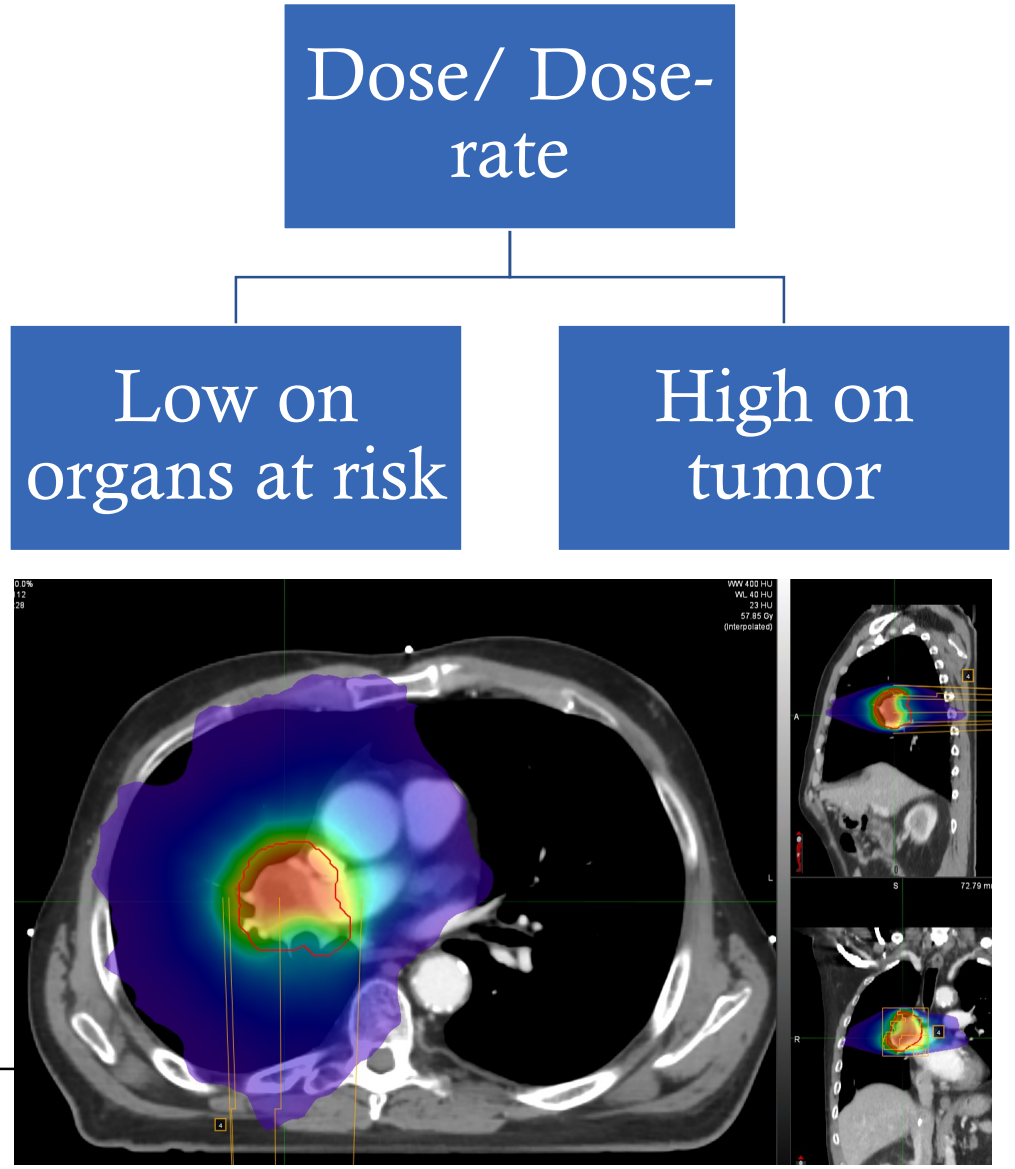
  To be delineated by the physician using multi-modality imaging

- ITV
  - 4DCT /SBRT optimal for target definition
- PTV
  - ITV + margin expansion according to the selected delivery strategy

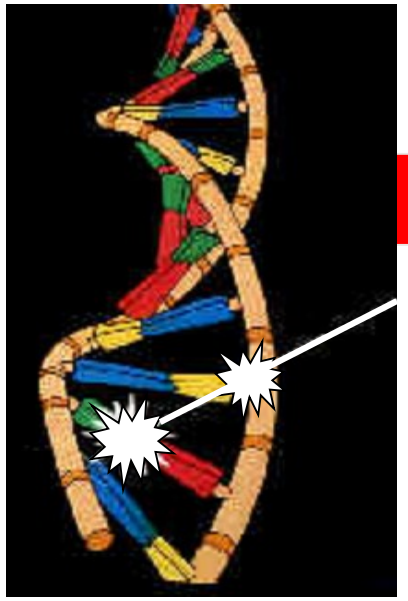
HALLMARKS OF SBRT

- Rapid **fall-off of radiation** dose at the periphery of target
  - Minimal dose to surrounding tissues
- High **dose conformity**
- **Small beams**

  Accurate dose calculation algorithms are mandatory (AAPM 101)

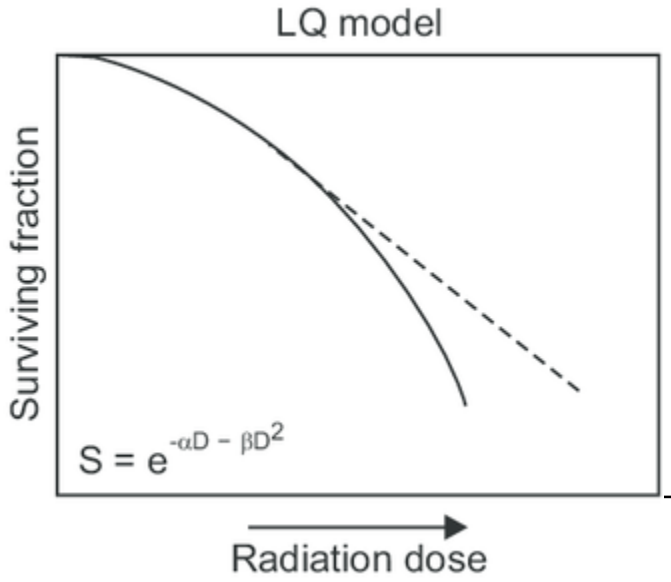


THE LINEAR QUADRATIC MODEL



"α-damage" → αD

"β-damage" → βD^2



The LQ model is simple and convenient better fit in the low dose–high survival region:

- α (lethal/non-repairable) & β (sub-lethal/reparable)
- α/β ratio for early and late reactions in human normal tissues consistent with results from experimental models

THE LINEAR QUADRATIC MODEL

- Cell survival:

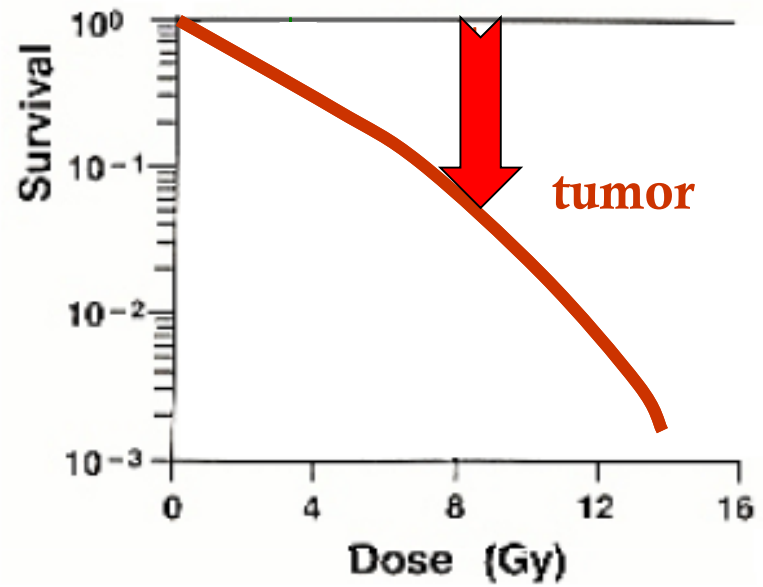
$$\text{single fraction: } SF = \exp(-(\alpha D + \beta D^2))$$

$$\text{(n fractions of size d: } SF = \exp(-n(\alpha d + \beta d^2))$$

- Biological effect:

$$E = -\ln(SF) = \alpha D + \beta D^2$$

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

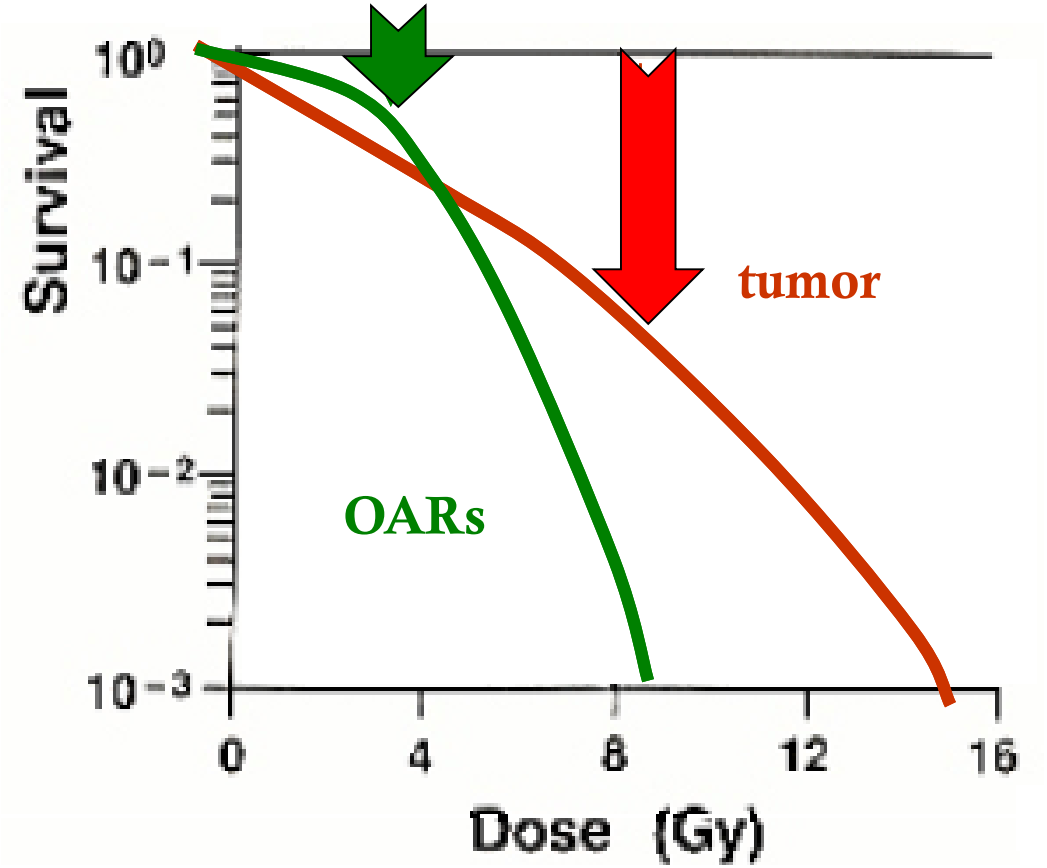


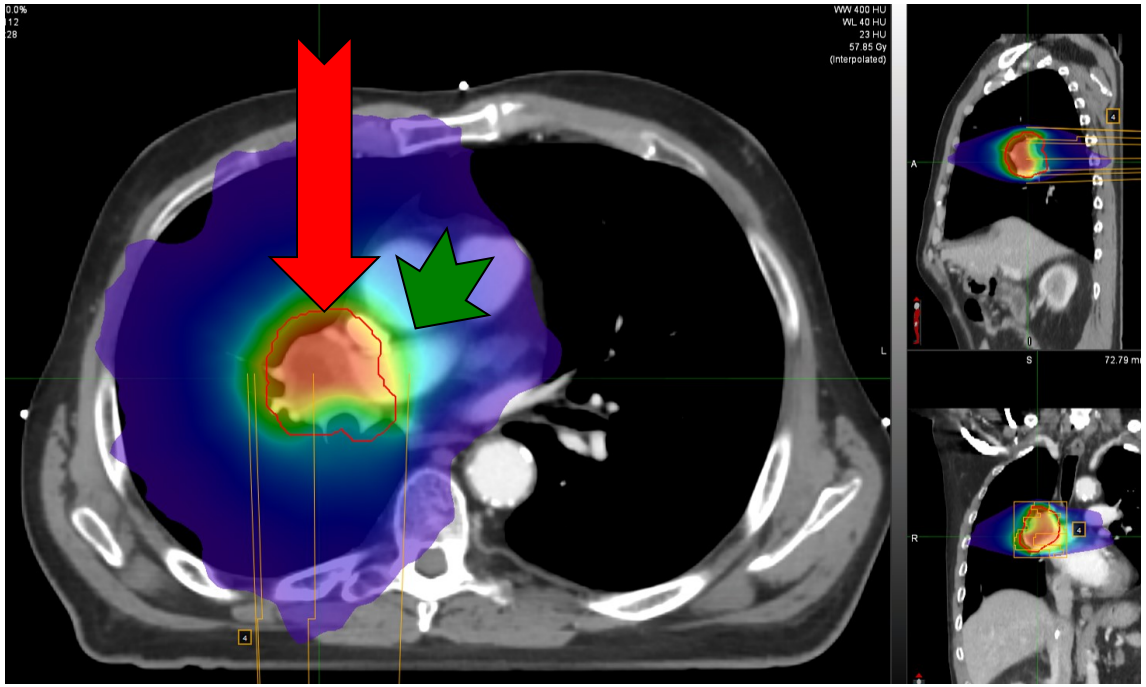
BIOLOGICAL EFFECTIVENESS

$$E/\alpha = - \ln (SF) /\alpha = BED = (1 + d / (\alpha/\beta)) * D = RE * D$$

- BED = biologically effective dose, the dose which would be required for a certain effect at infinitesimally small dose rate (no beta kill)
- RE = relative effectiveness

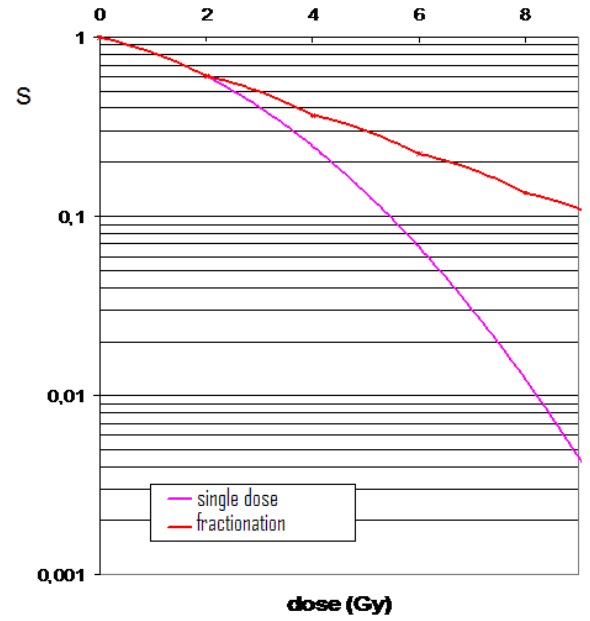
LQ MODEL



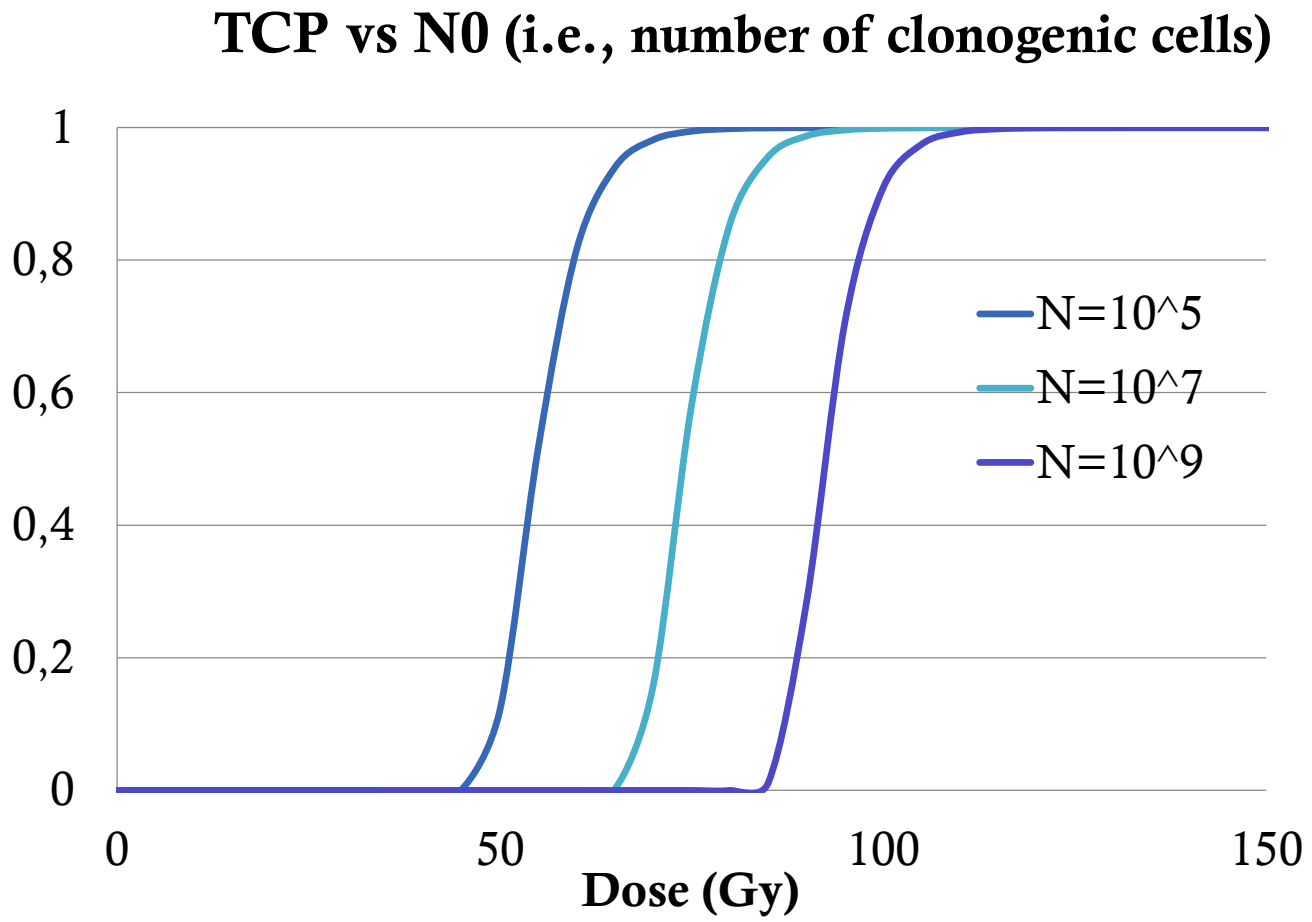


BIOLOGICAL EFFECTIVENESS

$$TCP(D_m) = \exp(-N_0 \cdot SF)$$



Are the lesions large or small?



EXTENSION OF LQ MODEL TO INCLUDE TIME:

$$E = -\ln S = n * d\,(\alpha + \beta d) - \gamma T$$

Including T_k ("kick off time") which allows for a time lag before the tumour switches to the fastest repopulation time:

$$BED = (1 + d / (\alpha/\beta)) * nd - (\ln 2\,(T - T_k)) / \alpha T_p$$

SBRT 4Rs REVISITED

- Reoxygenation: When tumors are treated with SBRT the intra-tumor environment will become hypoxic leading to secondary cell death due to **vascular damage**

- Repair: **Vascular damage** and ensuing chaotic intra-tumor environment may significantly hinder repair of radiation damage

- Redistribution: after irradiation with dose of >15-20 Gy, cells are indefinitely **arrested in the phases of cell cycle** where they were irradiated and undergo interphase cell death

- Repopulation: repopulation of tumor cells **will not be substantial** during the course of SBRT (1-2 weeks)

Differential biological effect between tumor and normal tissue is largely gained through minimization of normal tissue volume in SBRT

BED

Assuming an $\frac{\alpha}{\beta} = 10\text{Gy}$, what is the LQ BED of 50 Gy in 5 fractions?

a) 50 Gy

b) 60 Gy

c) 100 Gy

d) 105.5 Gy

e) 150 Gy

$$\text{BED}_{\text{LQ}} = \text{Nd}\left[1 + \frac{d}{\alpha/\beta}\right]$$

BED

Assuming an $\frac{\alpha}{\beta} = 10\text{Gy}$, what is the LQ BED of 50 Gy in 5 fractions?

$$\text{BED}_{\text{LQ}} = \text{Nd}\left[1 + \frac{d}{\alpha/\beta}\right]$$

a) 50 Gy

b) 60 Gy

c) 100 Gy

d) 105.5 Gy

e) 150 Gy

c) 50 Gy in 5 fractions = $50\ (1+10/10)=50(1+1)=100$ Gy

Assuming an $\frac{\alpha}{\beta} = 10\text{Gy}$, which prescription scheme have LQ BED <100 Gy?

a) 50 Gy in 5 fractions
b) 40 Gy in 4 fractions
c) 48 Gy in 4 fractions
d) 42 Gy in 3 fractions
e) 34 Gy in 1 fraction

Assuming an $\frac{\alpha}{\beta} = 10\text{Gy}$, which prescription scheme have LQ BED <100 Gy?

a) 50 Gy in 5 fractions

b) 40 Gy in 4 fractions

c) 48 Gy in 4 fractions

d) 42 Gy in 3 fractions

e) 34 Gy in 1 fraction

Ref: Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010 Jul;83(991):554-68.

$$BED_{LQ} = 4*10\left(1+\frac{10}{10}\right) = 40*2 = 80Gy$$

THE OTHER ANSWERS

- 50 Gy in 5 fractions = 50 (1+10/10)=50(1+1)=100 Gy
- 40 Gy in 4 fractions = 40 (1+10/10)=40(1+1)=80 Gy
- 48 Gy in 4 fractions = 48 (1+12/10)=48 (1+1.2)=105.6 Gy
- 42 Gy in 3 fractions = 42 (1+14/10)=42 (1+1.4)=100.8 Gy
- 34 Gy in 1 fraction = 34 (1+34/10)=34 (1+3.4)=149.6 Gy

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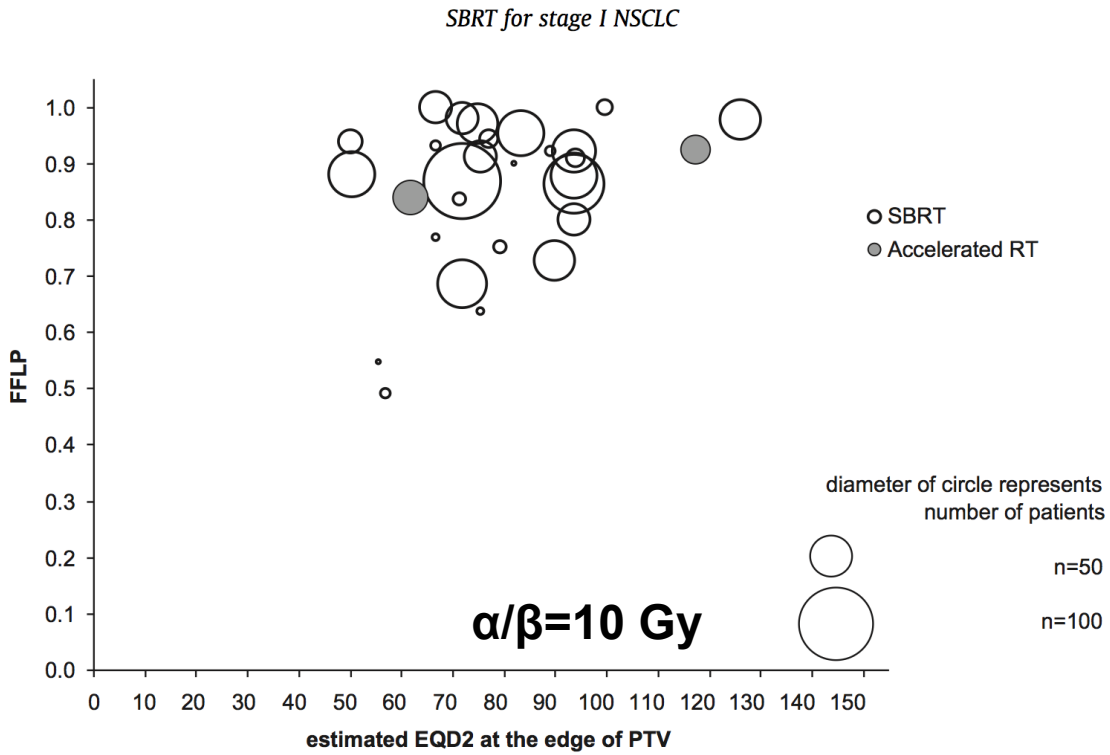
doi:10.1016/j.ijrobp.2008.06.1939

NSCLC

CLINICAL INVESTIGATION **Lung**

DOSE–RESPONSE RELATIONSHIP FOR IMAGE-GUIDED STEREOTACTIC BODY RADIOTHERAPY OF PULMONARY TUMORS: RELEVANCE OF 4D DOSE CALCULATION

MATTHIAS GUCKENBERGER, M.D.,* JOERN WULF, M.D.,*† GERD MUELLER, M.D.,* THOMAS KRIEGER, M.SC.,* KURT BAIER, M.SC.,* MANUELA GABOR, M.S.,* ANNE RICHTER, M.SC.,* JUERGEN WILBERT, PH.D.,* AND MICHAEL FLENTJE, M.D.*



The 3-ys local control rates were 89% and 62% for >100 Gy and <100 Gy BED (p = 0.0001)

effects. The EQD_2 was adjusted for overall treatment time ($EQD_{2,T}$) to take into account accelerated repopulation after 21 days [27], but knowing that these estimations may be less appropriate with fraction sizes over 10 Gy [28].

$$EQD_{2,T} = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta} - \mathrm{MAX}(0, T - T_{ref}) \cdot D_{prolif}$$

where the second term is zero for $T \leqslant T_{ref}$ and equal to D_{prolif} ($D_{prolif} = 0.6$) multiplied by the number of days beyond T_{ref} for $T > T_{ref}$. To compare SBRT with accelerated high-dose conformal

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α/β=8.6 Gy

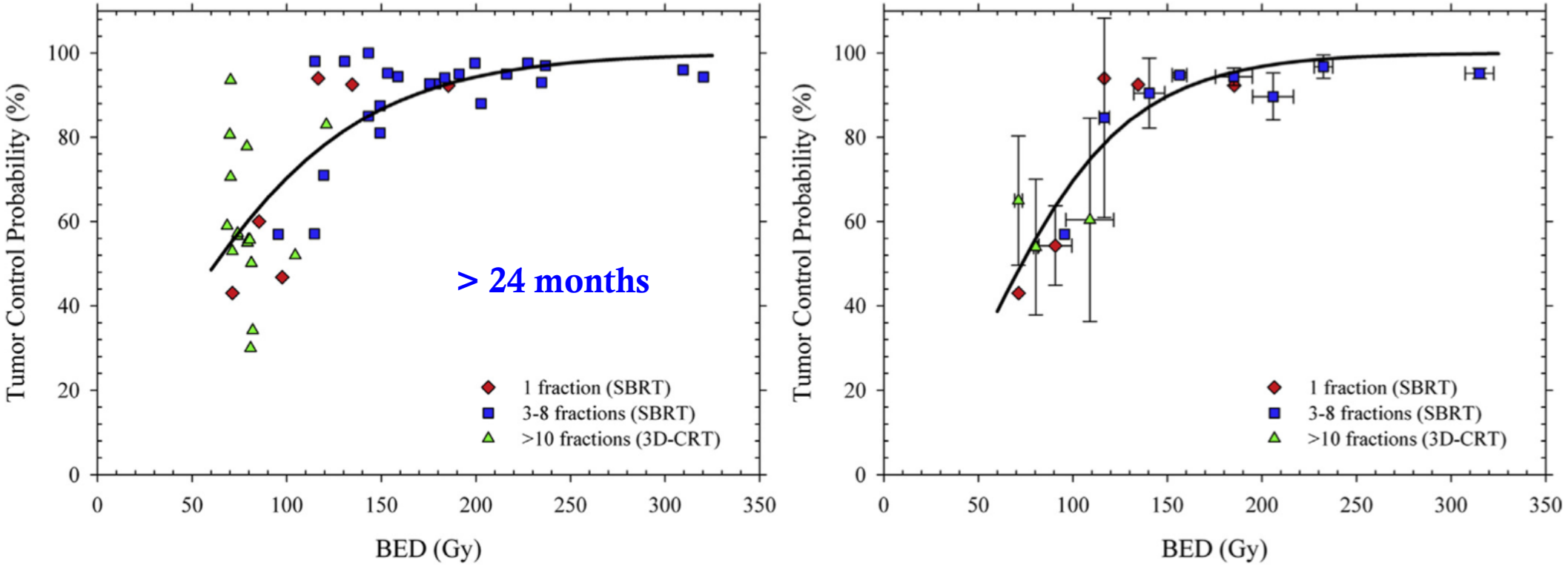
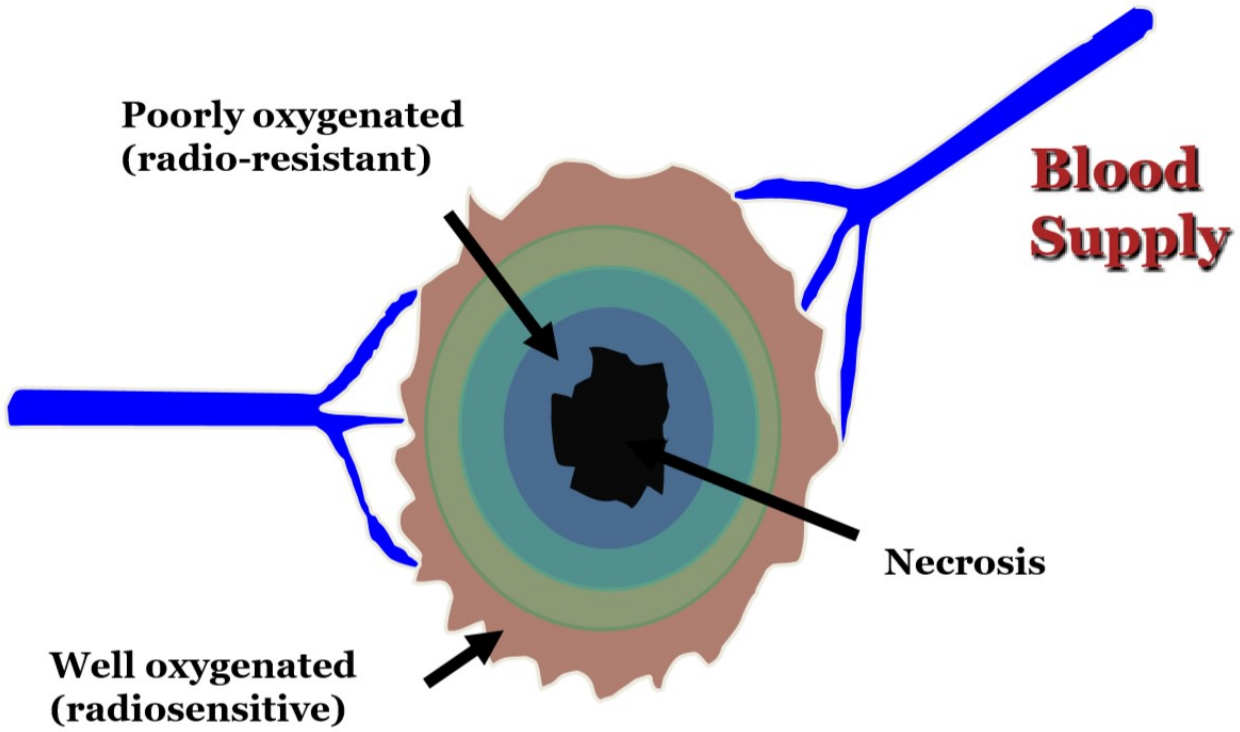


Fig. 8. Tumor control probability (TCP) as a function of biologically effective dose (BED) for stage I non-small cell lung cancer. Left, symbols show local control rates (≥2 years) from a pooled analysis reported by Mehta et al (27) with symbols distinguishing conventional and stereotactic body radiation therapy (SBRT) fractionations. Right, weighted mean TCP probabilities calculated to compensate for the different numbers of patients in each study. Solid lines show linear quadratic-based fits to the data showing that within the limits of clinical data, the efficacy of single doses, a few SBRT fractions, and conventional radiation therapy produce the same overall TCP for the same BED. From (58) with permission. 3D-CRT = 3-dimensional conformal radiation therapy.

SBRT

Dose heterogeneity within the PTV is desired!

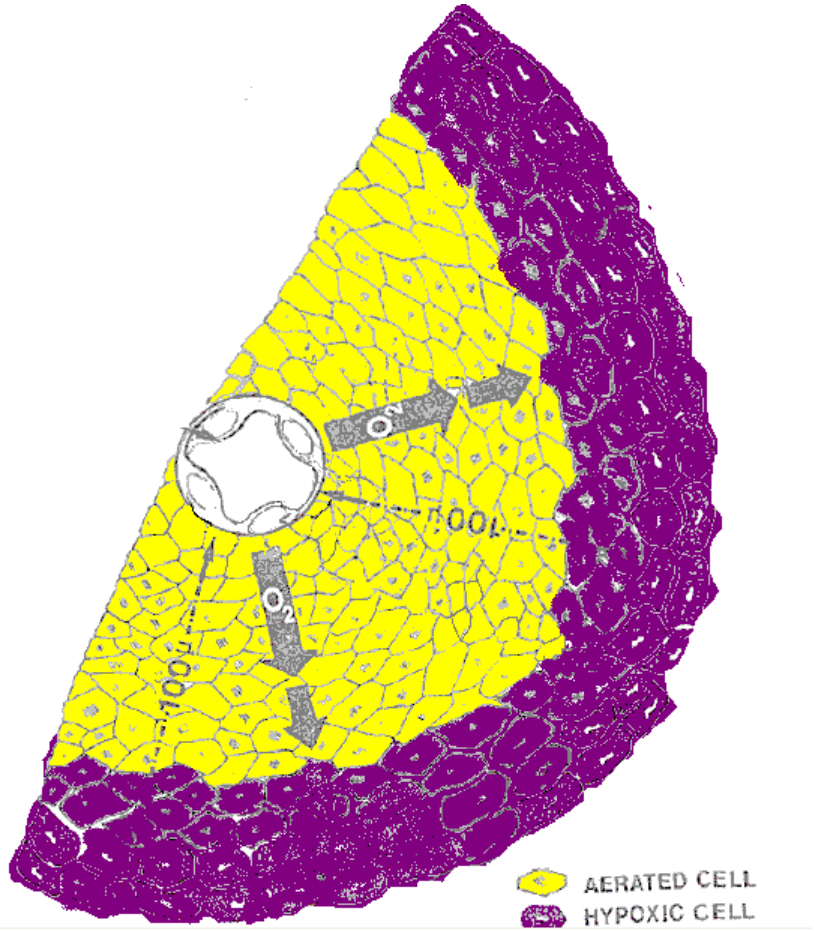


- Higher central dose to GTV because > hypoxic fraction.
- Optimally, the GTV will receive ~10% greater dose than the outside edges of the PTV.
- Sharp **dose gradient** outside the tumor is desired.
- Requires effective patient immobilization.
- Requires use of multiple non-coplanar static fields or dynamic arcs.

TYPE OF HYPOXIC CELLS

- **chronic hypoxia** results from the limited diffusion distance of oxygen through tissue, i.e. some cells may remain hypoxic for a long period of time;

- **acute hypoxia** is a result of the temporary closing of tumor blood vessels and is therefore transient.

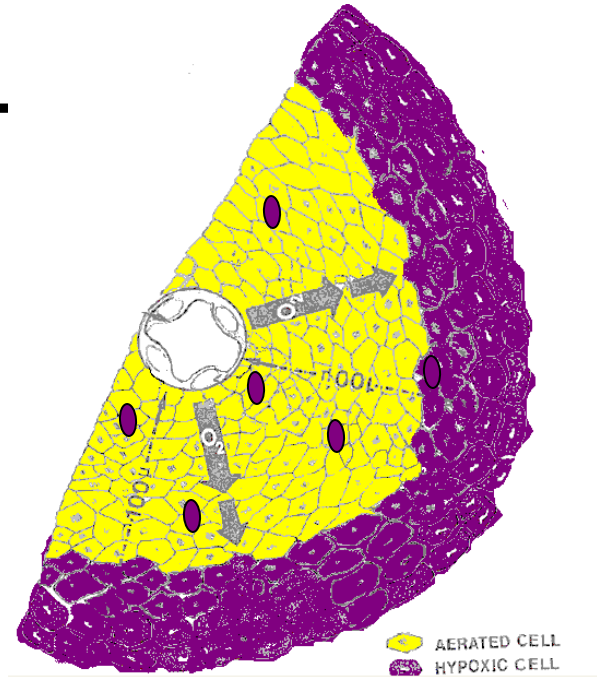


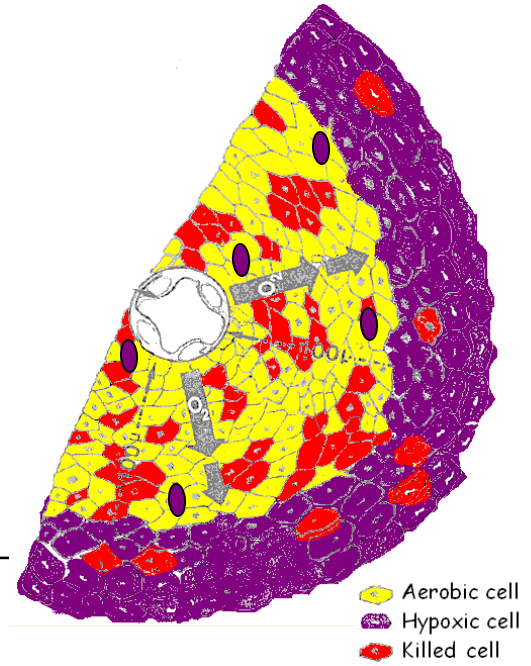
ACUTE HYPOXIA

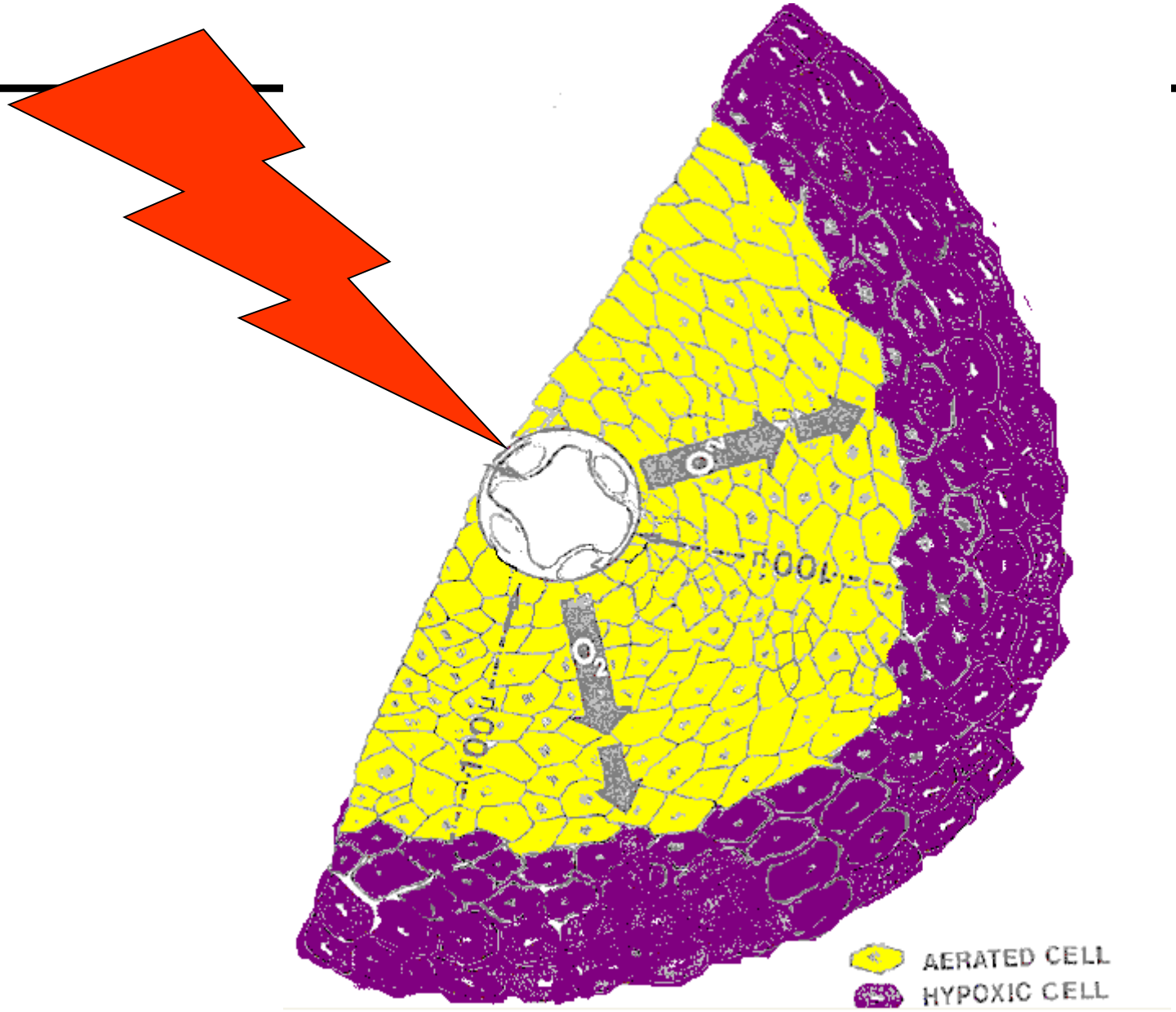
- Tumor blood vessels open and close in a random fashion so that different regions of the tumor become hypoxic ***intermittently***.

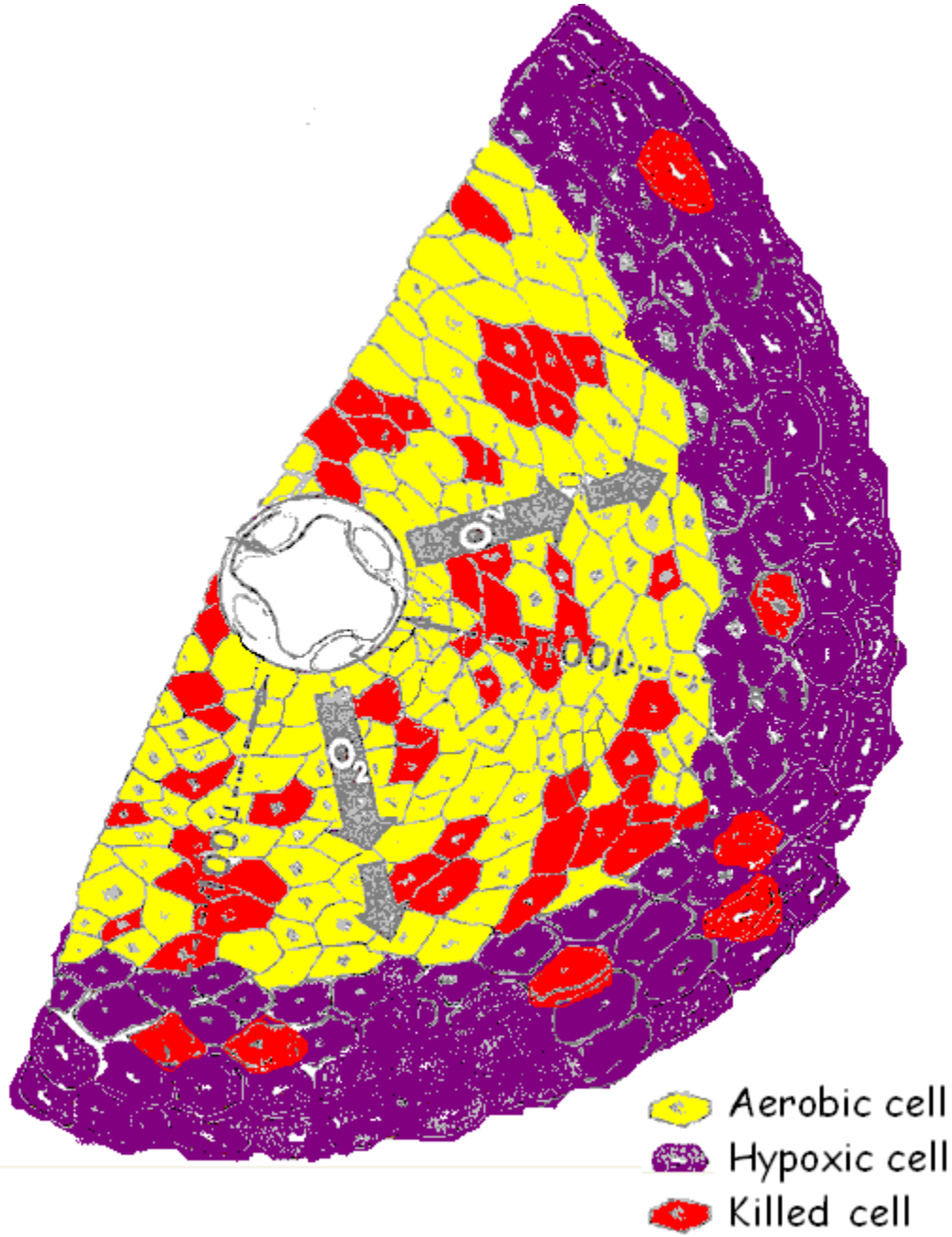
- When a dose of radiation is delivered a proportion of the tumor cells may be hypoxic but at the next dose of radiation a different group of cells may be hypoxic.

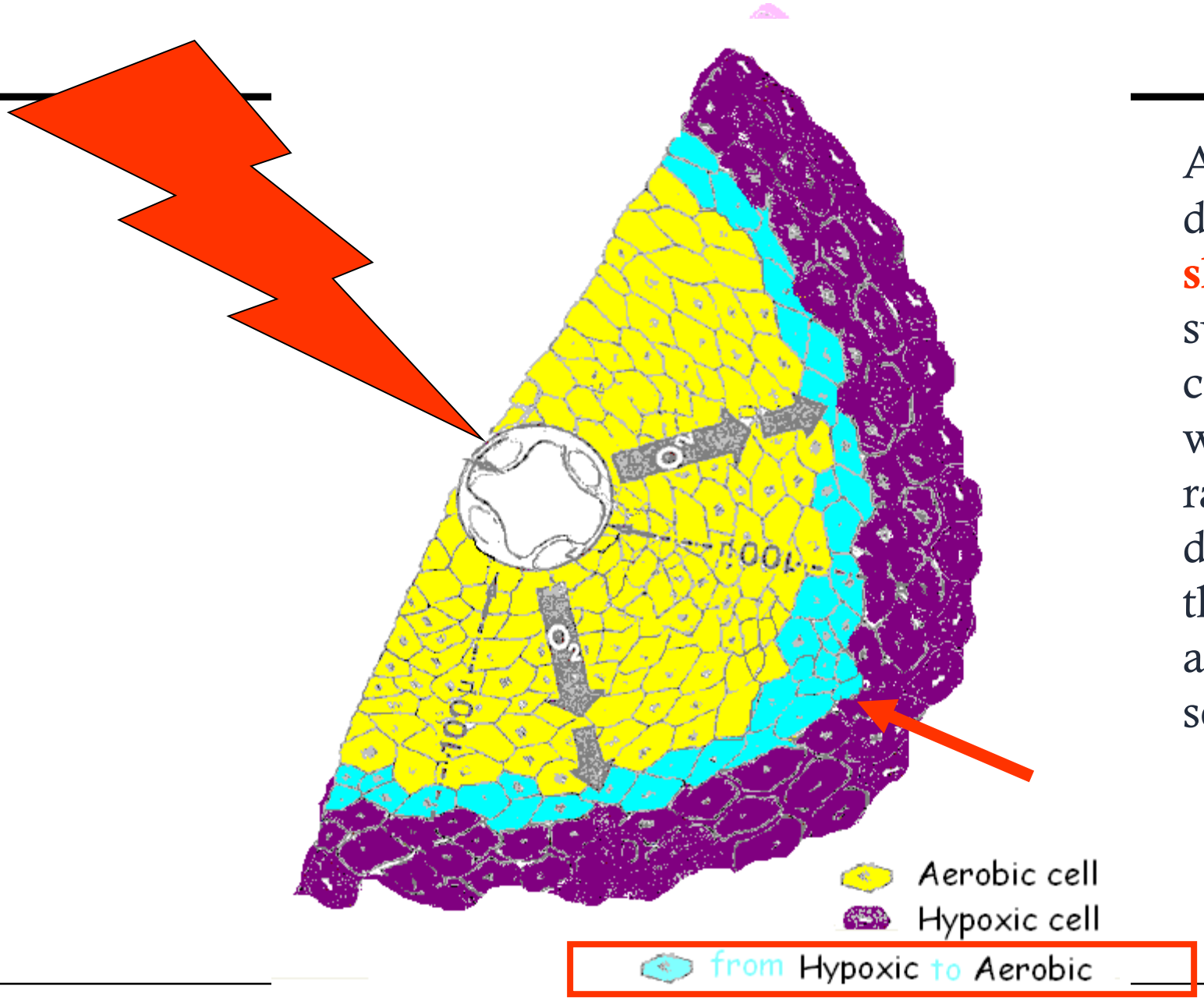
- When many doses of radiation are delivered the acute hypoxia is of no further importance.



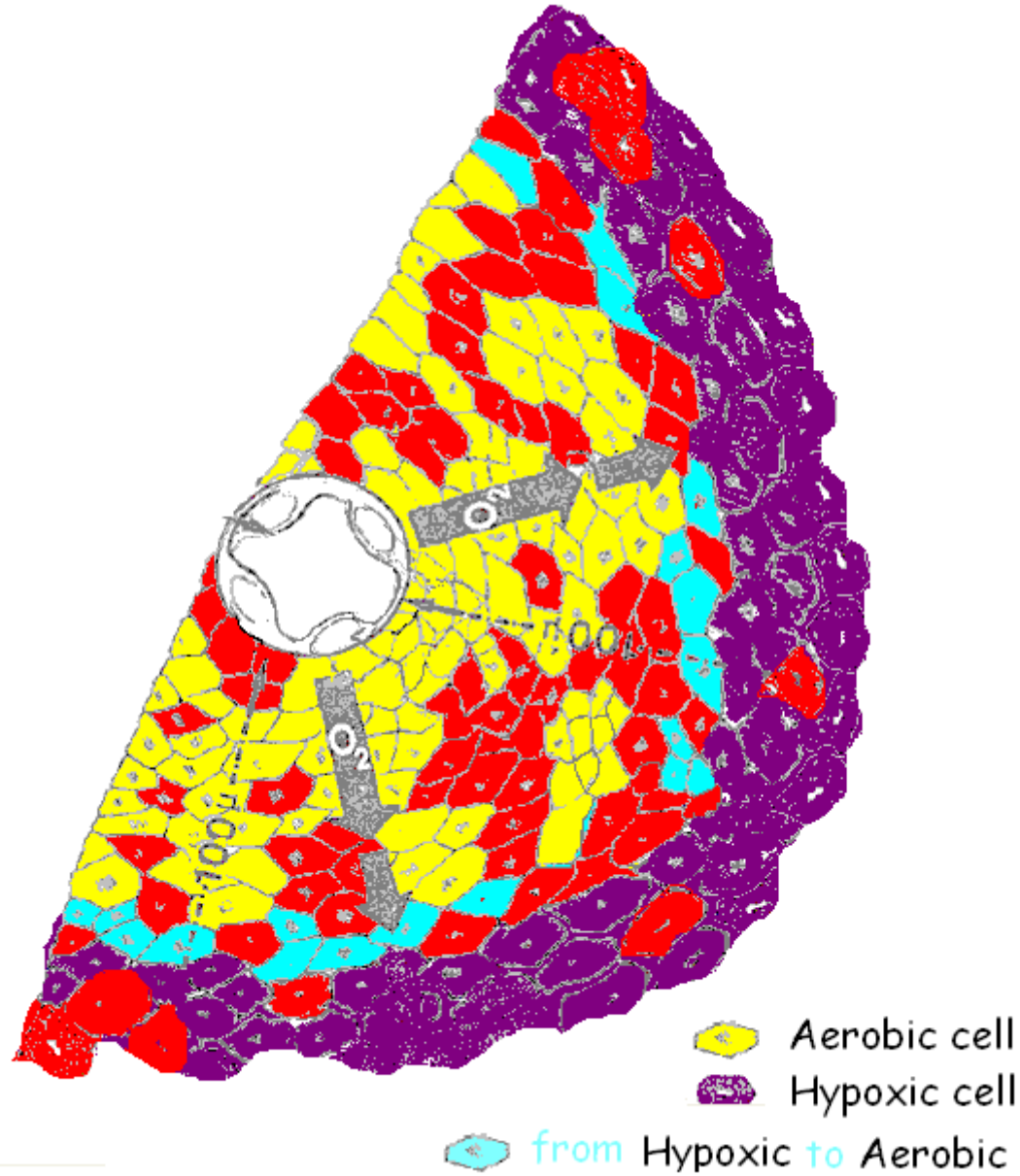


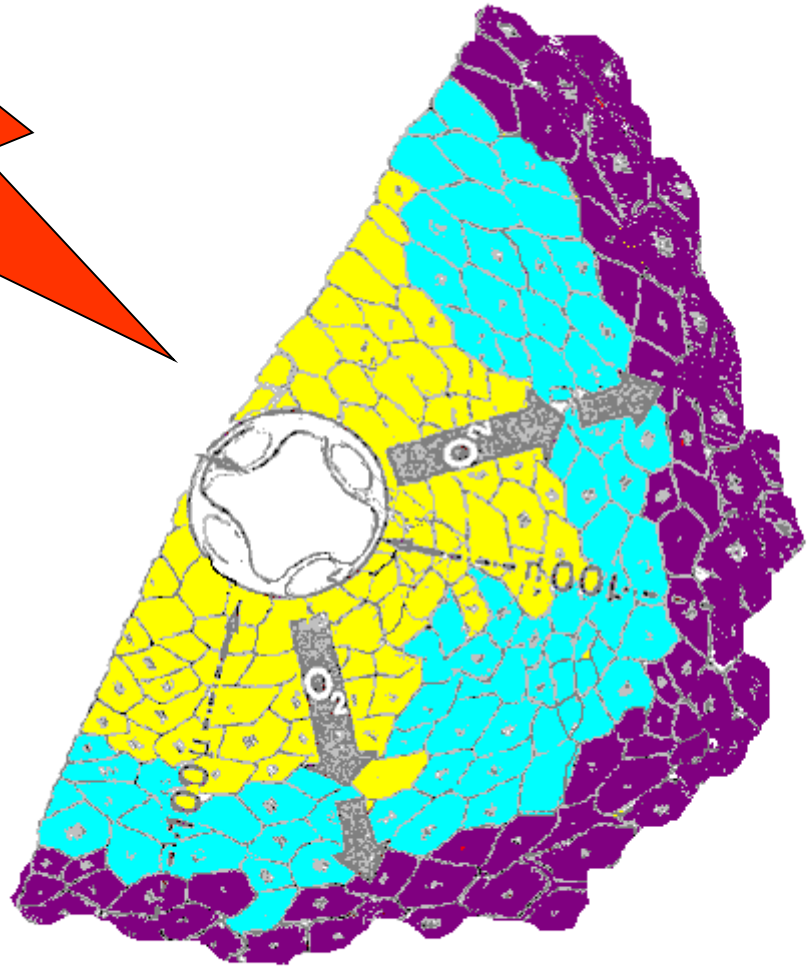

O2
100 µm
O2
100 µm
AERATED CELL
HYPOXIC CELL


O2
O2
Aerobic cell
Hypoxic cell
Killed cell

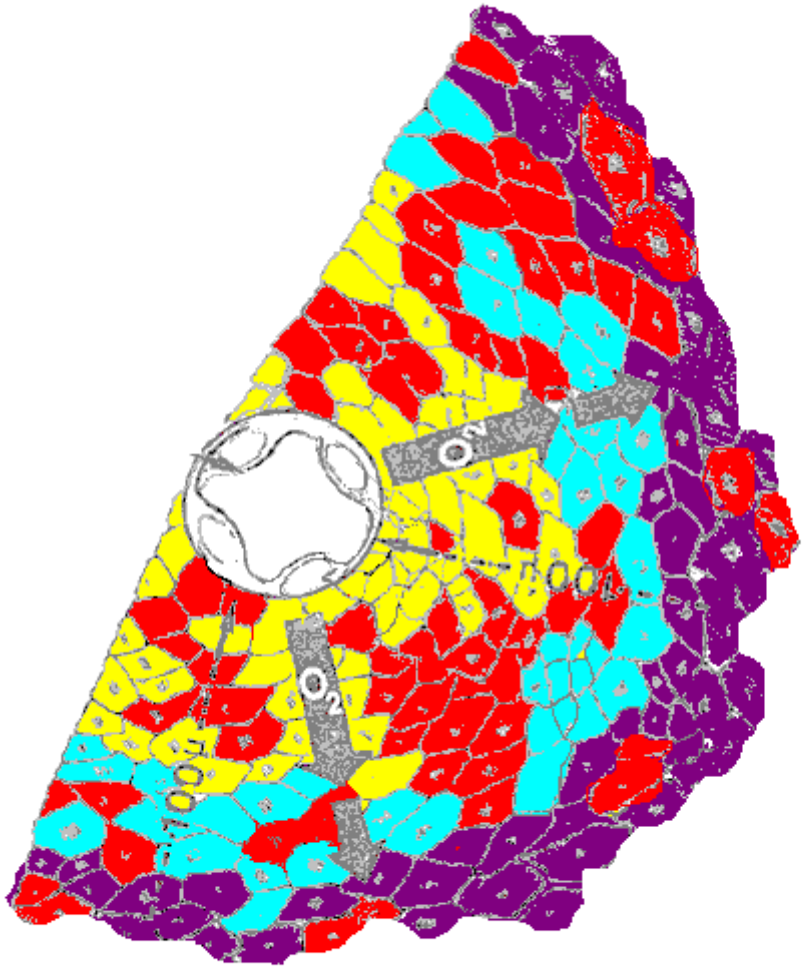


As the cells density decreases the tumor **shrinks** in size, surviving hypoxic cells that previously were beyond the range of oxygen diffusion find themselves closer to a blood supply and so reoxygenate.


O2
100
O2
100
Aerobic cell
Hypoxic cell
from Hypoxic to Aerobic

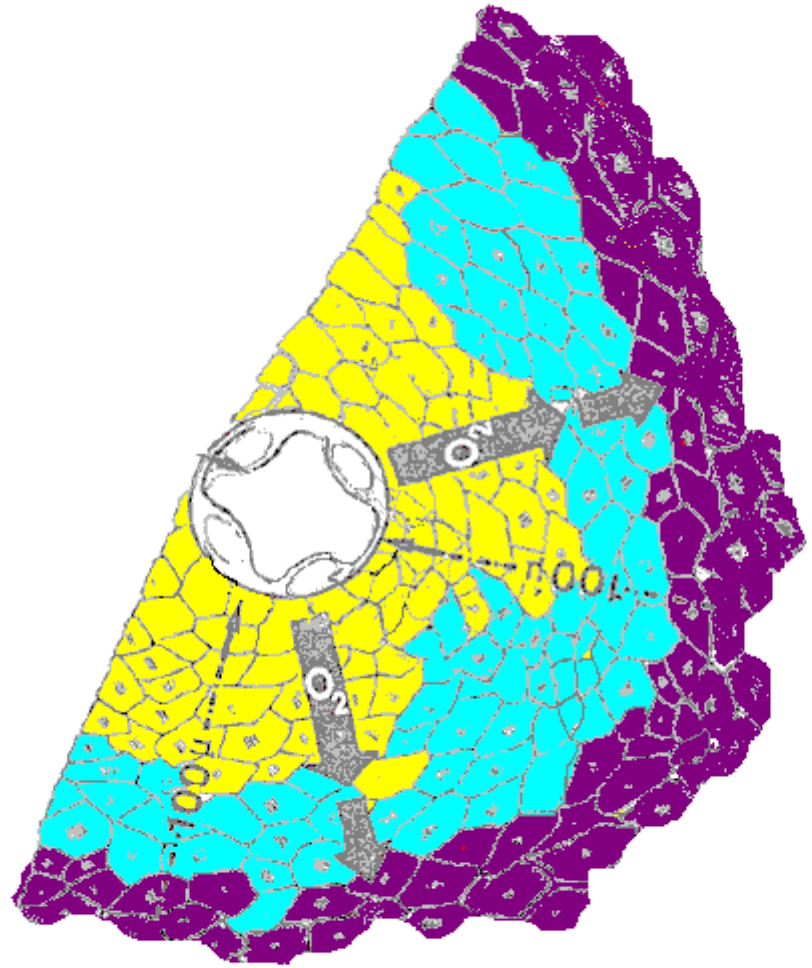


- This reoxygenation, taking place over a period of 1-2 days as the tumor shrinks, involves reoxygenation of cells that were chronically hypoxic.
- We assumed that the cells able to reoxygenate before the next dose fraction will be indicated by “B” varying in accordance with dose fraction.



There was a correlation between the magnitude of the **change in the Hypoxic Fraction (HF)** during therapy and the change in cell density which generally had a large decrease in hypoxic fraction and hence a large increase in PO2 during therapy.

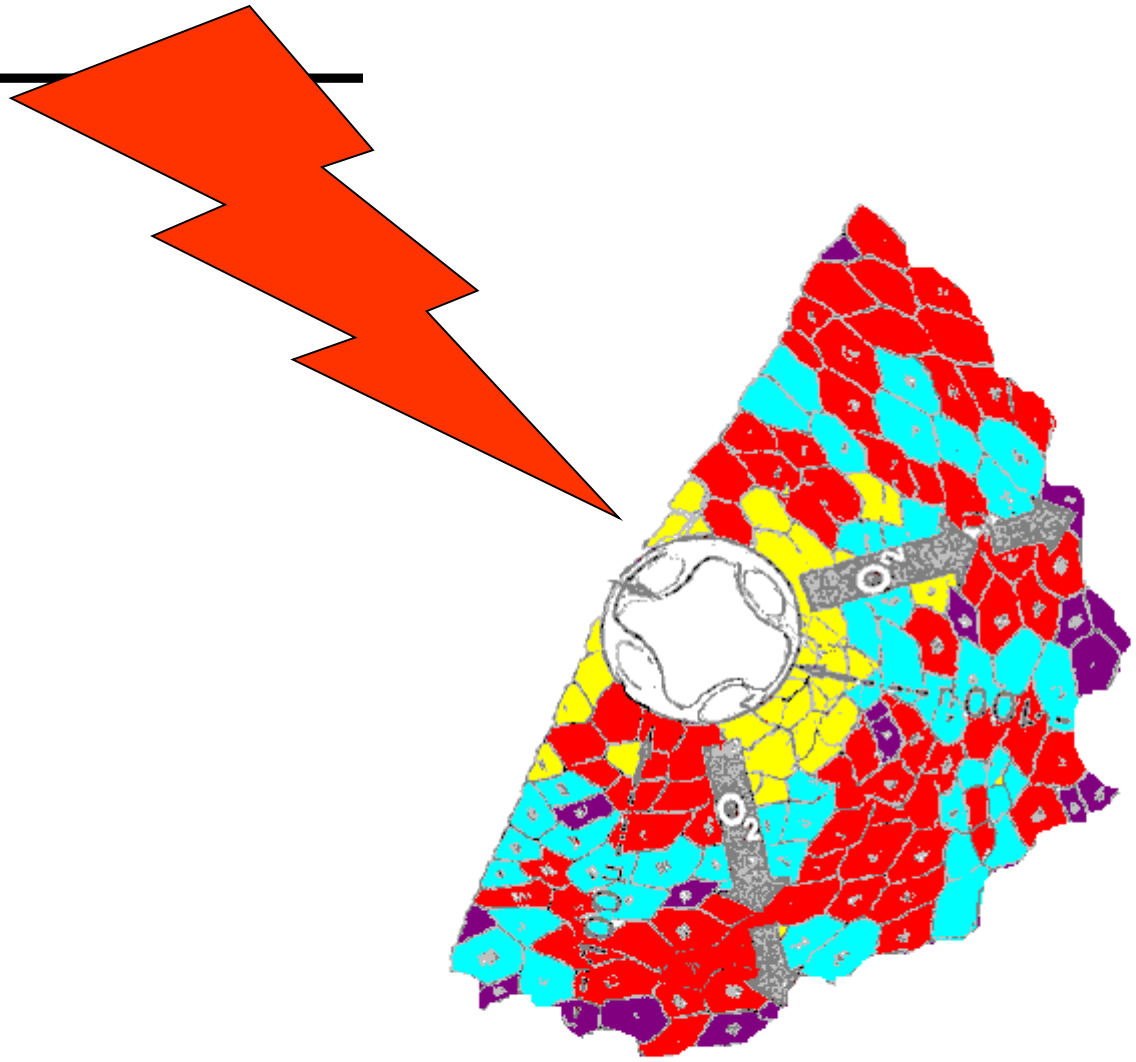
Ling H et al. IJROBP 2000, 46:935-946



Aerobic cell

Hypoxic cell

from Hypoxic to Aerobic



The decrease in cell density depends on dose fraction and α,β LQ model parameters

- When a tumor contains a sizeable fraction of hypoxic cells, its response to a course of fractionated radiation will be determined by several factors:
  - The fraction of hypoxic cells→ **η**
  - the Oxygen Enhancement Ratio → **OER**;
  - the extent of Reoxygenation → **B**;
  - and dose per fraction → **d**.

Lee SP, Withers R, 7th Int. Conf. on Dose, Time and fractionation in Radiation Oncology, Madison WI 2004

- The surviving fractions after *one* irradiation with a dose *d*, are given by:

$$S_0(d) = \exp\left[-d\left(\alpha_0 + \beta_0 d\right)\right]$$
$$S_h(d) = \exp\left[-d\left(\alpha_h + \beta_h d\right)\right]$$

- for *oxic* (o) and *hypoxic (h)* clonogens, respectively,

- where:

$$\begin{cases} \alpha_h = \dfrac{\alpha_0}{OER_\alpha}; & OER_\alpha = 1.7 \\ \beta_h = \dfrac{\beta_0}{OER_\beta{}^2}; & OER_\beta = 3.25 \end{cases}$$

- based on the modified Linear Quadratic (LQ) model for Tumor Control Probability from the Ruggeri and Nahum approach,

the *TCP* can be written:

$$TCP = \frac{1}{\sqrt{2\pi}\sigma_{\overline{\ln(N)}}} \int_0^{\infty} \exp\left[-\left(\frac{\ln(N) - \overline{\ln(N)}}{\sqrt{2} \cdot \sigma_{\overline{\ln(N)}}} \right)^2 \right] \exp\left[-N(P_o + P_h) \right] \cdot d\ln(N)$$

- where N is the number of tumour clonogens and P_o *and* P_h are the surviving fractions for *oxic and hypoxic* clonogens, respectively;

$\overline{\ln(N)}$ is the mean of number of tumour clonogens characterized by a standard deviation $\sigma_{\overline{\ln(N)}}$

Ruggeri and Nahum M.Phys. 2006; 33:4044-4055

- The P_i can be written as follows:

$$P_o = (1-\eta)\cdot S_0^n(d)$$

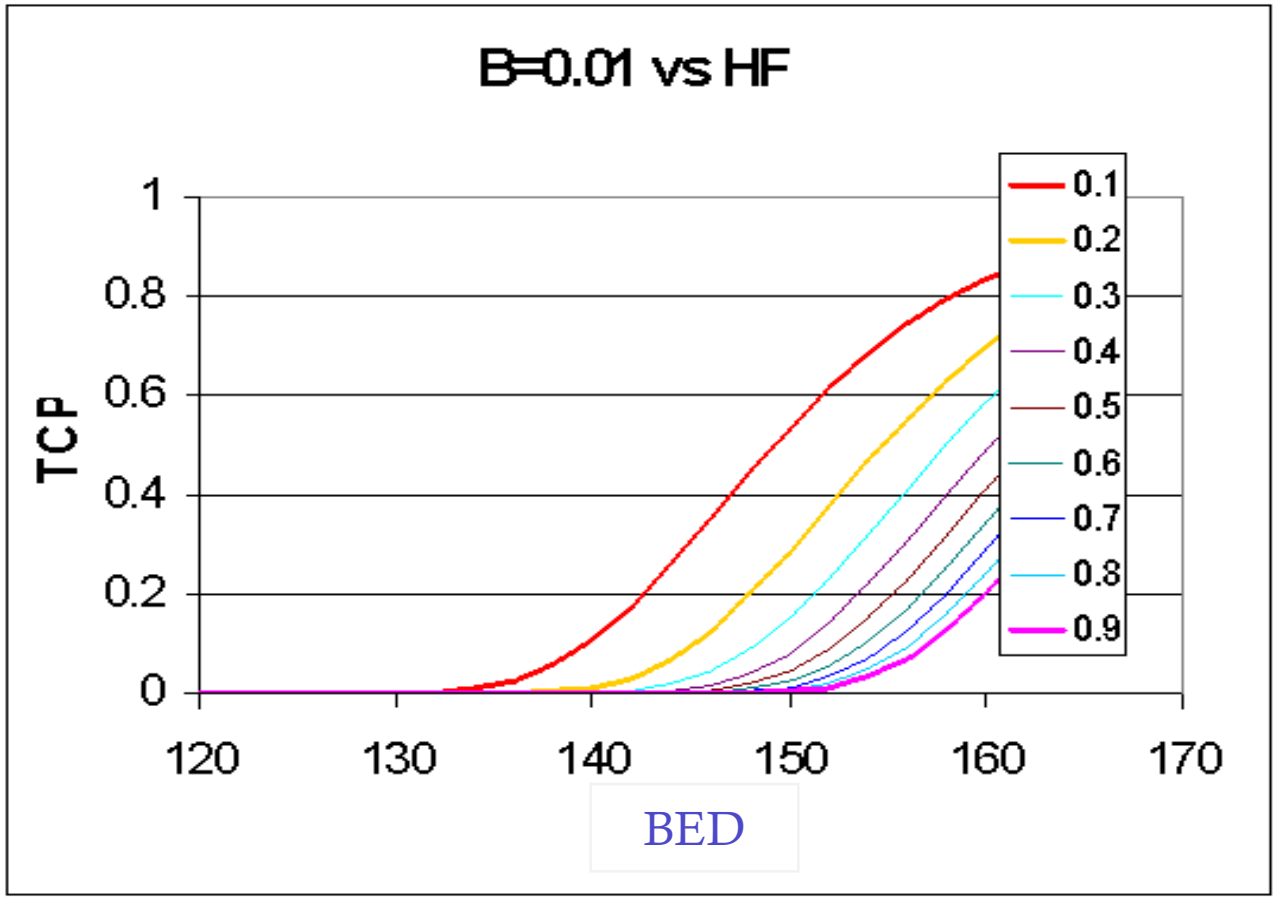
$$P_h = \eta(1-B)^{n-1}\cdot S_h^n(d) + \eta\cdot B\left\{\sum_{k=1}^{n-1}(1-B)^{n-1-k}S_h^{n-k}(d)\cdot S_0^k(d)\right\}$$

where:

- η is the ***hypoxic fraction***
- the *k*-th term in the summation takes into account that fraction of the *h*-clonogens which undergoes ***reoxygenation*** after (*n*-*k*) irradiations only, thus undergoing the remaining *k* fractions in a well-oxygenated state

VARYING HYPOXIC FRACTION IN A TUMOR

No	10^9	cells
HF	variable	
Teff	300	days
ΔT	1.4	days
B	0.01	
αo	0.21	Gy^{-1}
βo	0.14	Gy^{-2}
αh	0.12	Gy^{-1}
βh	0.013	Gy^{-2}



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Seminars in
RADIATION
ONCOLOGY

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.
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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"

Question 1: IS THE LQ MODEL APPROPRIATE TO MODEL EFFECTS IN SBRT?

POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Colin G. Orton, Professor Emeritus, Wayne State University, Detroit: ortonc@comcast.net. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery

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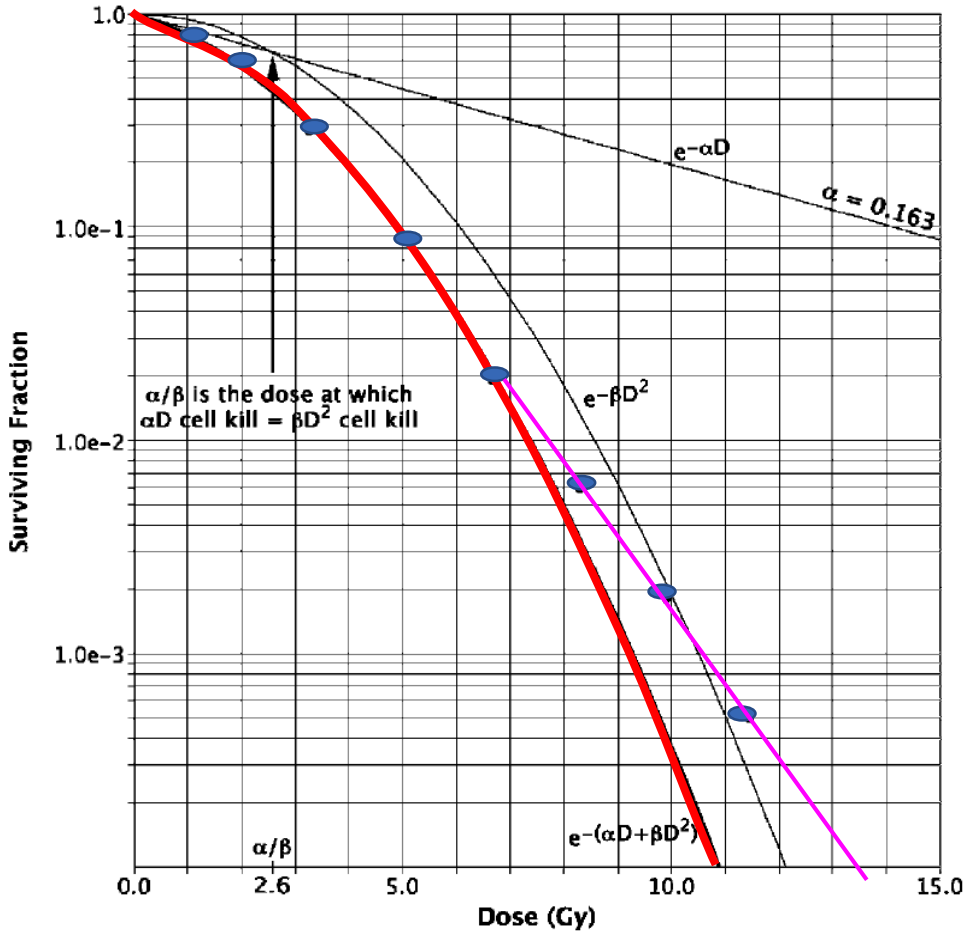
LQ poor

High-dose linear component could be achieved by assuming a higher α/β rationale for higher α/β in rapidly proliferating & hypoxic tumors

Fowler J F 2008 **Linear quadratics is alive and well**: in regard to Park et al. (Int J Radiat Oncol Biol Phys 2008;70:847-852) *Int J Radiat Oncol Biol Phys.* **72** 957

Astrahan, Med. Phys. 2008



$$D_T = 2\alpha / \beta$$

$$\gamma = tg\left(@\, D_T\right)$$

On the log-linear plot, the **LQ** curve closely fits these experimental results for Chinese hamster **cells** in culture up to a dose of 6 Gy, but then continues to bend.

The experimental results are observed to become **linear** at high dose.

$$BED_n(D) = D + \frac{D^2}{\alpha / \beta} \qquad D < D_T$$

$$BED_n(D) = D_T + \frac{D_T^{\,2}}{\alpha / \beta} + \frac{\gamma}{\alpha}\left(D - D_T\right) \qquad D \geq D_T$$

LQL

MODELS

LQ

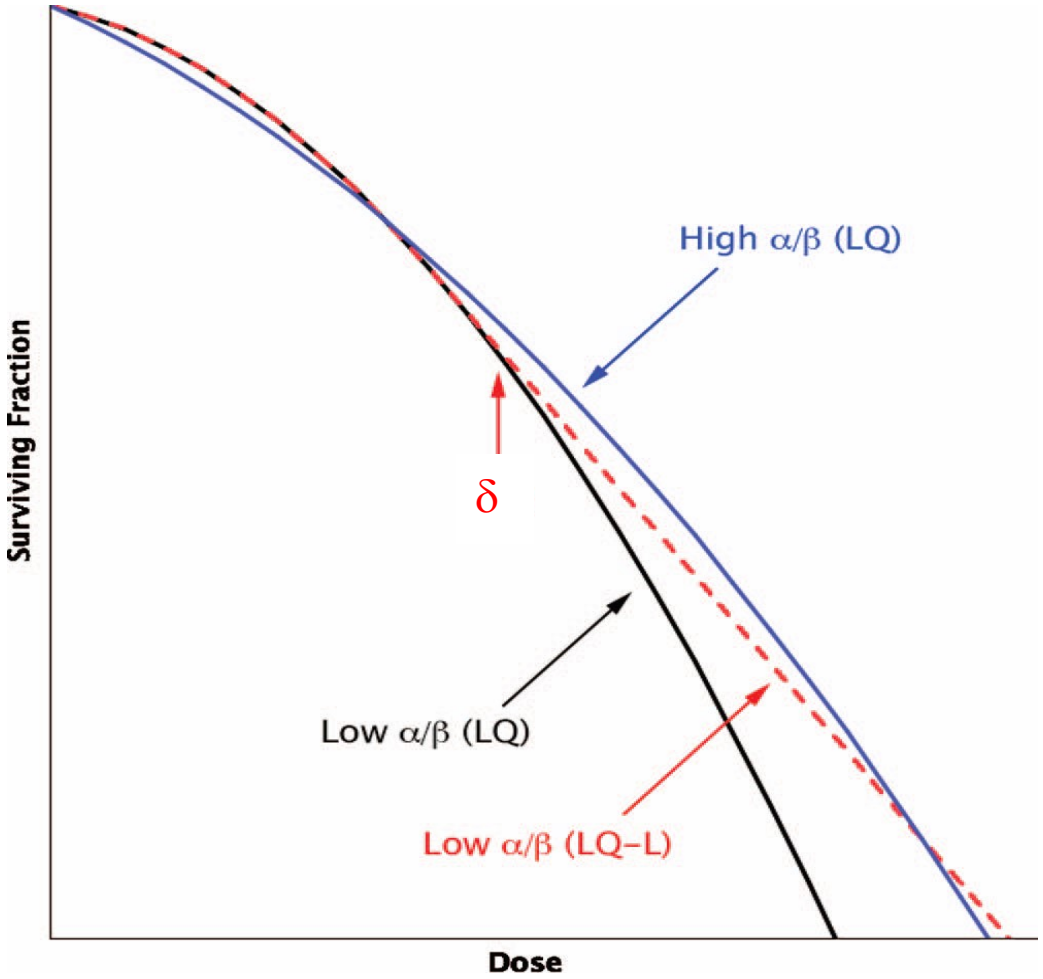
$$S_0(d) = \exp[-d(\alpha_0 + \beta_0 d)]$$

$$S_h(d) = \exp[-d(\alpha_h + \beta_h d)]$$

$$\alpha_h = \frac{\alpha_0}{OER_\alpha}$$

$$\beta_h = \frac{\beta_0}{OER_\beta{}^2}$$

$$R(\Delta t) = 2^{\frac{\Delta t}{T_{eff}}}$$



LQ-L

$$S_0(d) = \exp[-d(\alpha_0 + G(\lambda T)\cdot \beta_0 d)]$$

$$S_h(d) = \exp[-d(\alpha_h + G(\lambda T)\cdot \beta_h d)]$$

$$G(\lambda) = 2\frac{\lambda T + \exp(-\lambda T) - 1}{(\lambda T)^2}$$

$$\lambda = \lambda_0 + \delta \cdot \dot{d}$$

$$\alpha_h = \frac{\alpha_0}{OER_\alpha}$$

$$\beta_h = \frac{\beta_0}{OER_\beta{}^2}$$

Guerrero M et al. 2004

PARAMETERS

N_0, η, T_{eff}, α_0, β_0 Nahum et al. 2003

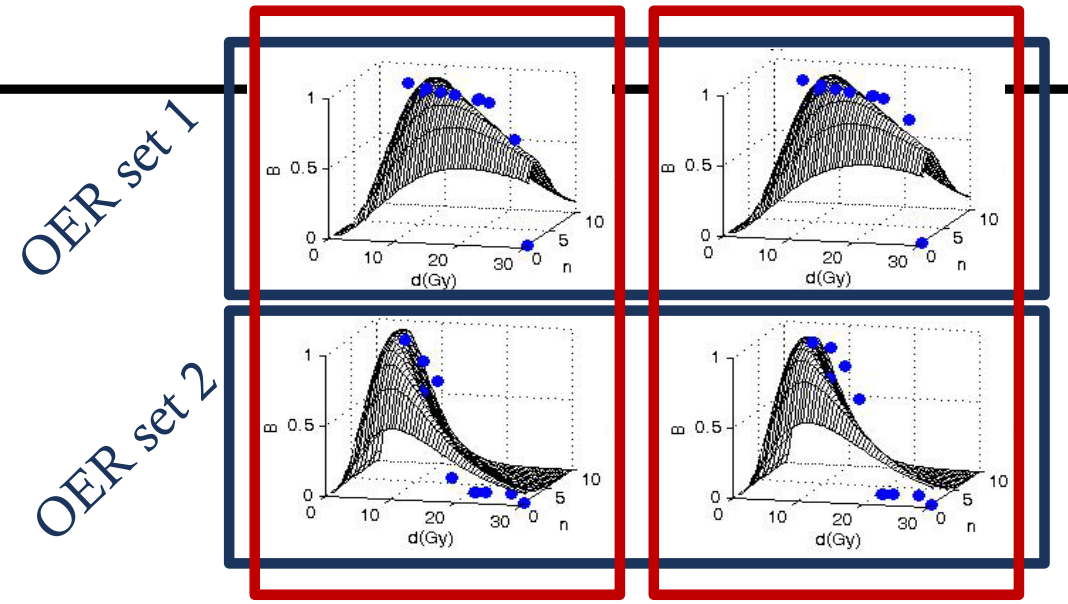
α_h, β_h Carlson et al. 2006

TABLE I. Schedules of stereotactic hypofractionated radiotherapy on stage I NSCLC with experimental LC3.

Authors	Year	# pat.	# fr.	d (Gy)	p.i. (%)	Δt (days)	LC3 (%)
Nyman *et al.*	2005	45	3	15	100	2	80
Nagata *et al.*	2005	45	4	12	100	4	97
Zimmerman *et al.*	2006	43	3	12.5	60	1	88
Baumann *et al.*[a]	2006	138	3.03	13.39	65	2.5	85
Fritz *et al.*	2007	40	1	30	100	0	81
Koto *et al.*[a]	2007	31	4.07	11.6	100	2	63
Baumann *et al.*	2009	57	3	15	67	2	92
Fakiris *et al.*[a]	2009	35	3	21.03	80	2.5	88.1
Kopek *et al.*[a]	2009	88	3	17.2	100	2.5	89
Mirri *et al.*	2009	40	5	8	95	2	72
Baba *et al.*[b]	2010	85	4	12	100	2.5	81
Baba *et al.*[b]	2010	37	4	13	100	2.5	74
Haasbeek *et al.*[a,b]	2010	193	4.85	12.37	80	1	89
Ricardi *et al.*[b]	2010	62	3	15	80	2	87.8
Matsuo *et al.*[b]	2011	101	4	12	100	3	86.8
Timmermann *et al.*[b]	2011	55	3	18	90	2.5	97.6

Note: abbreviations: d = dose/fraction; #pat. = number of patients; #fr = number of fractions; p.i. = prescription isodose; Δt = time between fractions; LC3 = local control at 3 yr. In the studies marked with 'a' multiple doses per fraction and fraction numbers were used, patient group-averaged values have therefore been calculated and listed in the table. 'b' indicates the validation set.

$B = f(d,n)$



LQ **LQ-L**

the extent of Reoxygenation

$$B = f(d,n)$$

Variable

TABLE III. Log-likelihood and AIC calculated using the validation set for different models (LQLM and LQM), OER parameter set, and fractions of hypoxic cells (η_h).

		LQM		LQLM	
η_h	Parameter	OER set 1	OER set 2	OER set 1	OER set 2
0.05	L	−588.1	−582.4	−589.8	−582.6
	AIC	−6.8	−6.7	−6.8	−6.7
0.10	L	−557.7	−554.9	−558.6	−554.8
	AIC	−6.6	−6.6	−6.7	−6.6
0.15	L	−545.6 (*)	−546.6(*)	−546.0(*)	−546.3(*)
	AIC	−6.6 (*)	−6.6(*)	−6.6(*)	−6.6(*)
0.50	L	−575.1	−600.8	−564.4	−596.4
	AIC	−6.7	−6.8	−6.7	−6.8
0.00	L	−1038.2		−1038.2	
	AIC	−12.9		−12.9	

Note: abbreviation: L = log-likelihood; AIC = Akaike information criterion see text; (*) indicates the maximum of the L or AIC values against the fraction of hypoxic cells.

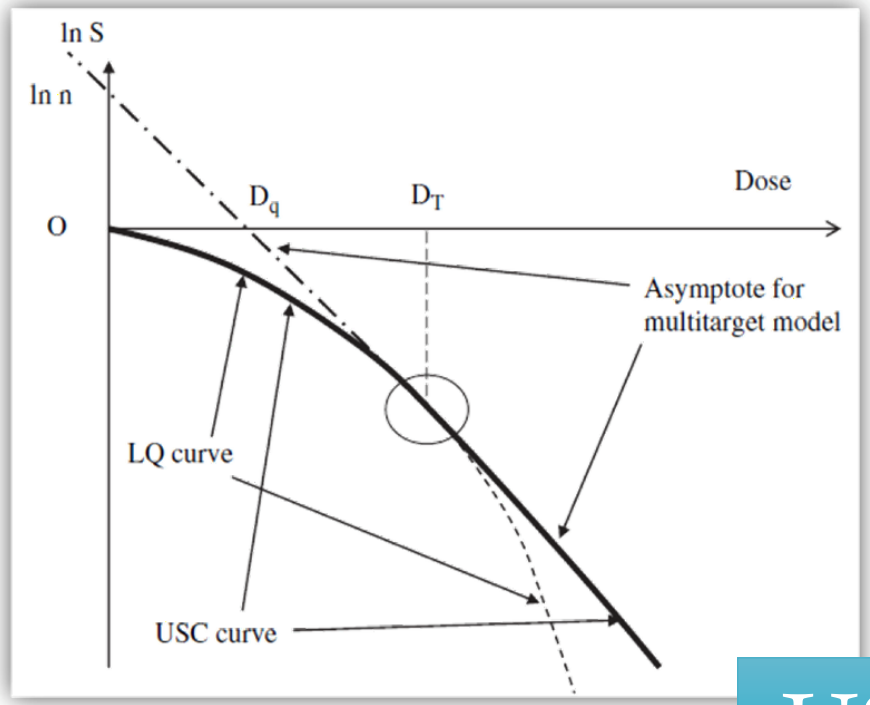
Strigari et al. 2012

Combine the LQ model with the multi-target model at high dose

$$S = e^{-d/d_1} \cdot \left\{1 - \left(1 - e^{-d/D_0}\right)^{\bar{n}}\right\}$$

$$\ln S \approx -\frac{1}{D_0}d + \ln(\bar{n}) = -\frac{1}{D_0}d + \frac{D_q}{D_0}$$

$$\ln S = \begin{cases} -(\alpha \cdot d + \beta \cdot d^2) & \text{if } d \le D_T \\ -\frac{1}{D_0}d + \frac{D_q}{D_0} & \text{if } d \ge D_T \end{cases}$$



USC

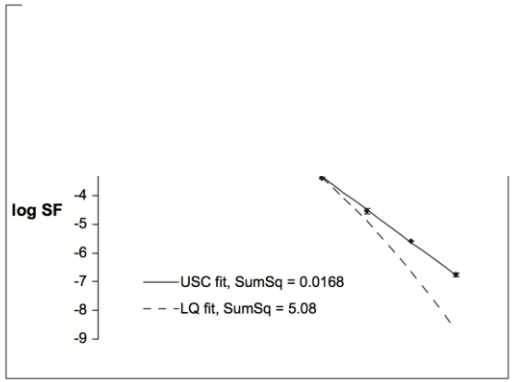
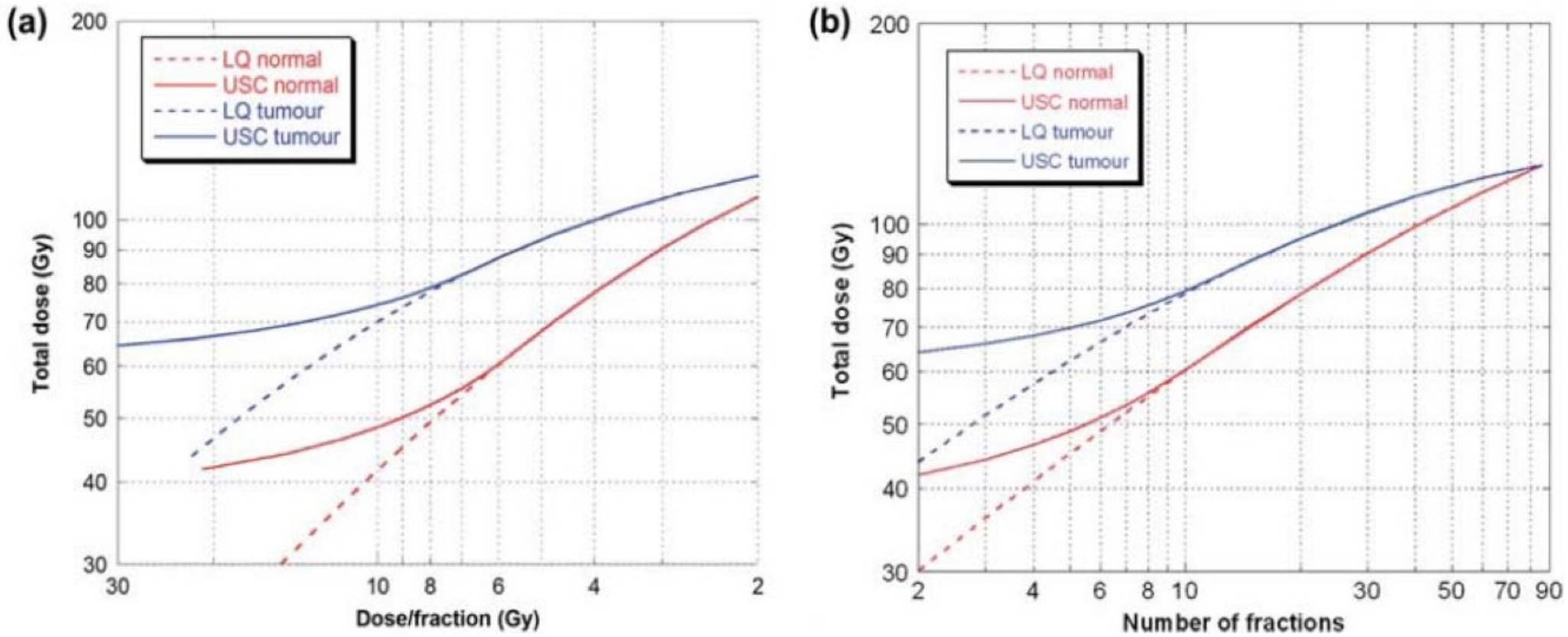


Fig. 4. Survival curve of H460 fitted with linear quadratic (LQ) model (using points ≤8 Gy) and with universal survival curve (USC) model. Fit over entire range drastically improved with USC model fit. If LQ model fit over entire dose range, sum of square improves compared with low-dose LQ model fit (sum of squares = 0.285) but still much inferior to USC model (data not shown). Details of generating this survival curve will be published separately.

$$D_{SBRT} = \alpha \cdot D_0 \cdot D_{CFRT} \cdot \left(1 + \frac{d_{CFRT}}{\alpha/\beta}\right) + n_{SBRT} \cdot D_q$$

$$D_{CFRT} = \frac{1}{\alpha \cdot D_0} \cdot \frac{D_{SBRT} - n_{SBRT} \cdot D_q}{\left(1 + \frac{d_{CFRT}}{\alpha/\beta}\right)}$$

Isoeffect curves for (a) tumors and (b) normal tissues, calculated with LQ and USC



The steepness of the curves differs considerably for d> 6 Gy
USC predicts greater sparing OARs outside PTV than LQ

Wennberg et al. 2013

LQ MODEL TENDS TO OVERESTIMATE THE EFFECTIVENESS OF CELL KILLING BY A SINGLE HIGH DOSE

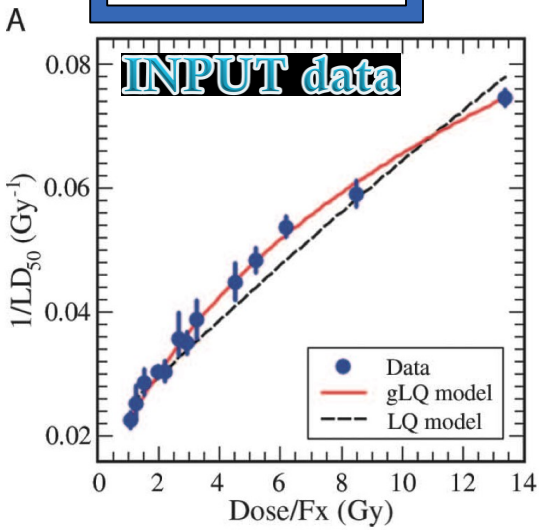
- The essential problem stems from ignoring the **reduction of sublethal damage after conversion to lethal damage**; therefore the pool size of the sublethals lesions which are available to be converted to lethal lesions with further irradiation is **overestimated** (*Wang JZ et al. Sci Transl Med. 2010*)

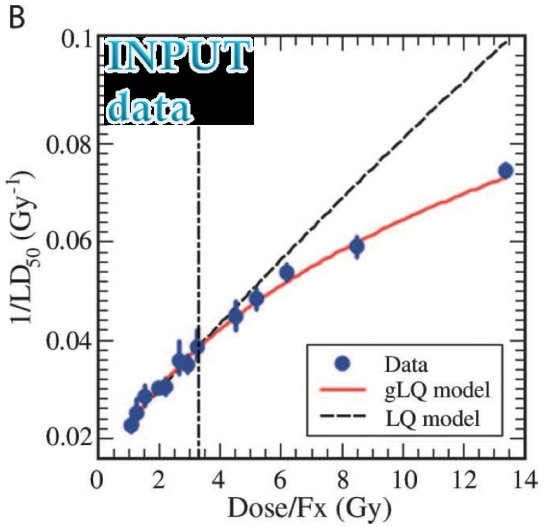
gLQ : α = 0.11/Gy, α/β=0.82 Gy

LQ: α=0.40/Gy **α/β= 16 Gy**

gLQ: α = 0.10/Gy, α/β = 0.80 Gy

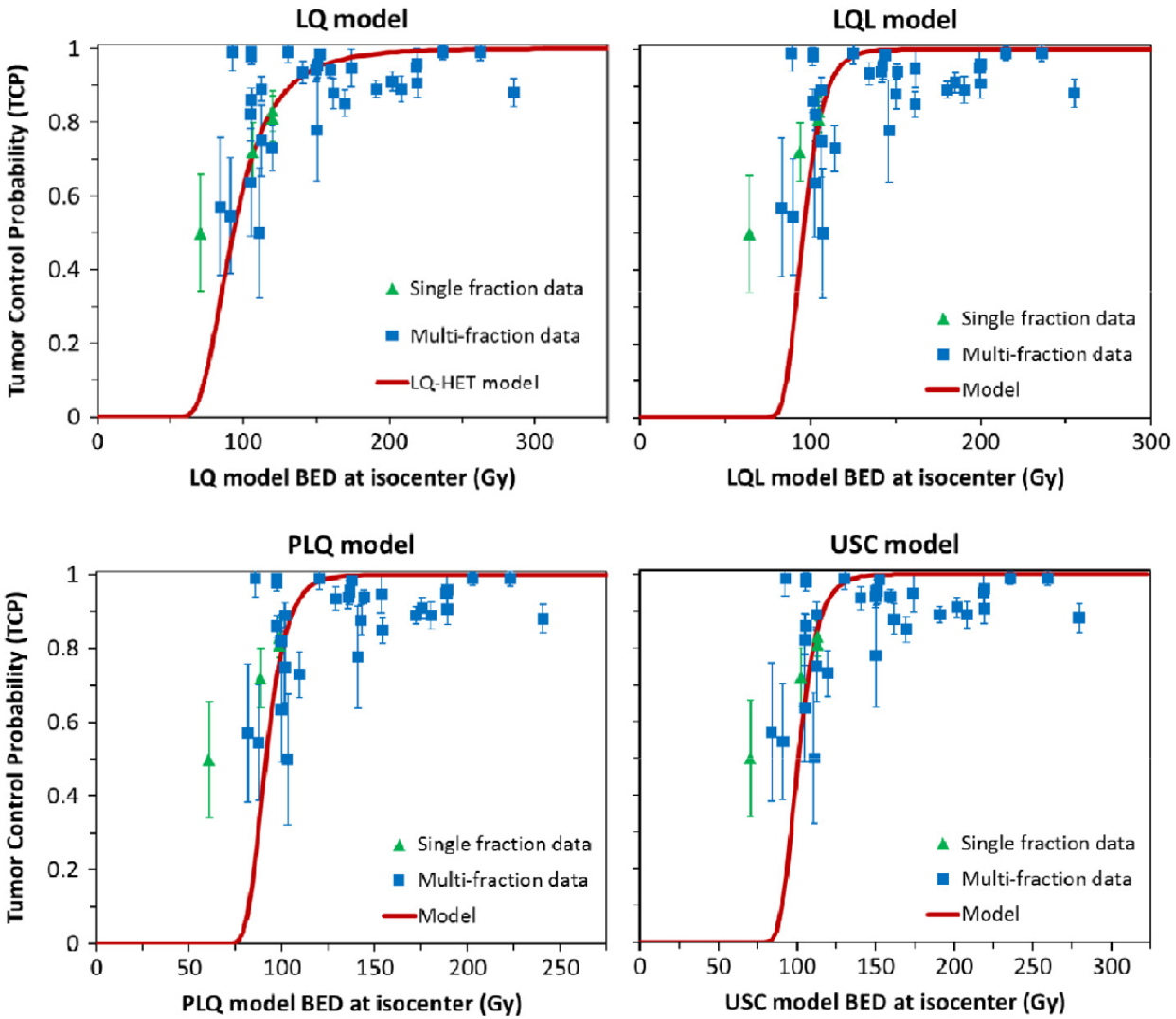
LQ: α = 0.15/Gy, α/β = 2.0 Gy





gLQ

Analysis of tumor control data from 2965 patients



Best fits to data on early-stage NSCLC from the LQ model with heterogeneous radiosensitivity (LQ), and from the LQL, PLQ and USC models with homogeneous radiosensitivity.

LQ model with heterogeneous radiosensitivity provides a much better description of the SBRT TCP data as compared with the models which include an extra high-dose mechanism.

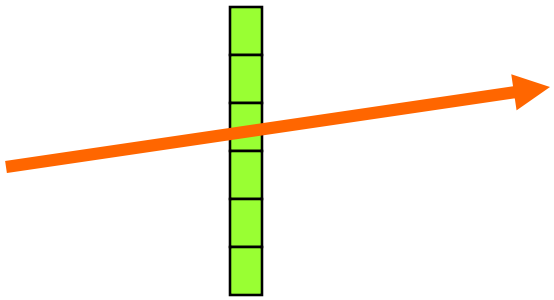
Shuryaka et al. 2015

RADIOBIOLOGY: NORMAL TISSUES

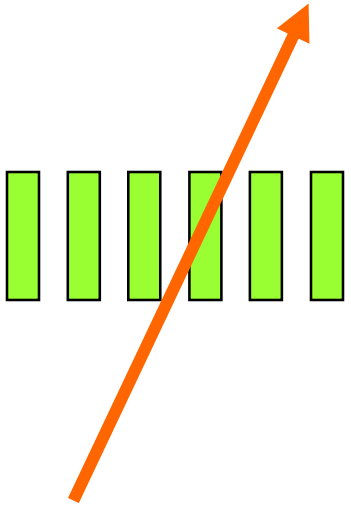
- Sparing of normal tissues is essential for good therapeutic outcome
- The radiobiology of normal tissues may be even more complex than tumours:
  - different organs respond differently
  - there is a response of a cell organization not just of a single cell
  - repair of damage is, in general more important

DIFFERENT TISSUE TYPES

- Serial organs (*e.g.* spine)



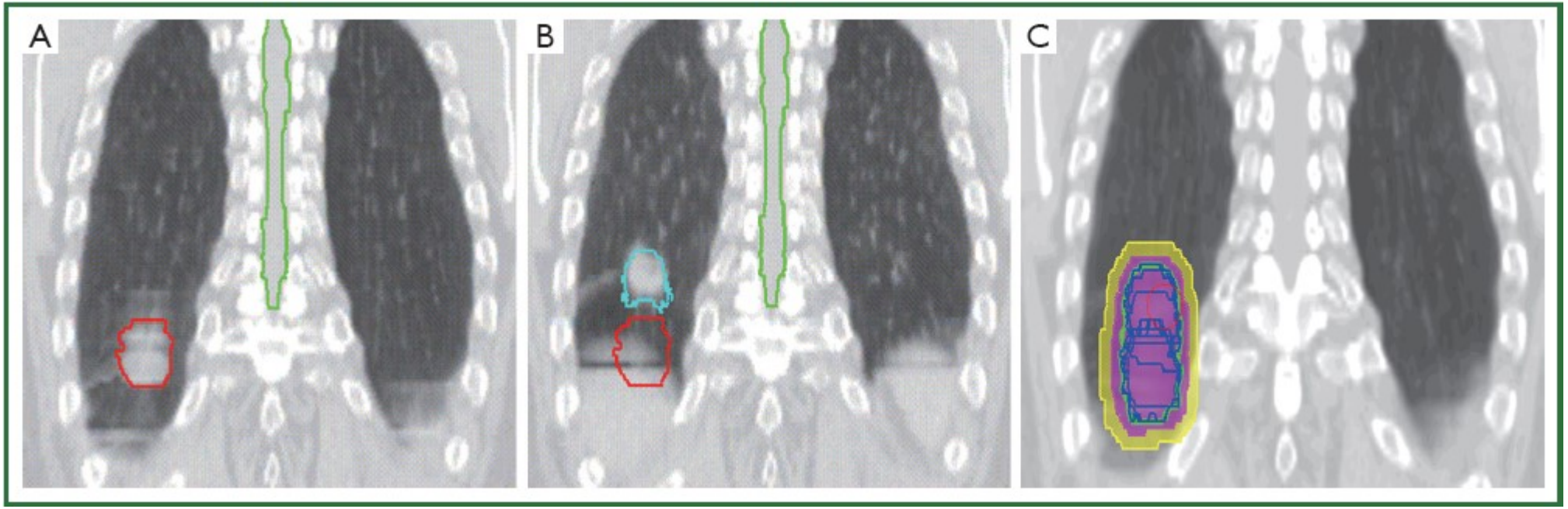
- Parallel organs (*e.g.* lung)



Effect of radiation on the organ is different

VOLUME EFFECTS

- The more normal tissue is irradiated in parallel organs
  - the greater the pain for the patient
  - the more chance that a whole organ fails
- Rule of thumb - the greater the volume the smaller the dose should be
- In serial organs even a small volume irradiated beyond a threshold can lead to whole organ failure (*e.g.* spinal cord)



- **Figure 1** 4DCT images of an early-stage lung cancer patient at end-inhalation (A); end exhalation (B); and contours from all 10 phases of the 4DCT combined (C).
  Abbreviation: 4DCT, four-dimensional computed tomography.

MODELING NTCP

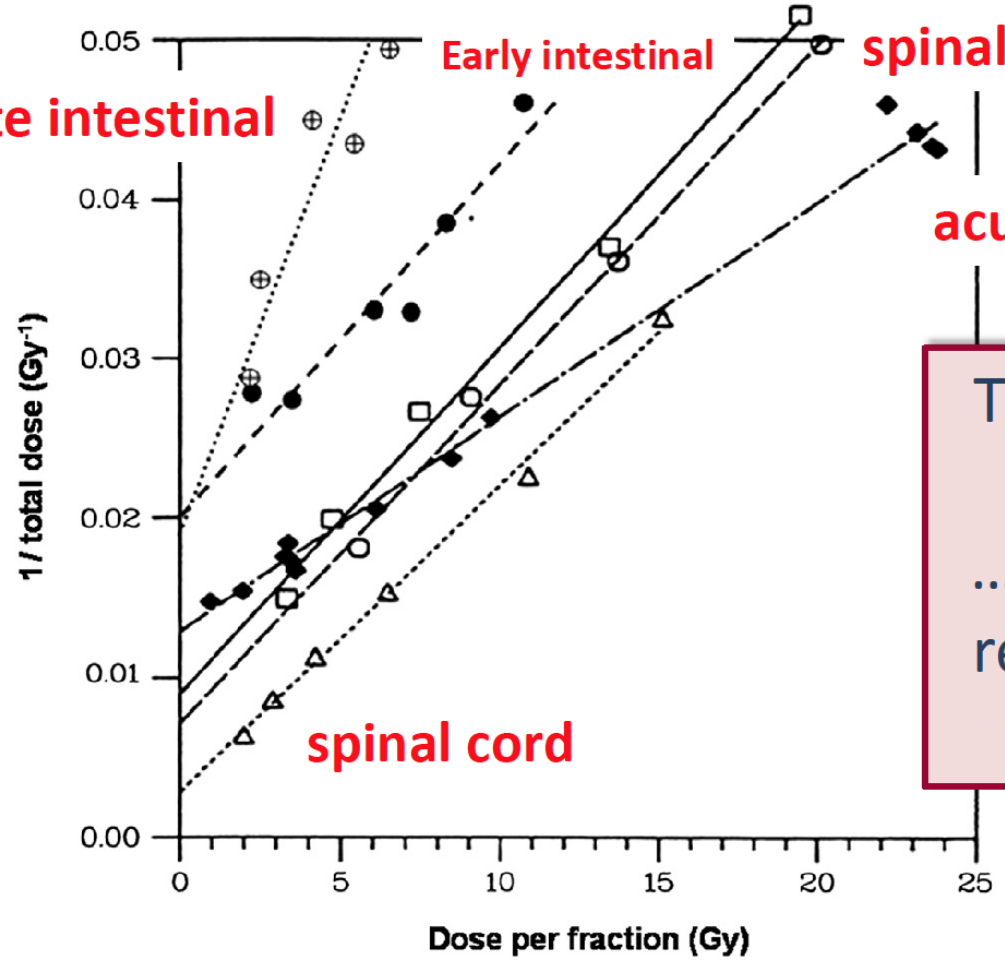
Mathematical models are useful to simulate the reality of experimental data and predict the behavior of an effect where data points are not readily available.

There are two different philosophies:

- an **empirical** approach
  - *the emphasis is on being able to describe the data using* ***simple mathematical functions***
- a **mechanistic** approach
  - *the emphasis is on being* ***able to describe the underlying mechanisms***

Ideally the best model should satisfy both goals

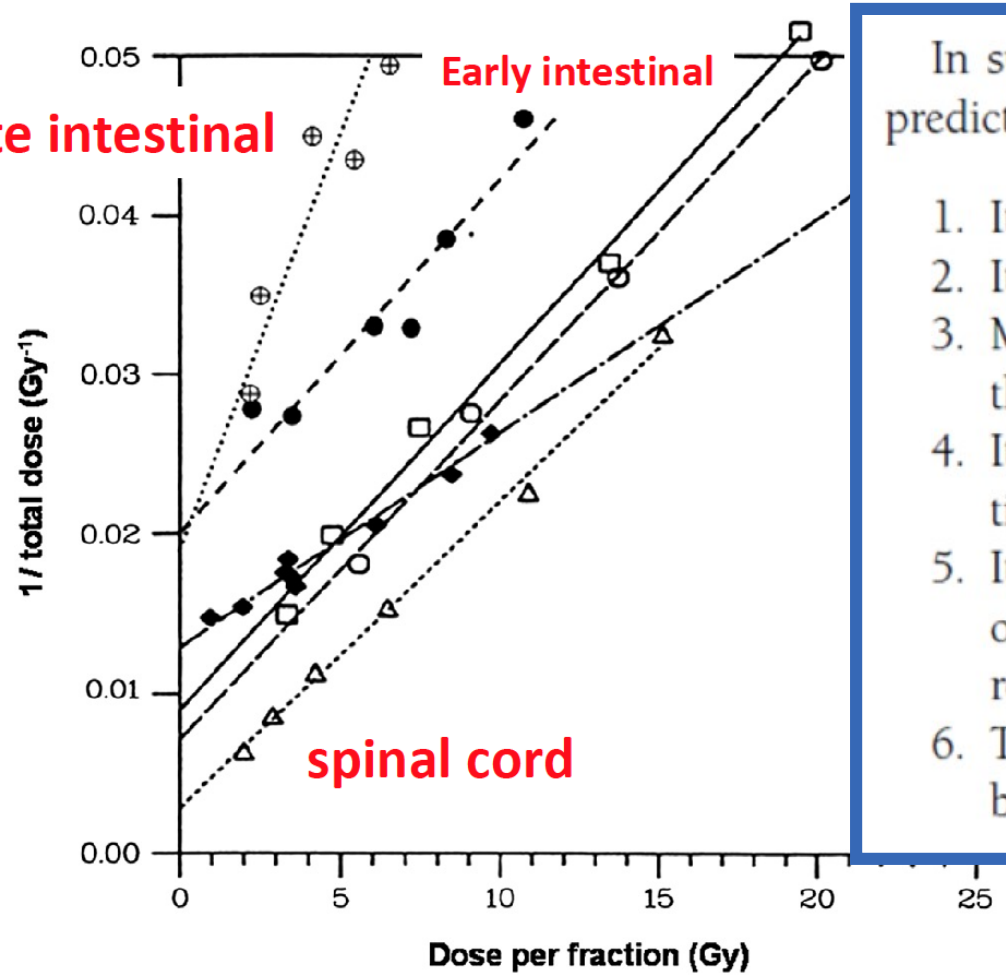
The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction



The data are plotted as "reciprocal-dose" .....if data follow an LQ relationship, the points fall on a straight line.

Brenner DJ, *Semin Rad Onc* 2008;**18**:234-239

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



In summary, LQ has the following useful properties for predicting isoeffect doses:

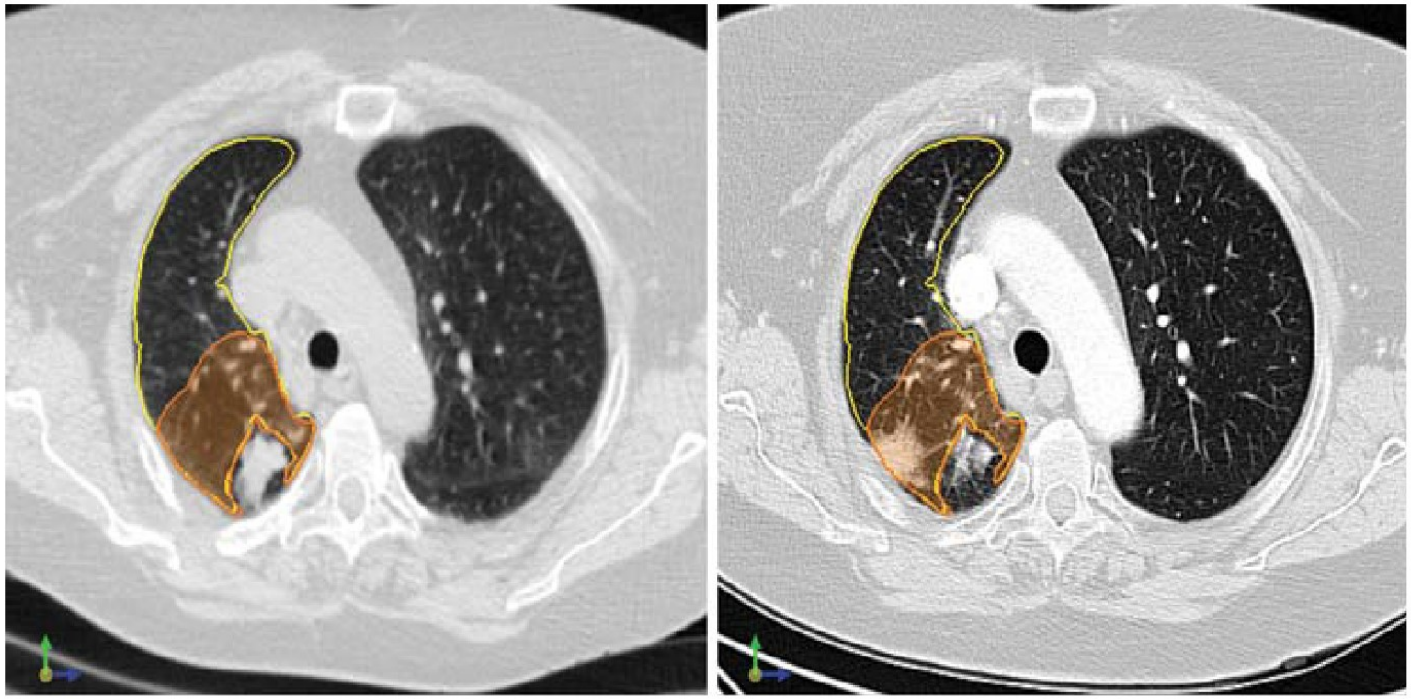
1. It is a mechanistic, biologically based model.
2. It has sufficiently few parameters to be practical.
3. Most other mechanistic models of cell killing predict the same fractionation dependencies as does LQ.
4. It has well-documented predictive properties for fractionation/dose-rate effects in the laboratory.
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.
6. To date, there is no evidence of problems when LQ has been applied in the clinic.

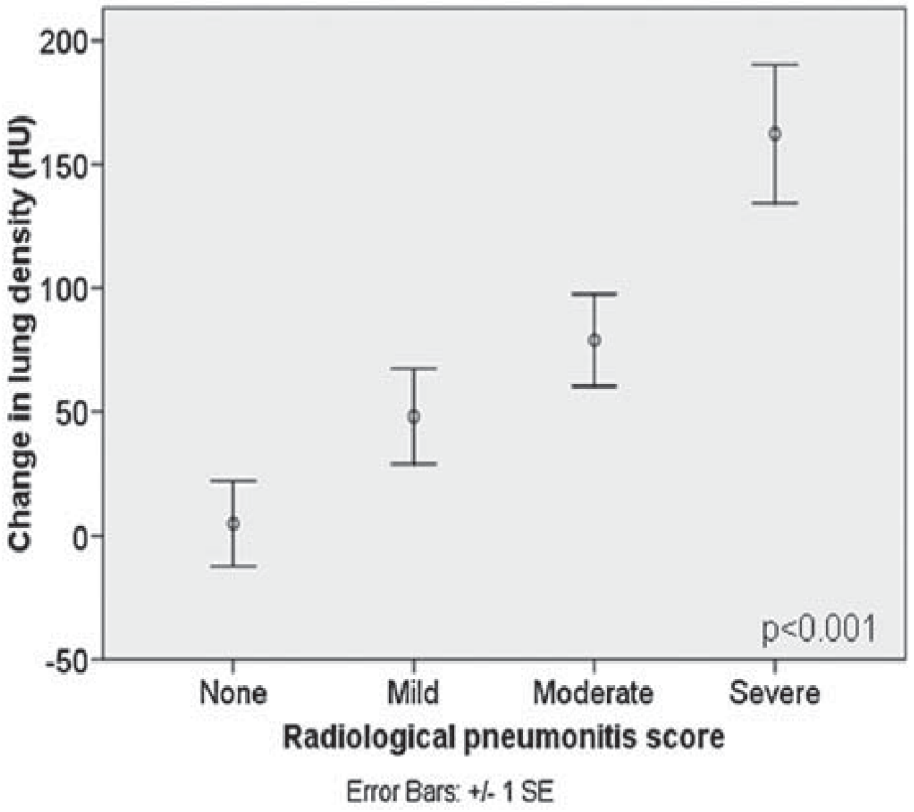
Brenner DJ, *Semin Rad Onc* 2008;**18**:234-239

From 10 to 18 Gy/fr.

DISCRIMINATION OF RADIOLOGICAL PNEUMONITIS AFTER SBRT

Changes in lung density in the peri-tumoral region (right) showed strong correlation with radiological pneumonitis.





Palma DA et al. 2011

VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

- IU 70 patient phase II study
- 20 Gy X 3 for T1
  22 Gy X 3 for T2
- NO restriction on tumor location

Zone of the Proximal Bronchial Tree

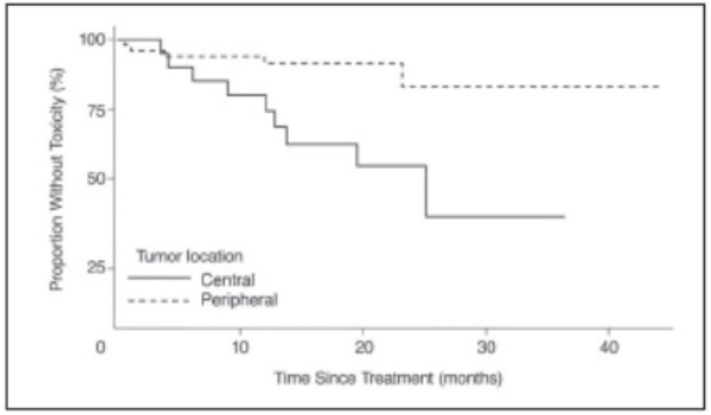
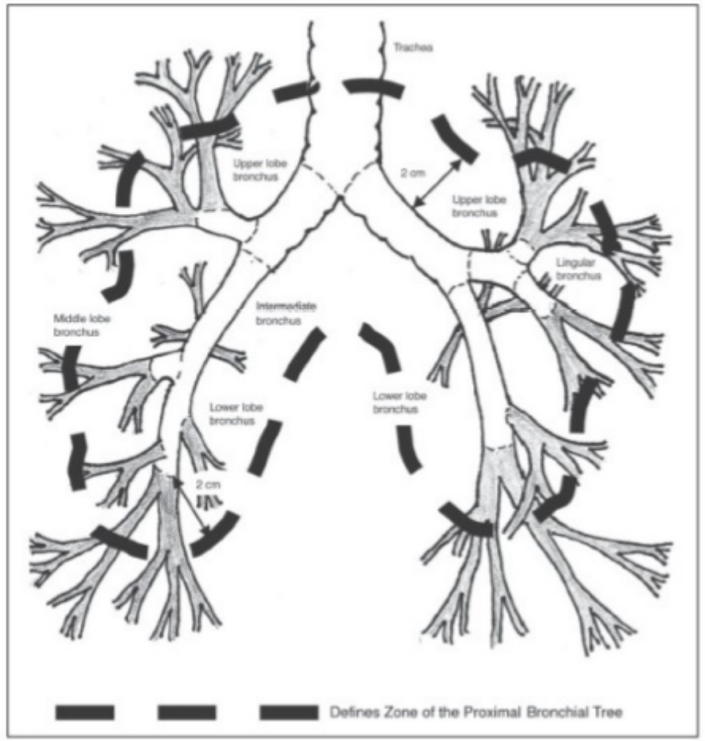


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.



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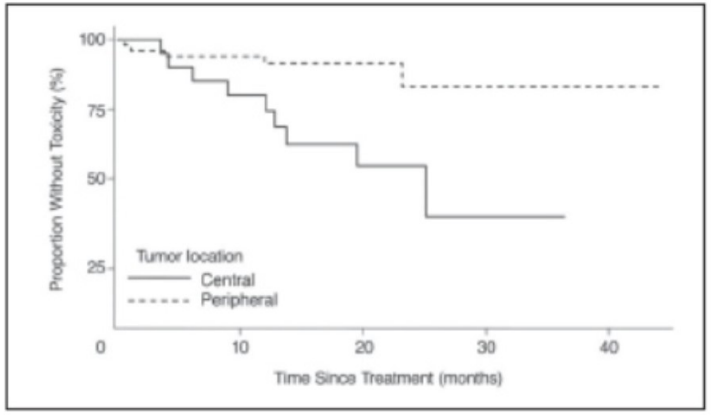


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

"Zone of the proximal bronchial tree" (figure)

Target dose homogeneity limits

Dose "isotropicity" limitation requiring falloff of approx 50% within 2 cm of PTV

V20 < 10%

Spinal cord, heart, esophagus, etc. limits

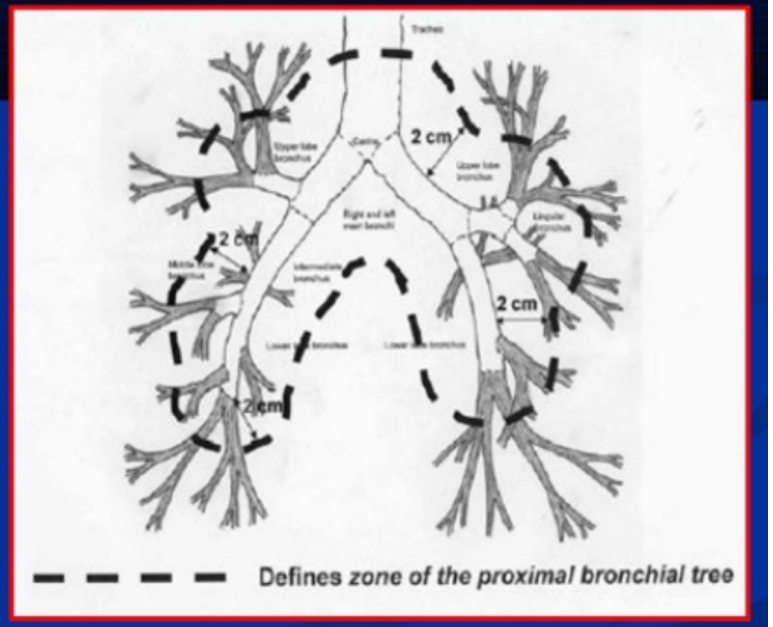
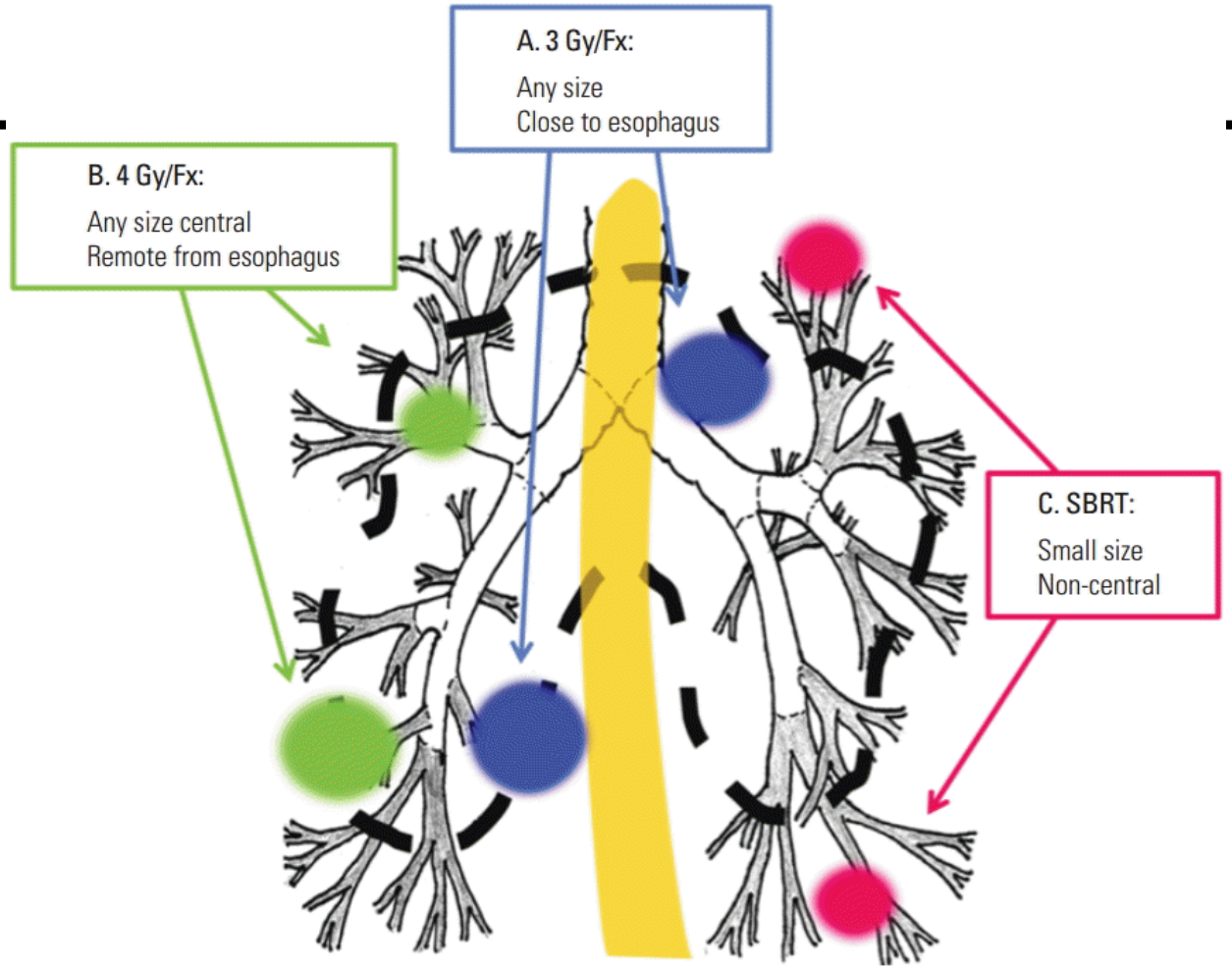


Illustration of selection criteria of fractionation scheme in the current study. SBRT, stereotactic body radiation therapy.

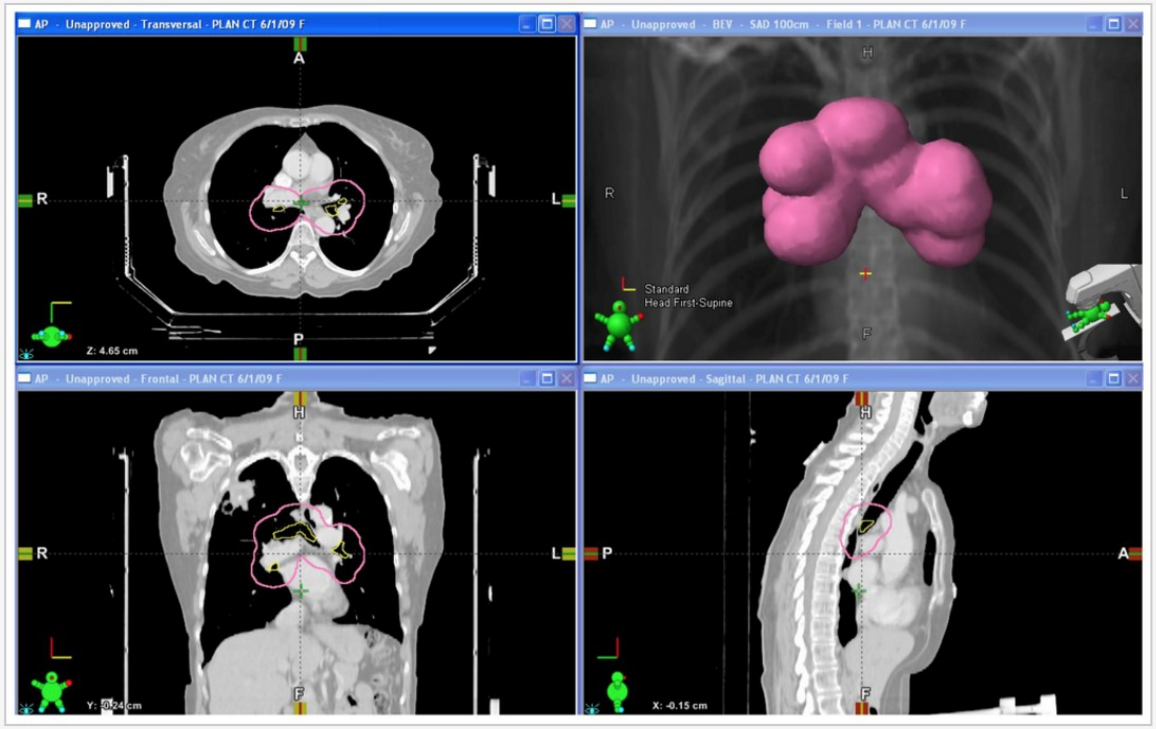
- Patients' characteristics
- Failure patterns and clinical outcomes
- Prognostic factors by uni- and multi-variate analysis
- Radiation therapy related morbidities



Period	A Any size, close to esophagus	B Any size, remote from esophagus	C Small size, non-central
2001-2010	Group 1: 60 Gy/20 fractions		SBRT: 60 Gy/4 fractions
2011~	Group 2: 60 Gy/20 fractions	Group 3: 60 Gy/15 fractions	

COMPLICATIONS FROM SBRT FOR LUNG CANCER

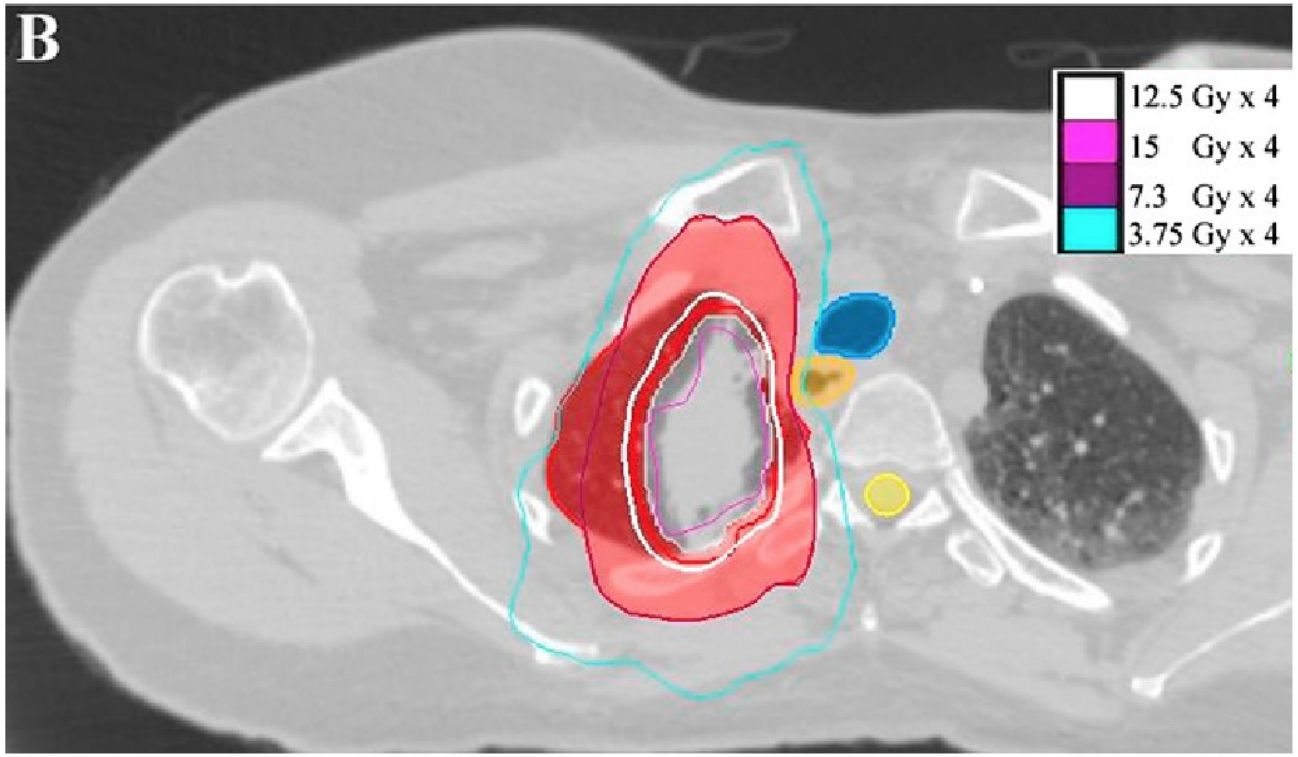
Figure 1. Diagrams of the proximal bronchial tree and the surrounding 2 cm avoidance zone. Upper left: Axial view; Lower left: Coronal view; Upper right: 3-dimensional representation of the avoidance zone; Lower right: Sagittal view.



Avoidance zone

Kang et al. 2015

Red Shell: High-risk Zone

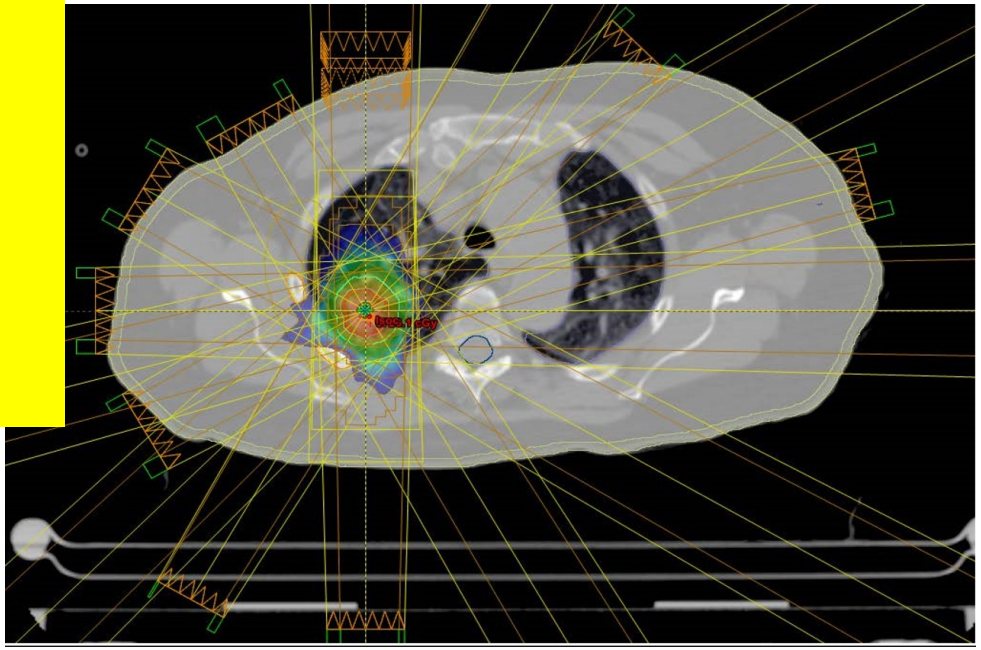


critical structures: esophagus in orange, spinal cord in yellow and trachea in blue.

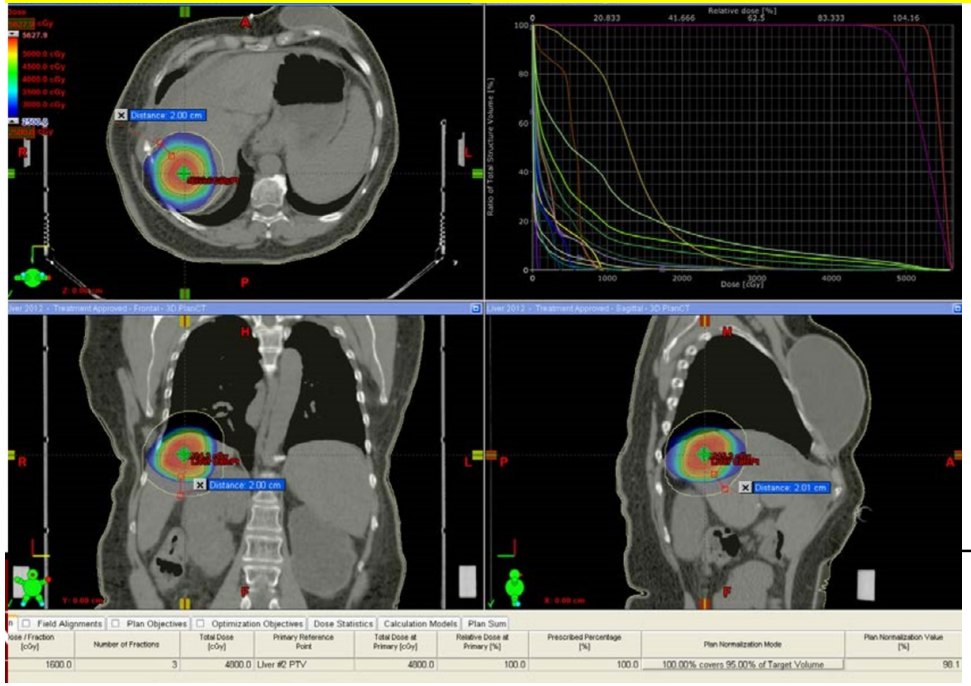
Yang et al. 2010

PLAN REVIEW

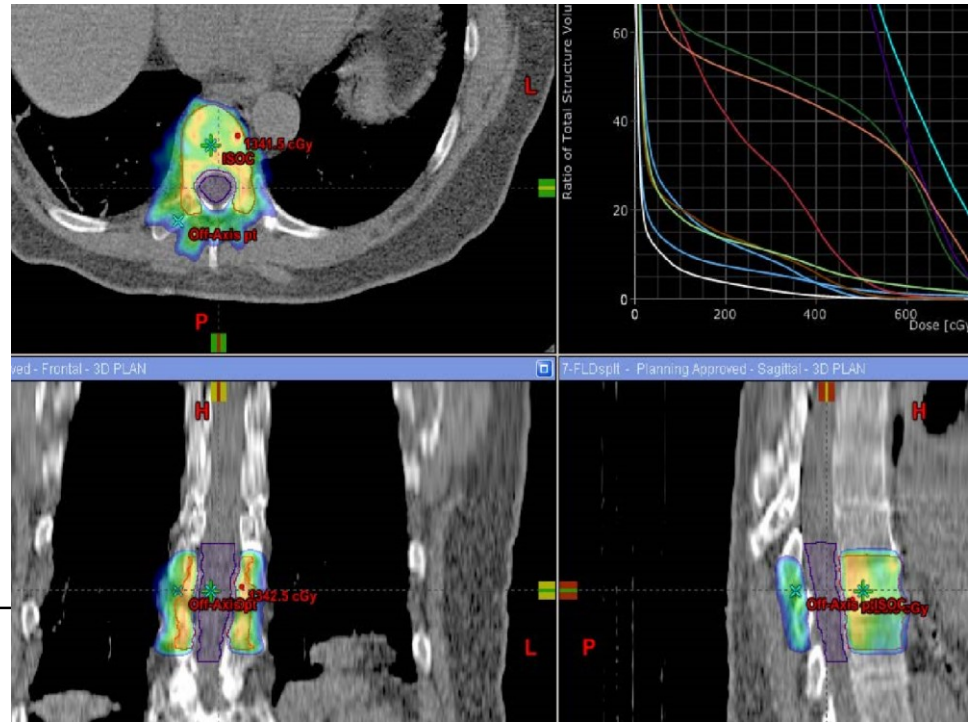
Example of Potential Toxicity:
- LOCATION
- Target is adjacent to chest wall and ribs.
- Target is lies in almost the same coronal plane as the spinal cord



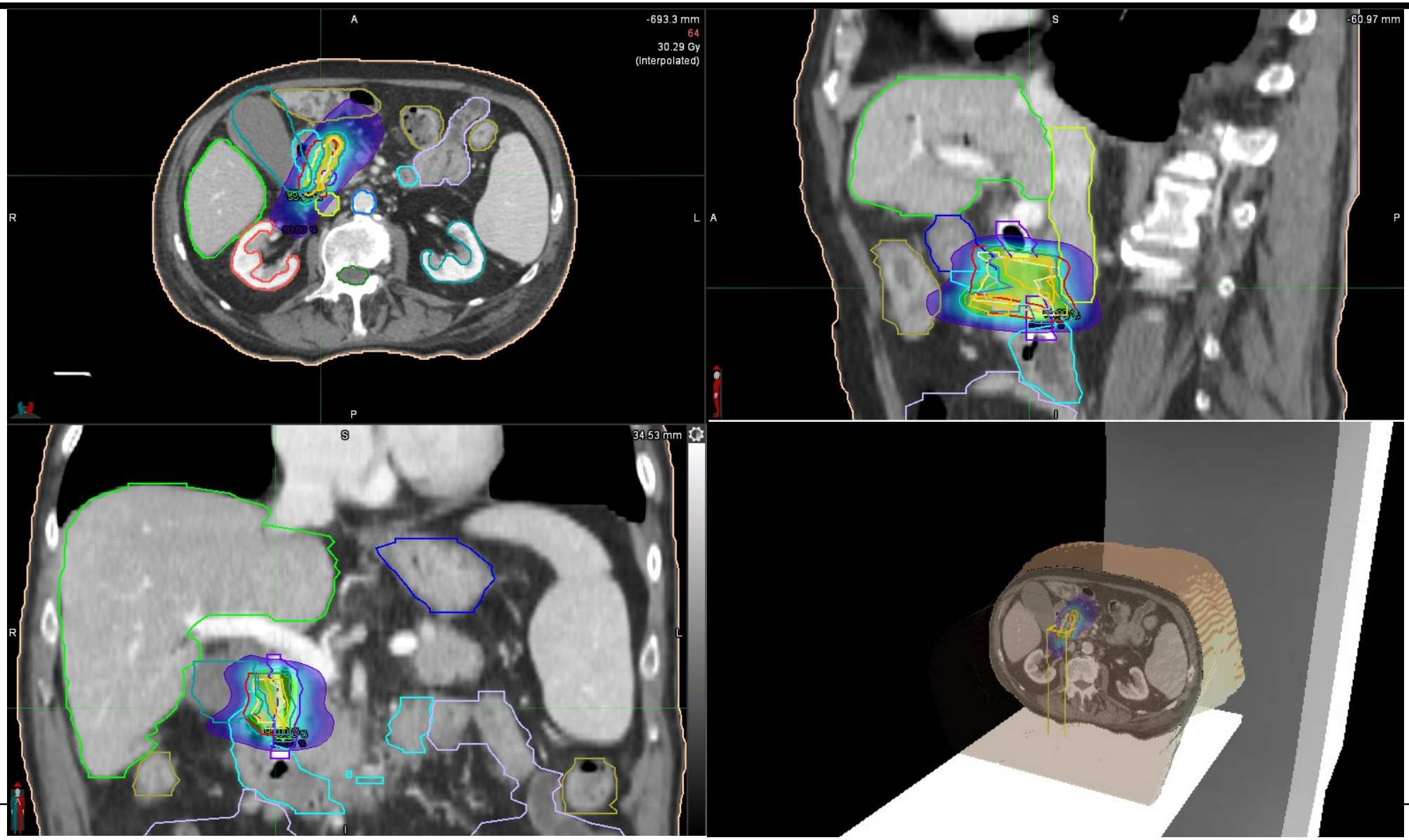
Example of Conformal Isodose plan meeting all published index guidelines. 50% isodose volume is not protruding through the PTV+2cm volume.



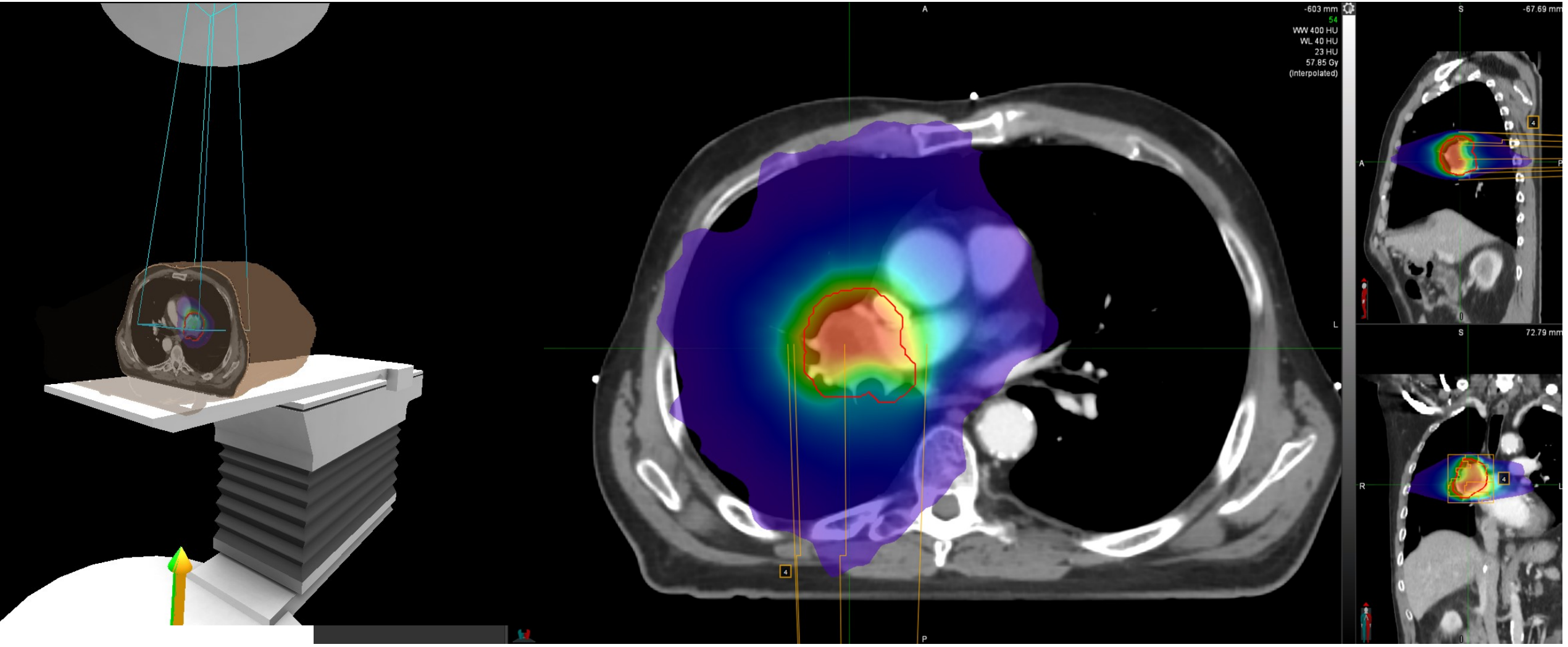
Spine with Cord Sparing



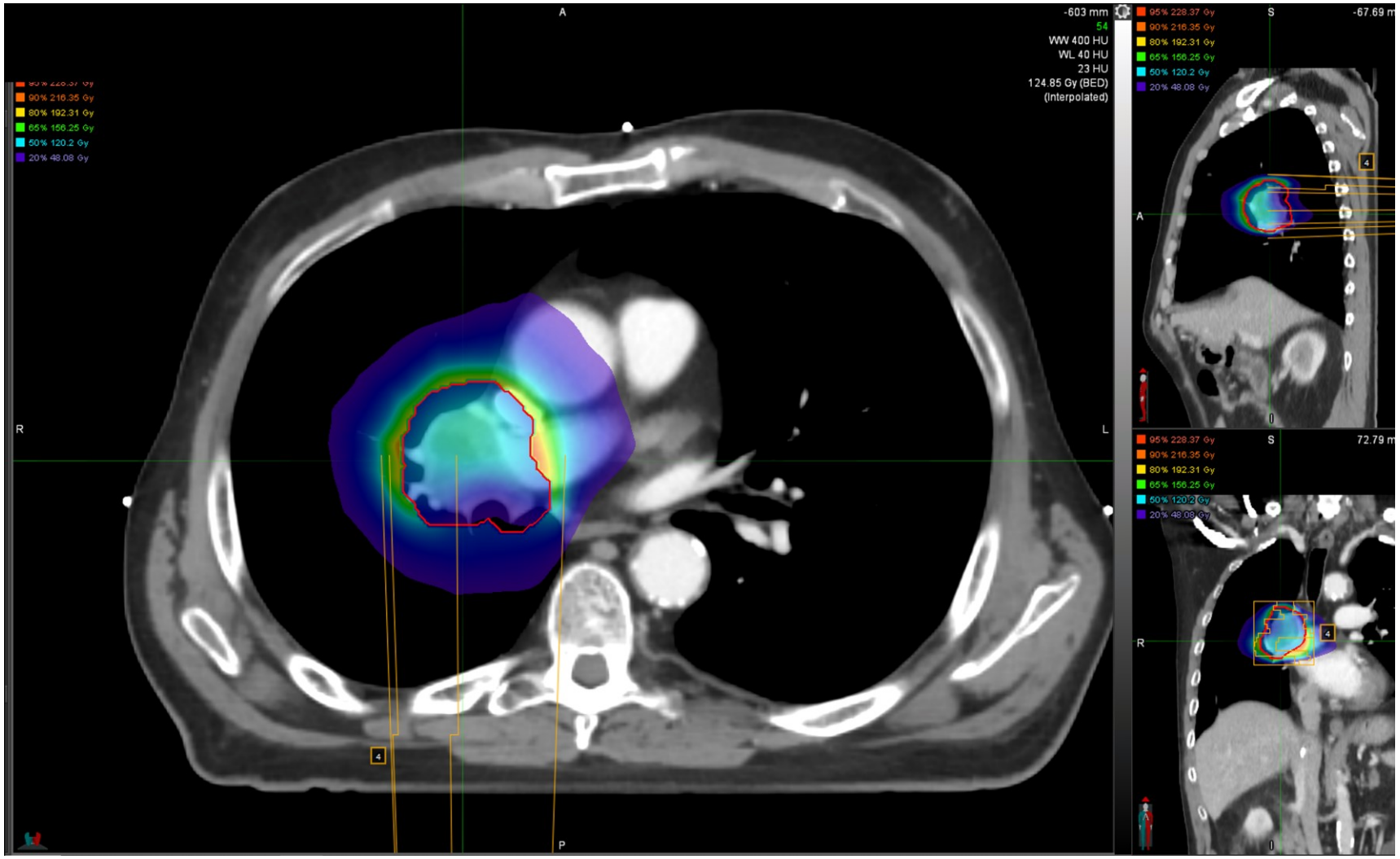
DETERMINING MATCHING PRIORITIES *Target volume vs Surrogate*



FROM ABSORBED DOSE TO BIOLOGICALLY EFFECTIVE DOSE



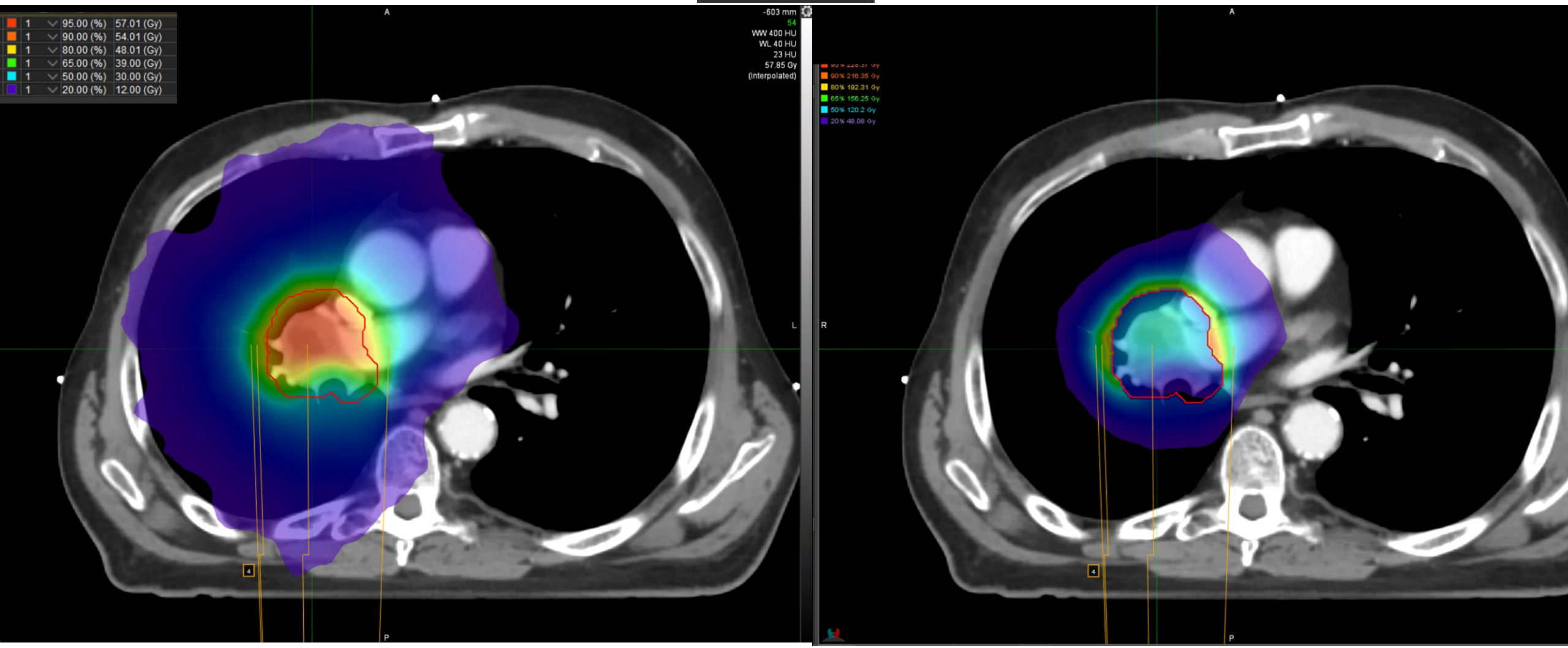
From absorbed dose to biologically effective dose



BED gradient

AD gradient

BED gradient



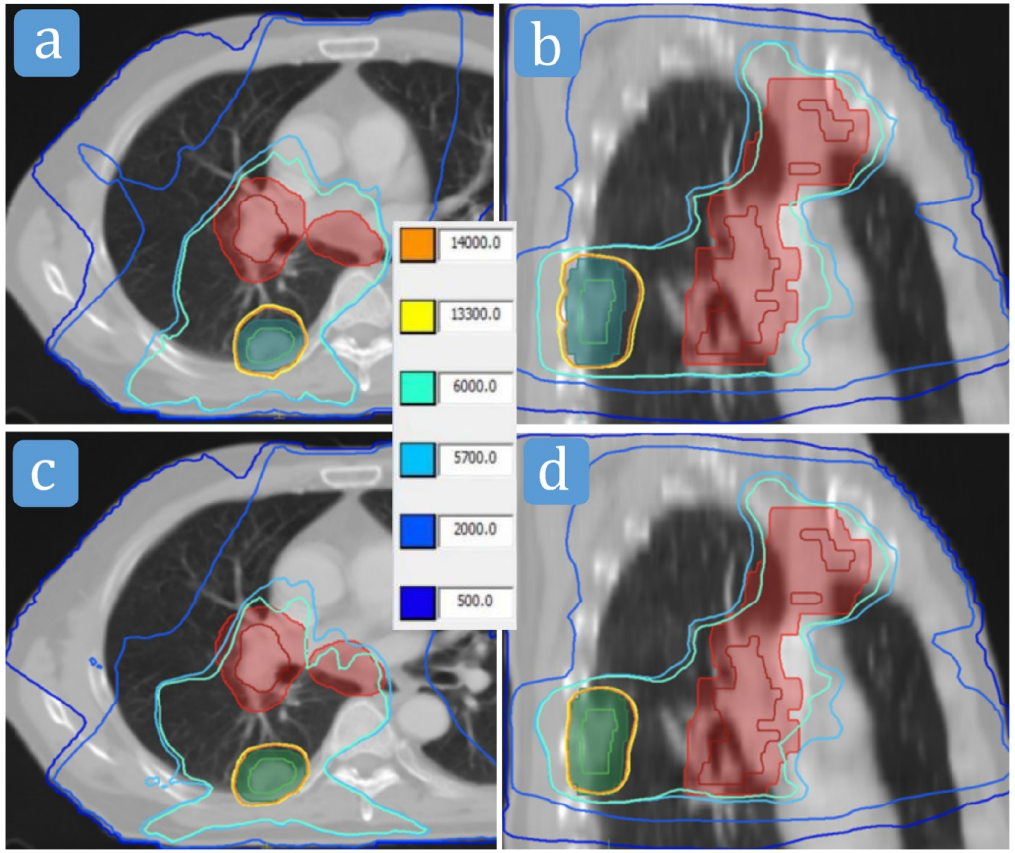


Figure 3. BED isodose lines of one patient's C & S plan were shown in axial (a) and coronal view (c). For comparison, BED isodose lines of the corresponding C & SIB plan were shown in axial view (b) and sagittal view (d). The absolute BED values were given in the legend as: 13 000 cGy (brown), 6800 cGy (yellow), 6000 cGy (green), 4500 cGy (dark green), 2000 cGy (blue), and 500 cGy (dark blue). α/β values: target 10, lung 3, spinal cord 2, esophagus 10, and heart 3.

Abbreviations: BED, biological equivalent dose; CFRT, conventional fraction radiotherapy; SBRT, stereotactic body radiotherapy; SIB, simultaneous integrated boost; C & S, CFRT and SBRT; C & SIB, CFRT and SIB.

Bold values in Table 2 indicate that the groups of data have statistical difference.

Voxel-Level BED Corrected Dosimetric and Radiobiological Assessment of 2 Kinds of Hybrid Radiotherapy Planning Methods for Stage III NSCLC

Wang, et al. 2022

IN PRACTICE ...

NORMAL TISSUES DOSE TOLERANCE IN SBRT

Hypofractionation Tissue Effects in Clinic (HyTEC)

ELSEVIER

2010

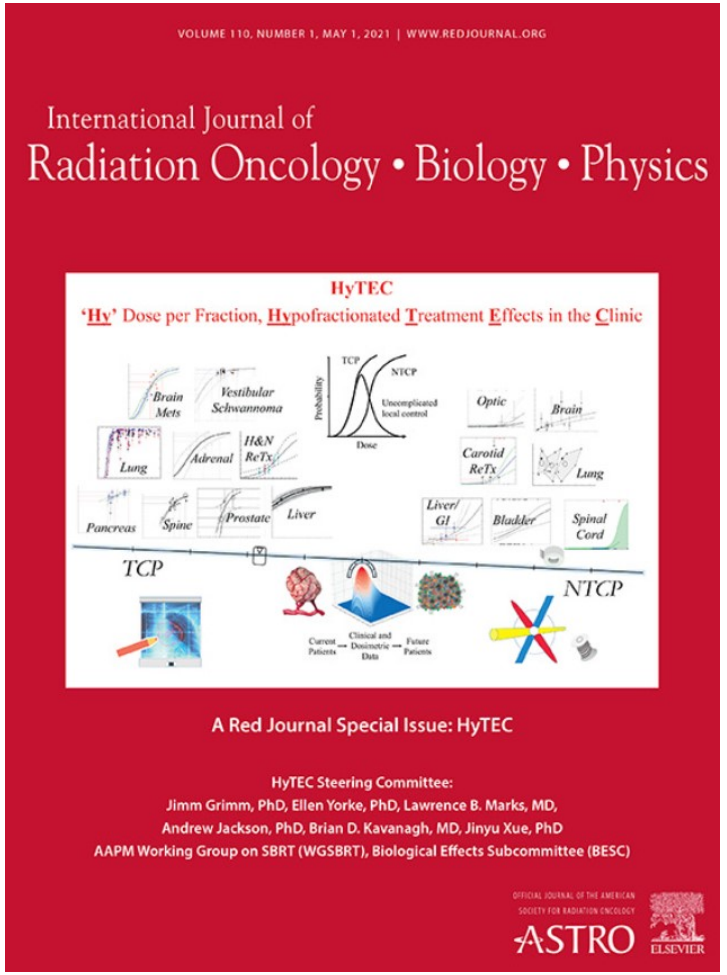
QUANTEC: ORGAN-SPECIFIC PAPER

ELSEVIER

2016

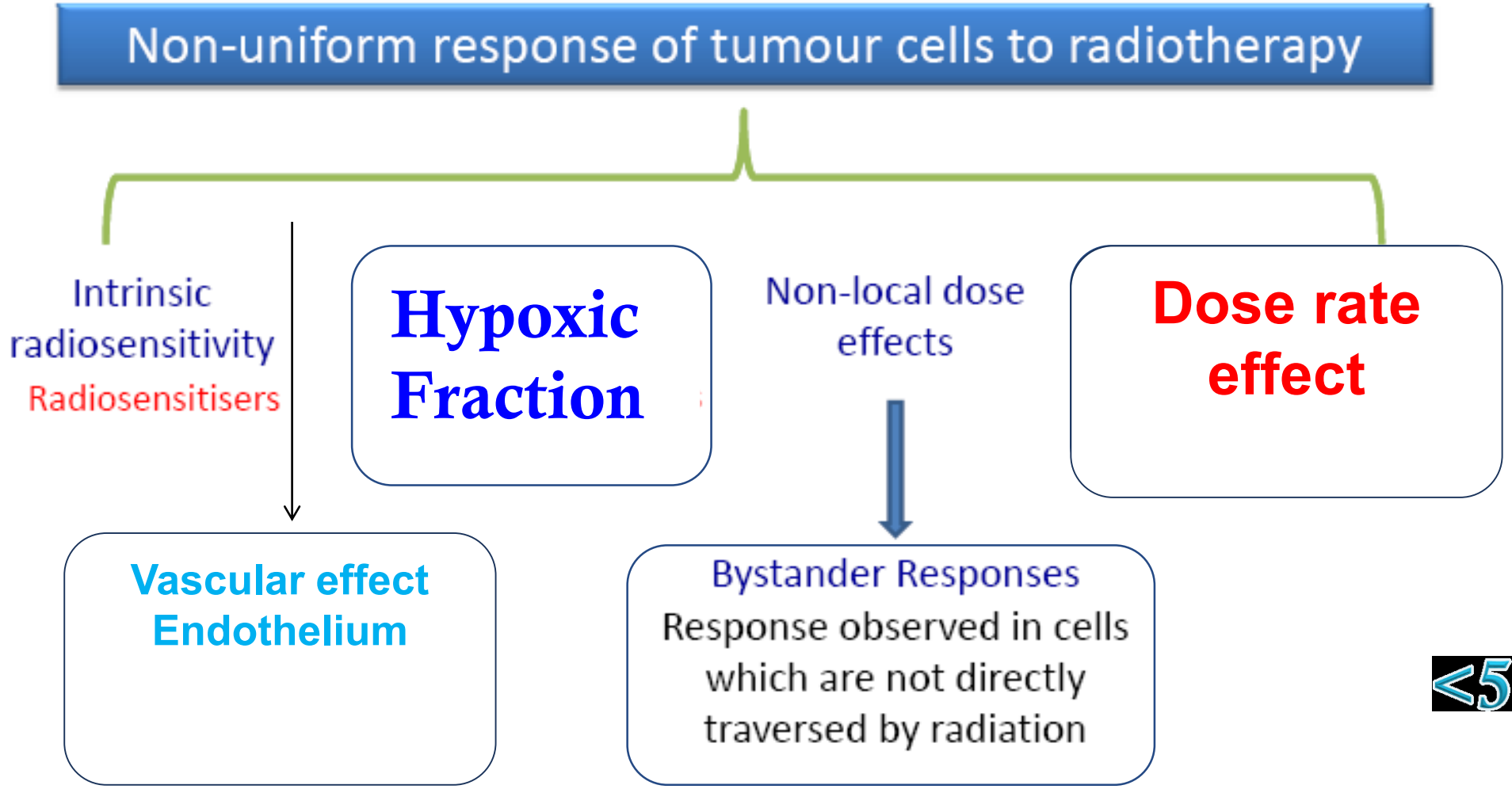
HyTEC

~~QUANTEC~~: ORGAN-SPECIFIC PAPER



OTHER PROPOSED MODELS FOR SBRT

Tumour responses to radiotherapy



<5 frs

RADIATION RESEARCH 177, 311–327 (2012)
0033-7587/12 $15.00
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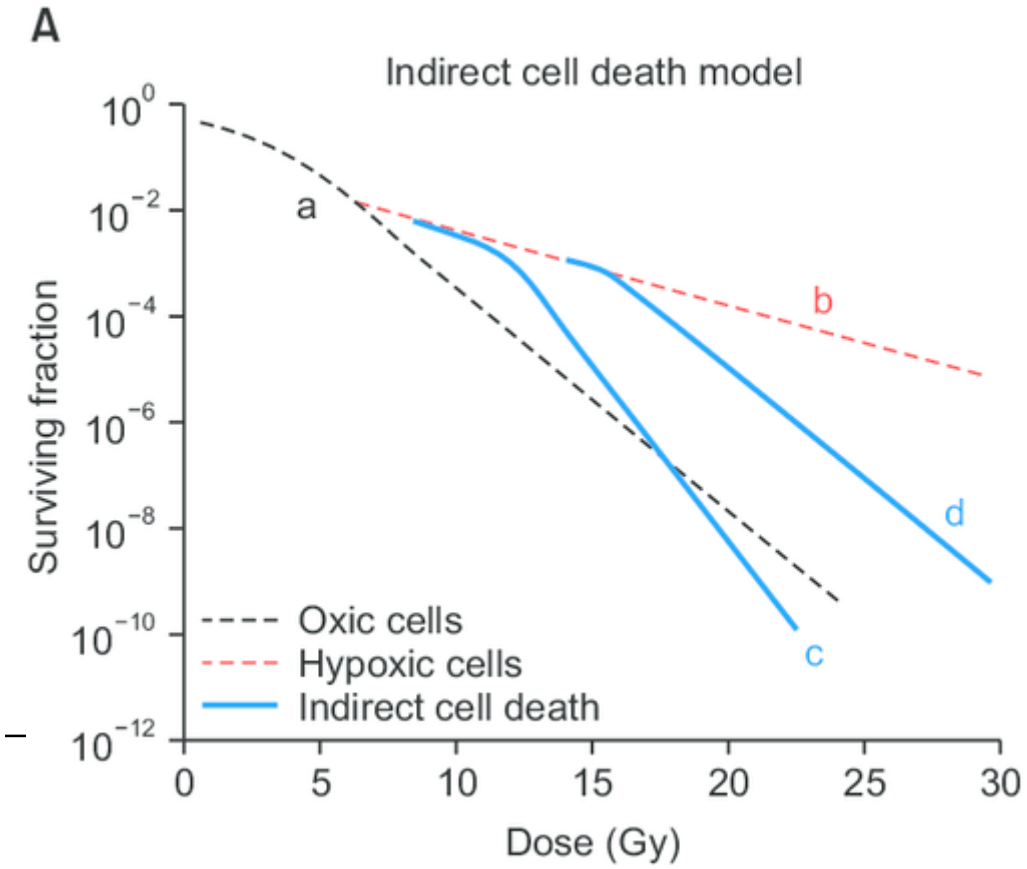
DOI: 10.1667/RR2773.1

REVIEW

Radiation-Induced Vascular Damage in Tumors: Implications of Vascular Damage in Ablative Hypofractionated Radiotherapy (SBRT and SRS)

Heon Joo Park,[a,b] Robert J. Griffin,[c] Susanta Hui,[a] Seymour H. Levitt[a,d] and Chang W. Song[a,1]

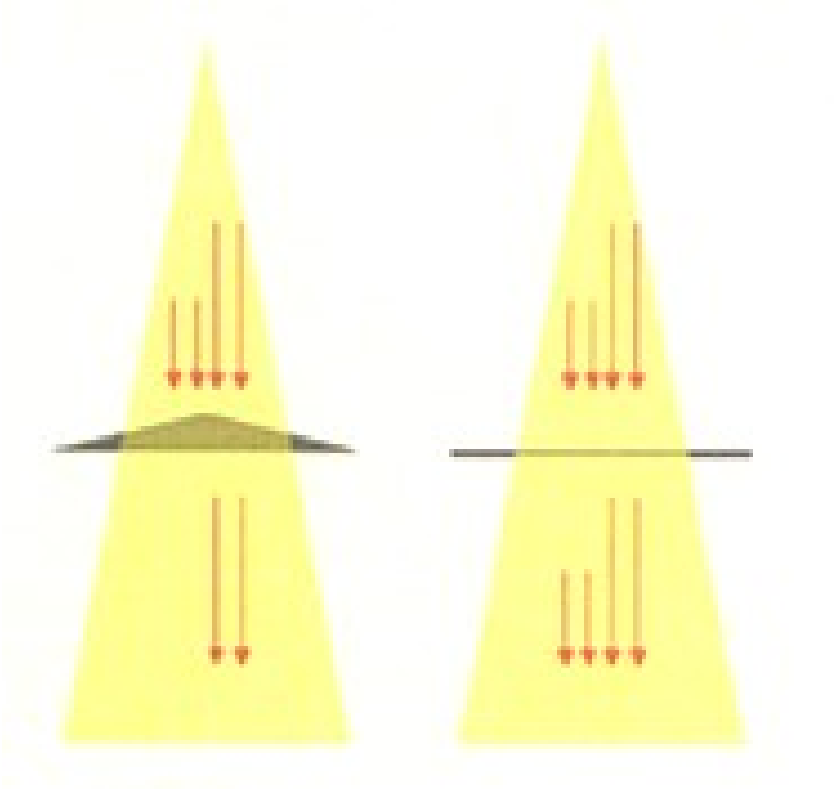


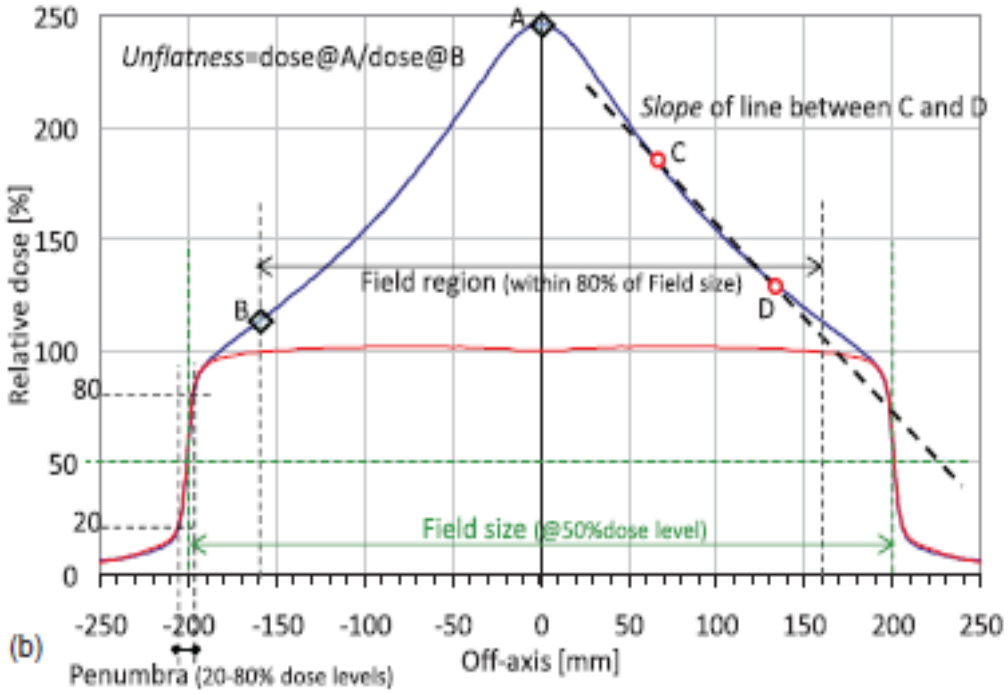
- For D < 5Gy oxic cells die
- For D > 5Gy hypoxic cells death dominates
- For D >10 Gy Vascular damage at high doses produces secondary cell killing, **suggests that radiation doses induce vascular damage leading to indirect tumor cell death**.
- For D >17 Gy indirect radiation effect due to the vascular damage

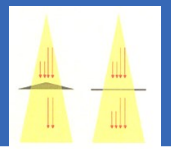
FIG. 7. Hypothetical cell death mechanism in the tumors by an exposure to various doses of ionizing radiation in a single dose assuming 10% of clonogenic cells in the tumors are radiobiologically hypoxic. The initial part of the radiation survival curve a shows the death of fully oxygenated cells. With the increase in radiation dose to higher than about 5 Gy, death of hypoxic cells dominates the cell death, as indicated by curve b. As the radiation dose is increased further to about to 12 Gy, vascular damage begins to occur in the tumors in which endothelial cells are relatively radiosensitive, thereby causing indirect tumor cell death, as shown by curve c. In the tumors in which endothelial cells are radioresistant, indirect cell death due to vascular damage begins when the radiation dose is increased to about 17 Gy, as indicated by curve d (*12*).

FFF VS FF: BEAM HARDENING

- Dose rate → 24 Gy/min





Ref.	Cells	E (MV)	Dose rate (Gy/min)	Modulated beam	Effect 
Sørensen et al. RO 2011	HN FaDu V79	6FFF 6X	5, 10, 30	No	No
Loshe *et al.*RO 2011	Gliomas T98G (mut-p53) U87MG	10FFF 10X	0.02, 4, 24	No	Yes at D≥10 Gy
King *et al.*PMB 2013	PCa DU 145, NSCLC H460	6FFF 6X	3, 11	Yes (bolus)	No
Verbakel et al. AO 2013	Lung SW1573 ; gliom T98 (Mut-p53); astroc D348	6/10 FFF/X	4, 8	Yes (IMRT)	No
Karan *et al.* PMB 2013	cervix SiHa; NSCLC H460; V79	6/10 FFF/X	3, 10	No	No
Bewes et al. 2008	melanoma MM576; NSCLC H460	6FFF 6X	1.2, 5	Yes	Dose rate effect on protracted delivery

THE ONCOLOGIST'S PROSPECTIVE

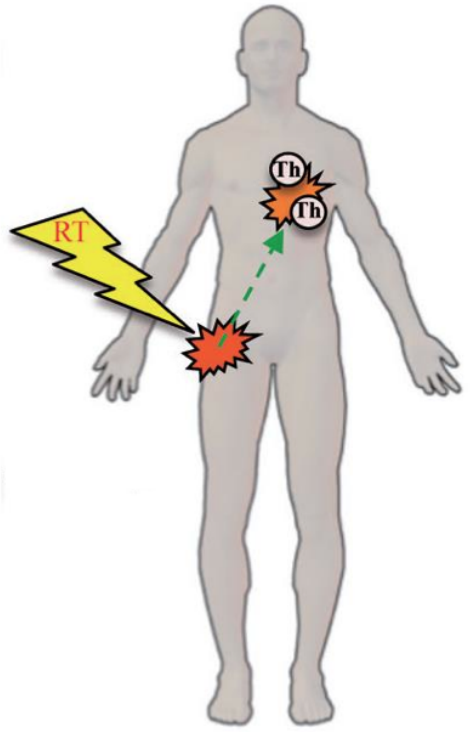
Most reports on abscopal effects refer to antitumor consequences outside the radiation field

Multiple mechanisms have been proposed to cause the abscopal effects, such as:

- **the systemic secretion of specific cytokines and chemokines,**
- **a systemic immune response against local tumor antigens released**
- **local inflammation that can lead to a distant effect.**

In any case, the hypothesis that the abscopal effect is immune-mediated is becoming stronger

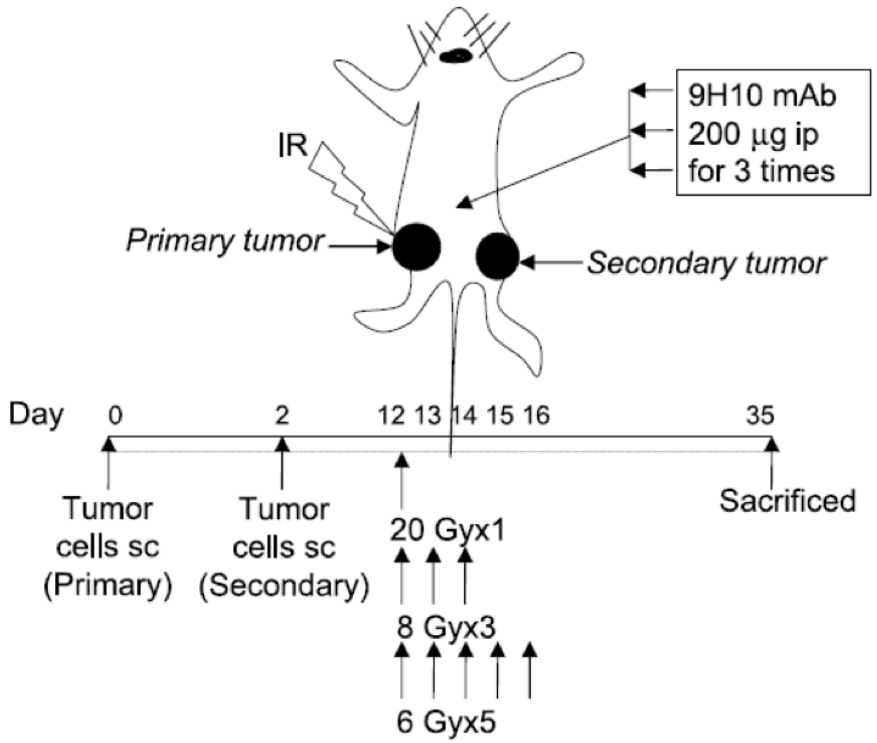
Distal areas to the primary tumor (metastasis)

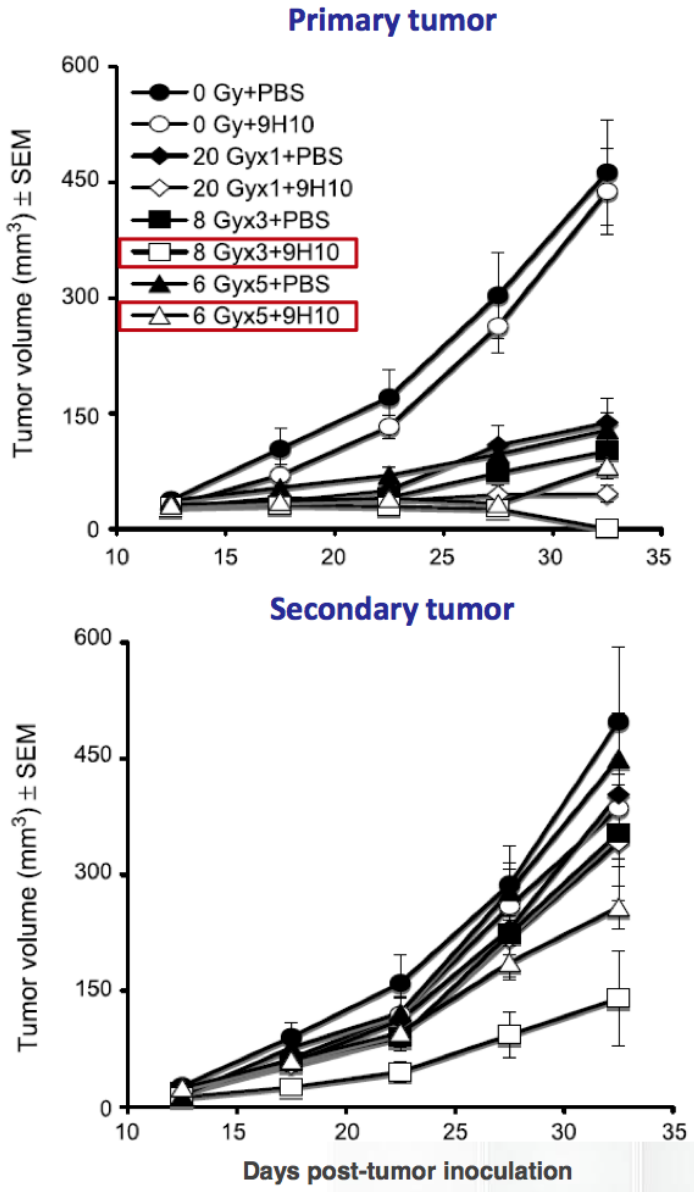


Anti-tumor T-cell response

Sologuren et al., 2014

ANIMAL MODEL

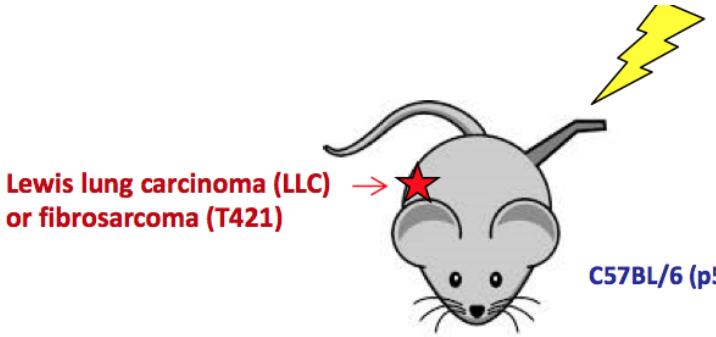


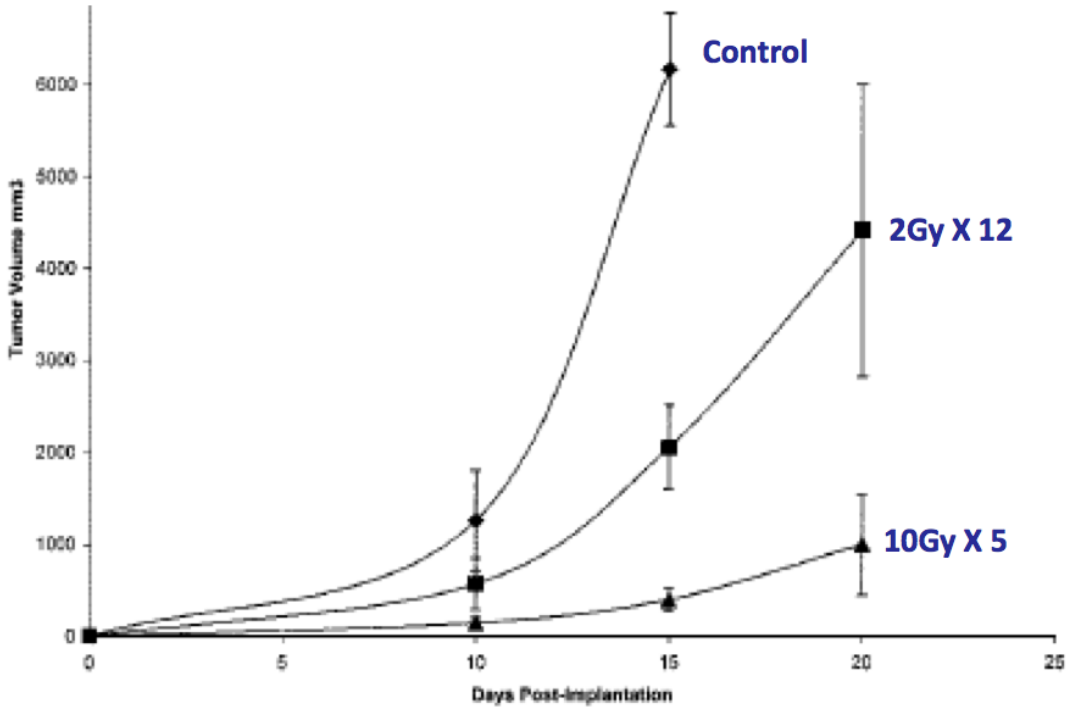


Only fractionated, and not RT administered as a single high dose, induced an immune-mediated abscopal effect in a secondary tumor when combined with anti-CTLA-4 antibody.

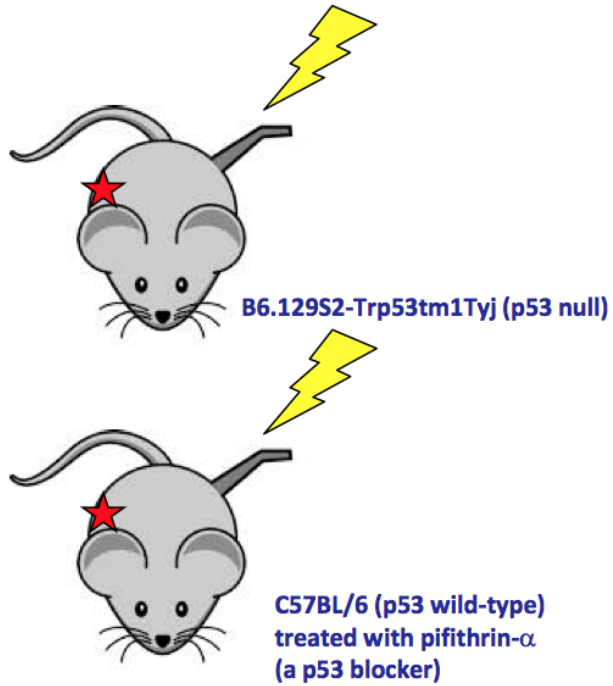
Dewan et al., 2009

ANIMAL MODEL





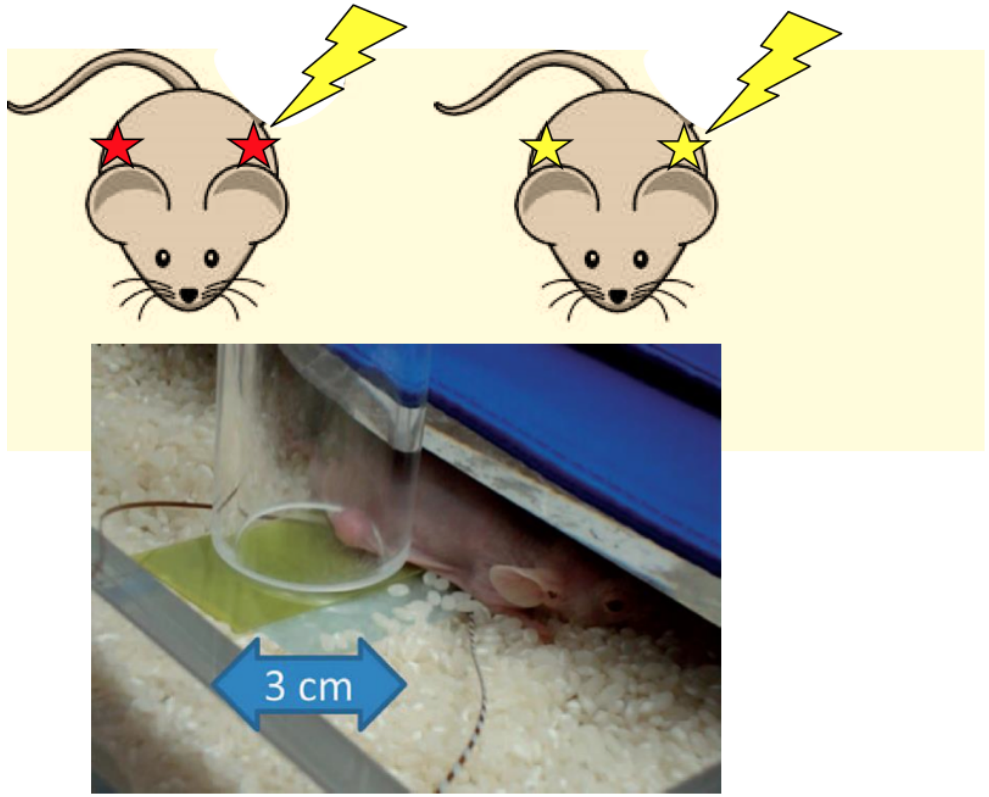
The abscopal effect is dose dependent and not tumor-specific



These data implicate p53 as a key mediator of the radiation-induced abscopal effect

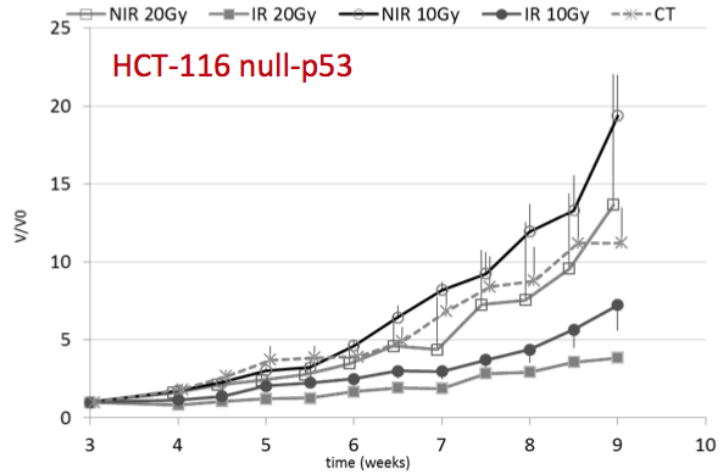
Camphausen et al., 2011

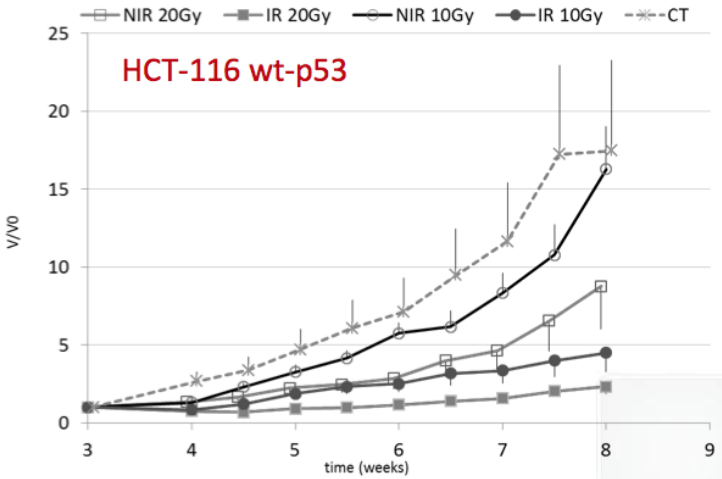
HCT116, p53-wt HCT116, p53-null



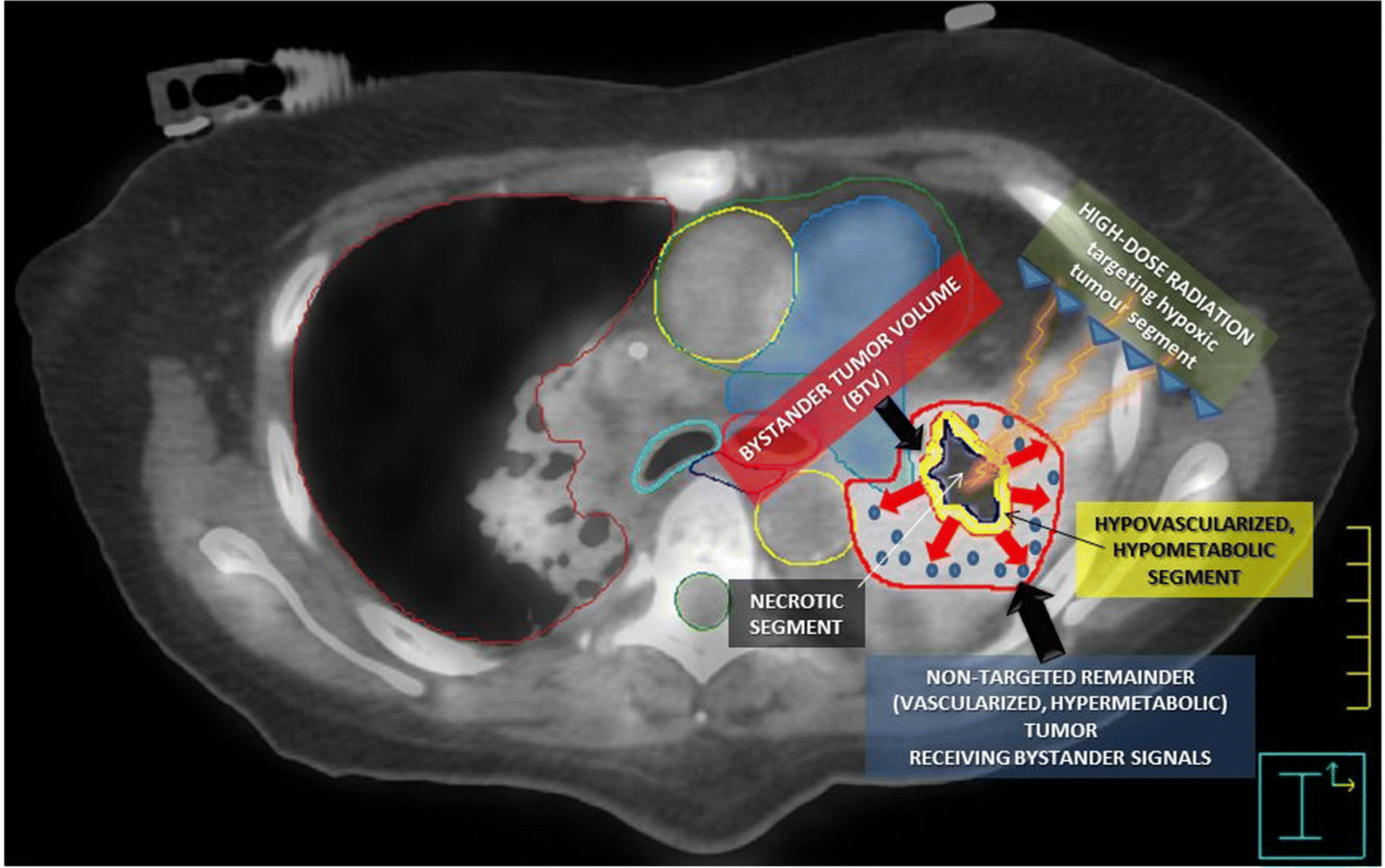
When tumours reached a volume of 0.2 cm^3, irradiation was performed, under strict dose monitoring, with a dedicated mobile accelerator designed for intra-Operative-RT (IORT). A dose of 10 or 20 Gy delivered by a 10 MeV electron beam, was delivered to a tumour established in one side flank (IR groups), leaving the other non-irradiated (NIR groups).

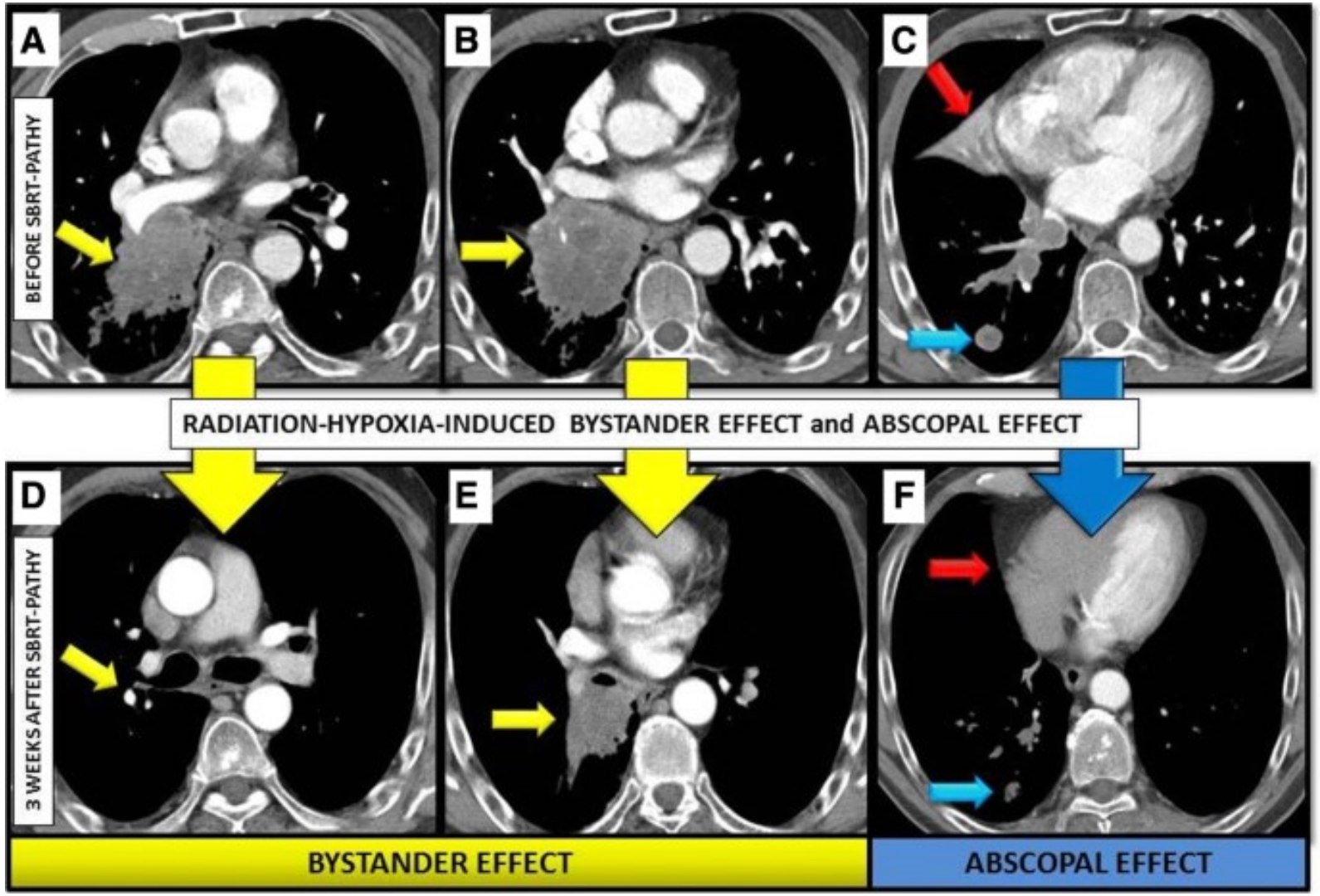
Strigari et al., 2014





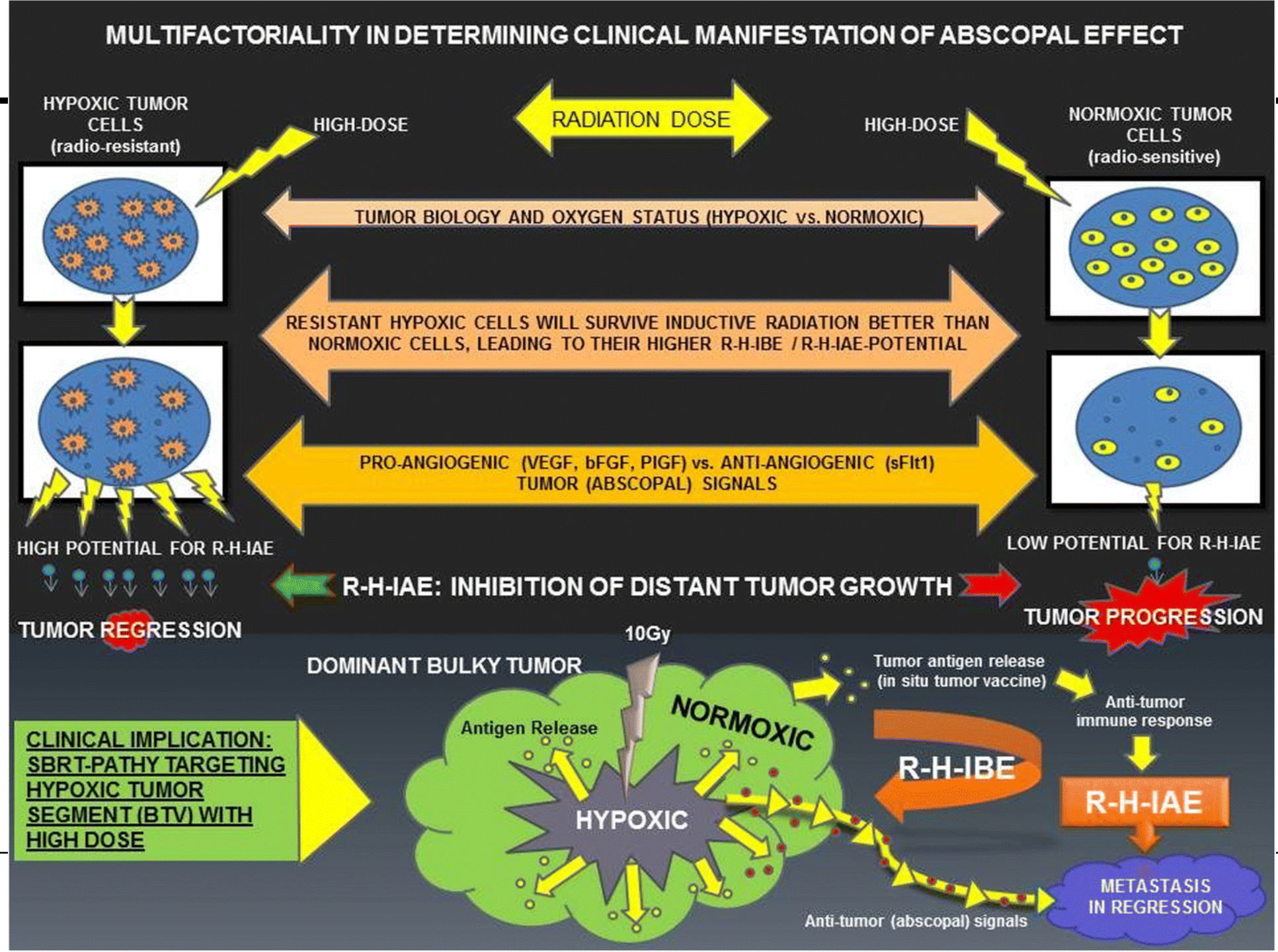
Our results suggest that the interplay between radiation dose and p53 status plays a critical role in the RT-induced bystander effects


HIGH-DOSE RADIATION
targeting hypoxic
tumour segment
BYSTANDER TUMOR VOLUME
(BTV)
HYPOVASCULARIZED,
HYPOMETABOLIC
SEGMENT
NECROTIC
SEGMENT
NON-TARGETED REMAINDER
(VASCULARIZED, HYPERMETABOLIC)
TUMOR
RECEIVING BYSTANDER SIGNALS



NEOADJUVANT SBRT-PATHY: **a-c**) diagnostic CT of the patient with unresectable squamous-cell lung cancer (yellow arrows), separate lung lesion (blue arrow), and an atelectasis (red arrow). 3 weeks after SBRT-PATHY, preoperative restaging CT **(d-f)** showed a 60% reduction of partially treated tumor (bystander effect: yellow arrows), a 50% reduction of unirradiated lung lesion (abscopal effect: blue arrows), and complete regression of atelectasis (red arrows)

Novel stereotactic body radiation therapy (SBRT)-based partial tumor irradiation targeting hypoxic segment of bulky tumors (SBRT-PATHY): improvement of the radiotherapy outcome by exploiting the bystander and abscopal effects


MULTIFACTORIALITY IN DETERMINING CLINICAL MANIFESTATION OF ABSCOPAL EFFECT
HYPOXIC TUMOR CELLS (radio-resistant)
HIGH-DOSE
RADIATION DOSE
HIGH-DOSE
NORMOXIC TUMOR CELLS (radio-sensitive)
TUMOR BIOLOGY AND OXYGEN STATUS (HYPOXIC vs. NORMOXIC)
RESISTANT HYPOXIC CELLS WILL SURVIVE INDUCTIVE RADIATION BETTER THAN NORMOXIC CELLS, LEADING TO THEIR HIGHER R-H-IBE / R-H-IAE-POTENTIAL
PRO-ANGIOGENIC (VEGF, bFGF, PIGF) vs. ANTI-ANGIOGENIC (sFlt1) TUMOR (ABSCOPAL) SIGNALS
HIGH POTENTIAL FOR R-H-IAE
LOW POTENTIAL FOR R-H-IAE
R-H-IAE: INHIBITION OF DISTANT TUMOR GROWTH
TUMOR REGRESSION
TUMOR PROGRESSION
DOMINANT BULKY TUMOR
10Gy
Tumor antigen release (in situ tumor vaccine)
Anti-tumor immune response
CLINICAL IMPLICATION: SBRT-PATHY TARGETING HYPOXIC TUMOR SEGMENT (BTV) WITH HIGH DOSE
Antigen Release
NORMOXIC
HYPOXIC
R-H-IBE
R-H-IAE
METASTASIS IN REGRESSION
Anti-tumor (abscopal) signals

FROM THE RADIOBIOLOGICAL POINT OF VIEW

- SBRT seems to be capable of overcoming hypoxic radioprotection through mechanisms other than directly killing tumor cells via DNA damage.
- Important mechanisms for cell inactivation has been hypothesized to become important at doses >10 Gy
  - Vascular effects occurs increasingly at higher doses per fraction
  - Immunological effect
  - Bystander effect

FUTURE DIRECTIONS

- Functional Liver, Functional Lung Based Planning
- MR based Planning
  - For more precise targeting and improved assessment of motion/tumor margins
- Analysis of Plan Robustness
  - To measure and quantify the uncertainty of the setup
- Reproducibility of Setup, Management of Motion, IGRT Methods
- Defining Normal Structures and dose Limits
- FLASH (?)

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SPARE

LQ MODEL

$$S_{LQ} = e^{-\alpha d - \beta d^2}$$

LQ model - heterogeneity in tumor cell radiosensitivity

$$S_{LQ,hetero} = \frac{(\alpha BED + g + 1)^{g+1}}{(g+1)^{g+1}}$$

$g \geq 2$

LQL model

$$S_{LQL} = e^{-\alpha d + 2\beta \frac{\left(p_1 d - 1 + e^{-p_1 d}\right)}{p_1^2}}$$

USC MODEL

$$S_{USC} = e^{-(\alpha d+\beta d^2)} \quad for \quad d \le \frac{\alpha}{\beta}\frac{(1+\alpha p_1)}{2\alpha p_1}$$

$$S_{USC} = e^{-\left(\frac{d}{p_1}-\frac{\alpha(1+\alpha p_1)^2}{\beta\ 4\alpha p_1^2}+\beta d^2\right)} \quad for \quad d > \frac{\alpha}{\beta}\frac{(1+\alpha p_1)}{2\alpha p_1}$$

Padé linear quadratic (PLQ) model

$$S_{PLQ} = \exp\left[-\frac{\alpha d+\beta d^2}{1+p_1 d}\right]$$

the dose response shape is gradually altered, becoming less curved at high doses, by the presence of a term $[1 + p_1 d]$ in the denominator of the function

SIMPLIFIED PTV MARGIN RECIPE FOR DOSE PROBABILITY

- To cover the CTV of the 90% of patients with 95% of isodose (analytical solution) :

$$\text{PTV margin} = \mathbf{2.5}\ \Sigma + \mathbf{0.7}\ \sigma$$

Σ = quadratic sum of SD of all the preparation (**systematic**) errors

σ = quadratic sum of SD of all the execution (**random**) errors

For a big CTV with smooth shape and penumbra 5mm

(van Herk et al. IJROBP 2000)

PTV MARGINS IN SBRT

- **Smaller number of fractions** has an impact on the model
- "**Random errors**" become systematic errors in the limit of 1-5 fractions

Daily image guidance allows the planning target volume (**PTV**) **to be reduced**, but **uncertainties** (in processes such as **image registration and corrections**) **still be taken into account**

RT – LIVER

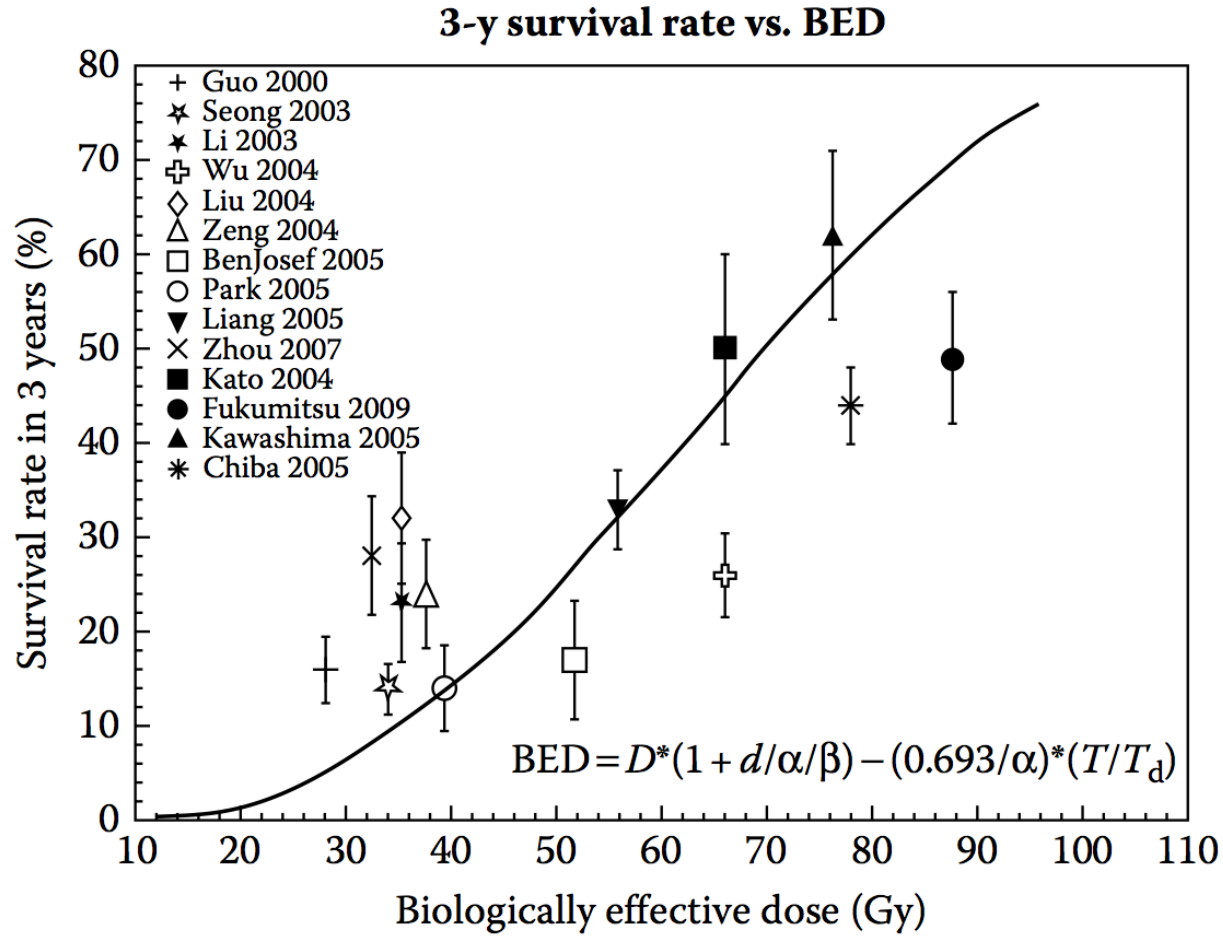
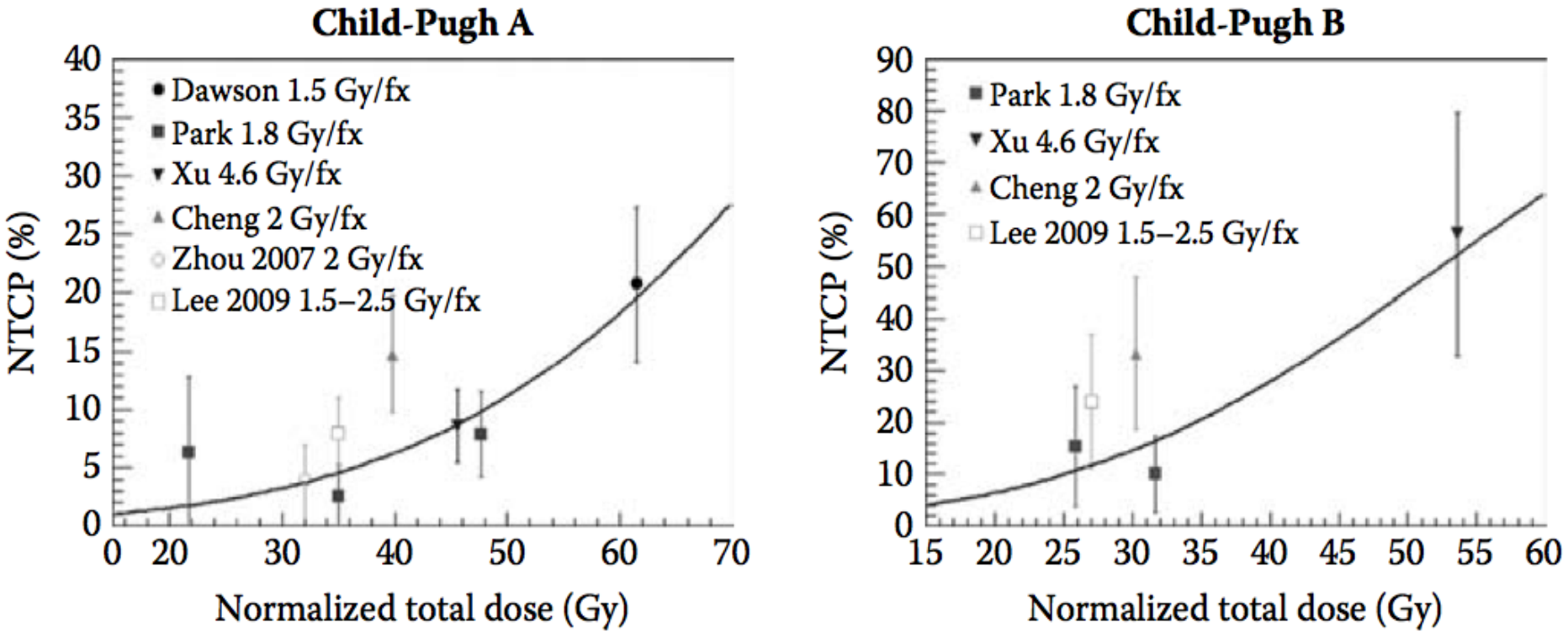


FIGURE 20.1 Three-year overall survival rate as a function of biologically effective dose (BED) for primary liver tumors. BED and the curve were calculated using the model described by Tai, A., et al. (2008). Note that in the studies by Wu, D. H., et al. (2004), Liu et al. (2004), and Zeng, Z. C., et al. (2004) the follow-up time was recorded from the beginning of diagnosis, whereas in other studies it was recorded from the start of treatment.

RT – LIVER



Normal tissue complication probability (NTCP) data plotted as a function of normalized total dose (NTD) from he
CC) patients of Child-Pugh A (left panel) and Child-Pugh B (right panel). NTD was calculated by $\left(\frac{\alpha/\beta+d+f\times N}{\alpha/\beta+d_{ref}+f\times N_{ref}}\right)D(d)$, w
ctions and f is a fitting parameter (0.156 and 0 for Child-Pugh A and B, respectively; Tai 2009). The subscript refers to t
scheme at which the Lyman model parameters were derived. (Adapted from Tai, A., B. Erickson, and X. A. Li. 2009. *Int J I*
83–9. With permission.)

Clinical Oncology xxx (2014) 1–14

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Original Article

Is Biochemical Relapse-free Survival After Profoundly Hypofractionated Radiotherapy Consistent with Current Radiobiological Models?

A.C. Tree *, V.S. Khoo *†, N.J. van As *, M. Partridge †[1]

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† Institute of Cancer Research, London, UK

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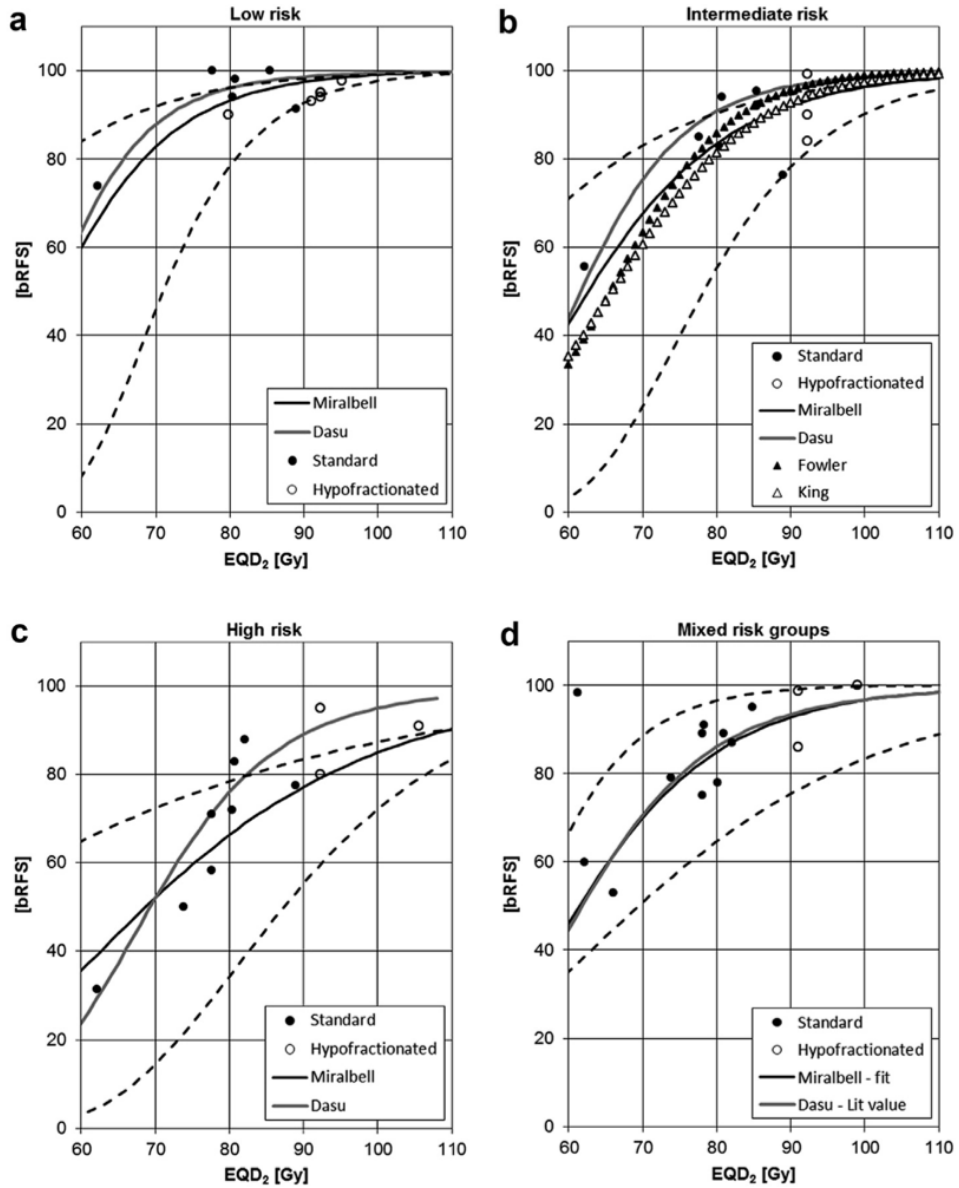

Fig 1. Biochemical relapse-free survival against EQD_2 for low-, intermediate- and high-risk patients and for mixed-risk groups (a, b, c and d, respectively). Data points show the result of trials of standard and moderate hypofractionation (●) and profound hypofractionation (○). Solid lines show published model fits, with the exception of the Miralbell model for mixed-risk group data, which is fitted to the data in (d). Dotted lines show 95% confidence intervals for the Miralbell fit.

Recommendations, thorax and abdomen region

	Absorbed dose recommendations	**EQD2/BED/NTCP recommendations**	**Prob.curve**
Heart/cardiac mort Heart/pericarditis.	Yes, new data needed	NTCP α/β=3Gy	RS LKB
Lung /RP	Yes, new data keep coming	MLD, EQD2 (SBRT open)	Function of MD + clin/risk factors + genetic
Esophagus/acute	Yes, but limited evidence	Mean dose	
Ribs/fracture	Yes,but few data	LQ	Logistic - D_{2cm3} V_{30}
Chest wall/pain	Yes, but few data		
Liver/RILD	Yes	Primary,and metastatic EQD2 α/β=2Gy (SBRT open)	Function of MD + clin/risk factors
Spine/myelitis	Yes, but few data	EQD2 α/β=3Gy	Function of EQD2