Radiobiology of SBRT

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Outline

- Introduction
- Cell killing at high dose for fraction: the linear quadratic model
- Tumor Control Probability function
- Normal Tissue Complication Probability function
- How to use radiobiological knowledge in planning

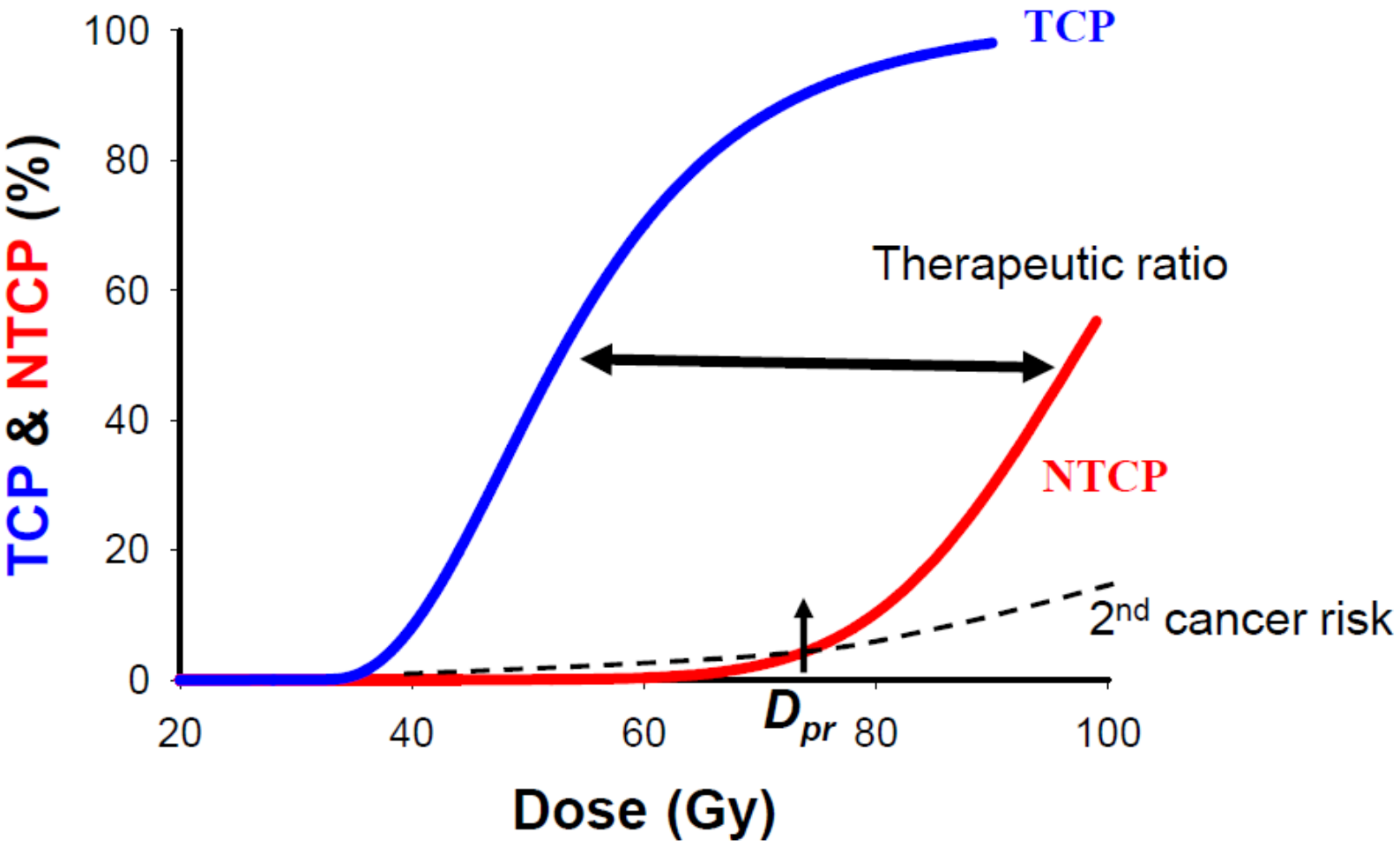
Introduction

- High dose per fraction (7-20 (~ 5?))
- Small number of fractions (1-5 (~10?))
- Used for small tumors wherever in the body. Primary or metastases
- Usually dose prescription is at the hedge of PTV and doses up to 120% at the PTV center are allowed
- Excellent immobilization and image guidance. This allows:

i) Local control comparable or superior to conventional fractionation

ii) Serious complication rate is low … but there have been some unexpected complications along the way

Introduction



Uzan, and A E Nahum, The British Journal of Radiology, 85 (2012), 1279–1286

Introduction

- **Linear quadratic model well describes cell killing at low dose per fraction and low dose rate:**

ACTION OF X-RAYS ON MAMMALIAN CELLS*·‡

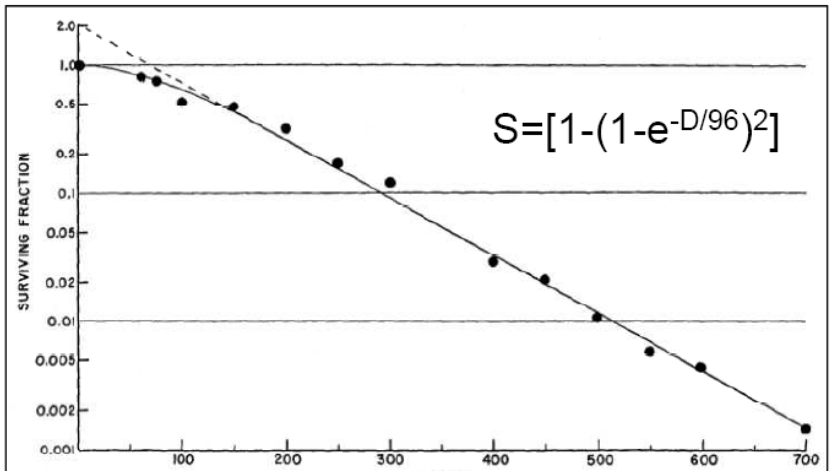
BY THEODORE T. PUCK, PH.D., AND PHILIP I. MARCUS

(From the Department of Biophysics, Florence R. Sabin Laboratories, University of Colorado Medical Center, Denver)

(Received for publication, February 3, 1956)

PLATES 26 AND 27

Study of the mechanisms of action of ionizing radiation in higher animals has been impeded by lack of a precise method for measurement of reproductive potential in single mammalian cells comparable to that available for micro-



$$SF = \frac{\overline{N_s}}{N_o} = \exp\left\{-\alpha d - \beta d^2\right\}$$

$$SF = \left[\exp\left(-\alpha d - \beta d^2\right)\right]^n.$$
$$= \exp\left(-\alpha\, nd - \beta\, nd^2\right)$$

$$SF = \exp(-\alpha D - \beta\, d\, D)$$
$$= \exp\left[-\alpha D\left(1 + \frac{d}{\alpha/\beta}\right)\right]$$

Biological Effective Dose

Introduction

Cell cycle effect

$$S/S_o = \Sigma n_x \left[e^{-\alpha_x D - \beta_x DD} \right]$$

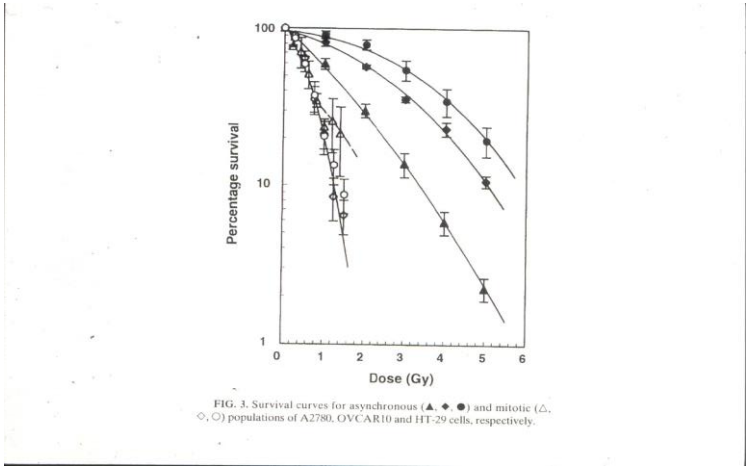
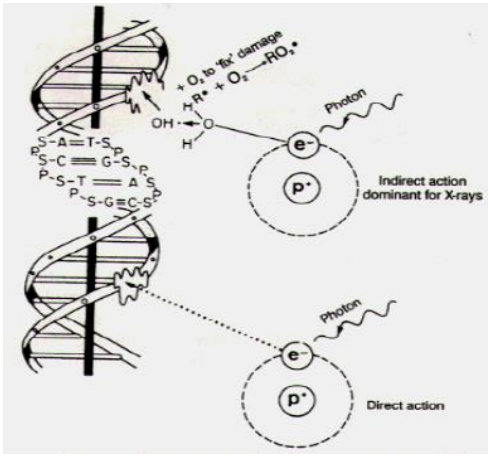
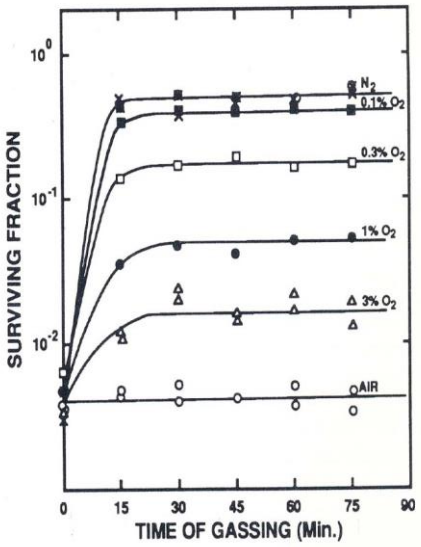


FIG. 3. Survival curves for asynchronous (▲, ◆, ●) and mitotic (△, ◇, ○) populations of A2780, OVCAR10 and HT-29 cells, respectively.

Oxygen effect





Tumor Control Probability Function

- The probability of **tumor control** follows the **Poisson statistic**, were N is the number of clonogens i.e. cells that can proliferates

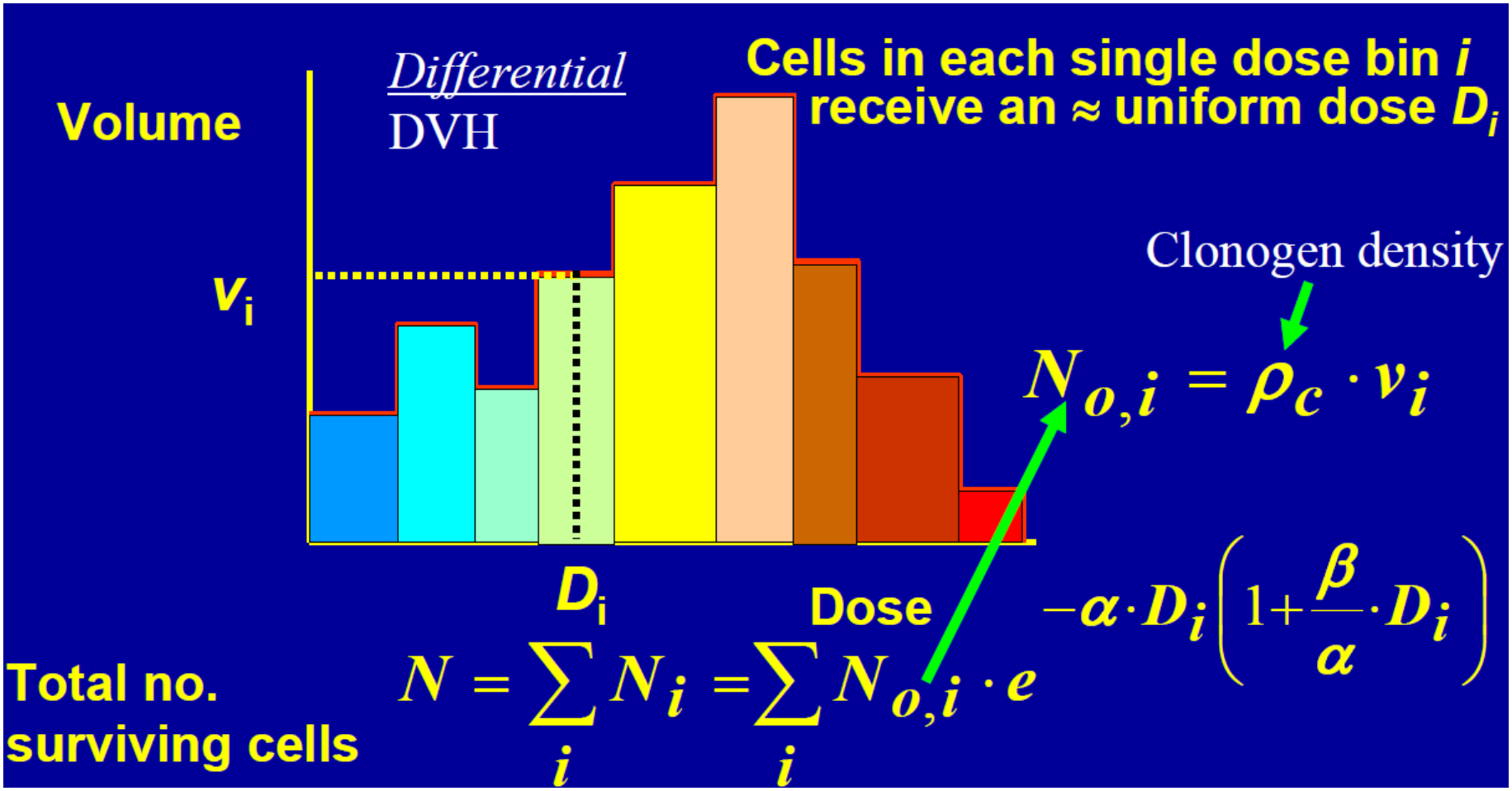
$$\mathrm{TCP} = \exp(-SN)$$

$$\mathrm{TCP} = \prod_{i=1}^{M} P(D_i)^{v_i}$$

$$P(D_i) = \exp\left(-\exp\left(e\gamma - \alpha D_i - \beta \frac{D_i^2}{n}\right)\right)$$

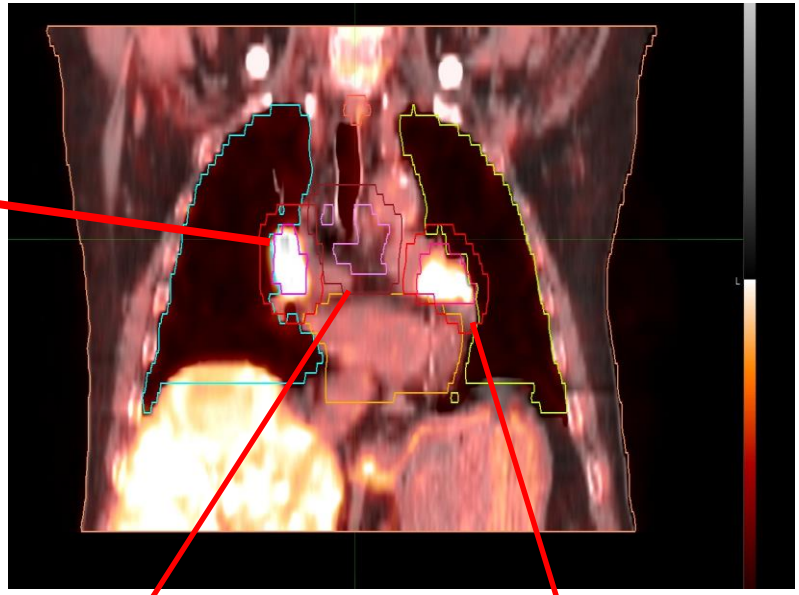
$$TCP = \exp\left\{-N_o \exp\left[-\alpha D\left(1 + \frac{\beta}{\alpha} d\right)\right]\right\}$$

TCP voxel based



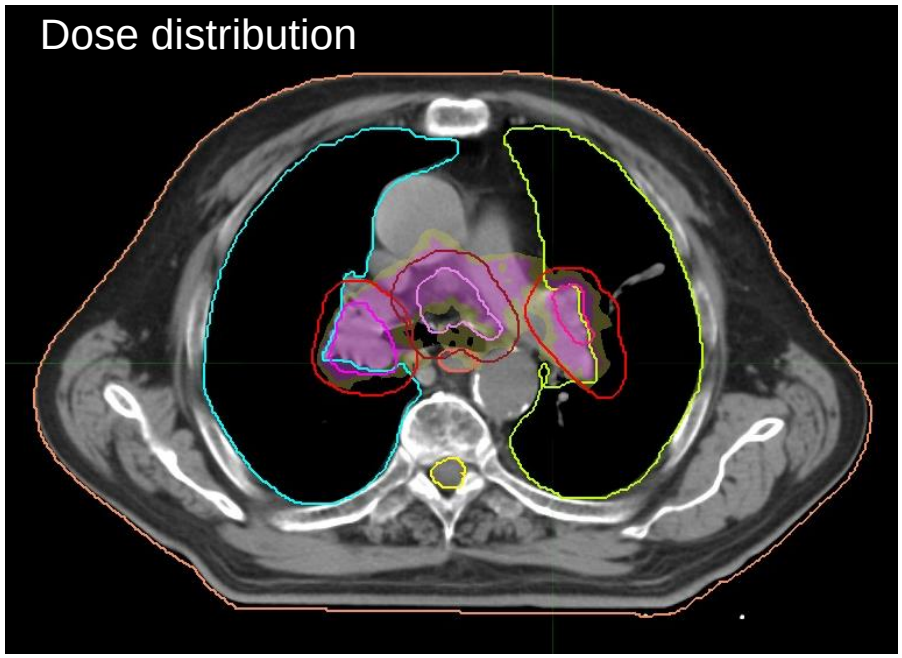
TCP voxel based

PET FDG: SUV correlated with clonogens number



PTV N

PTV T

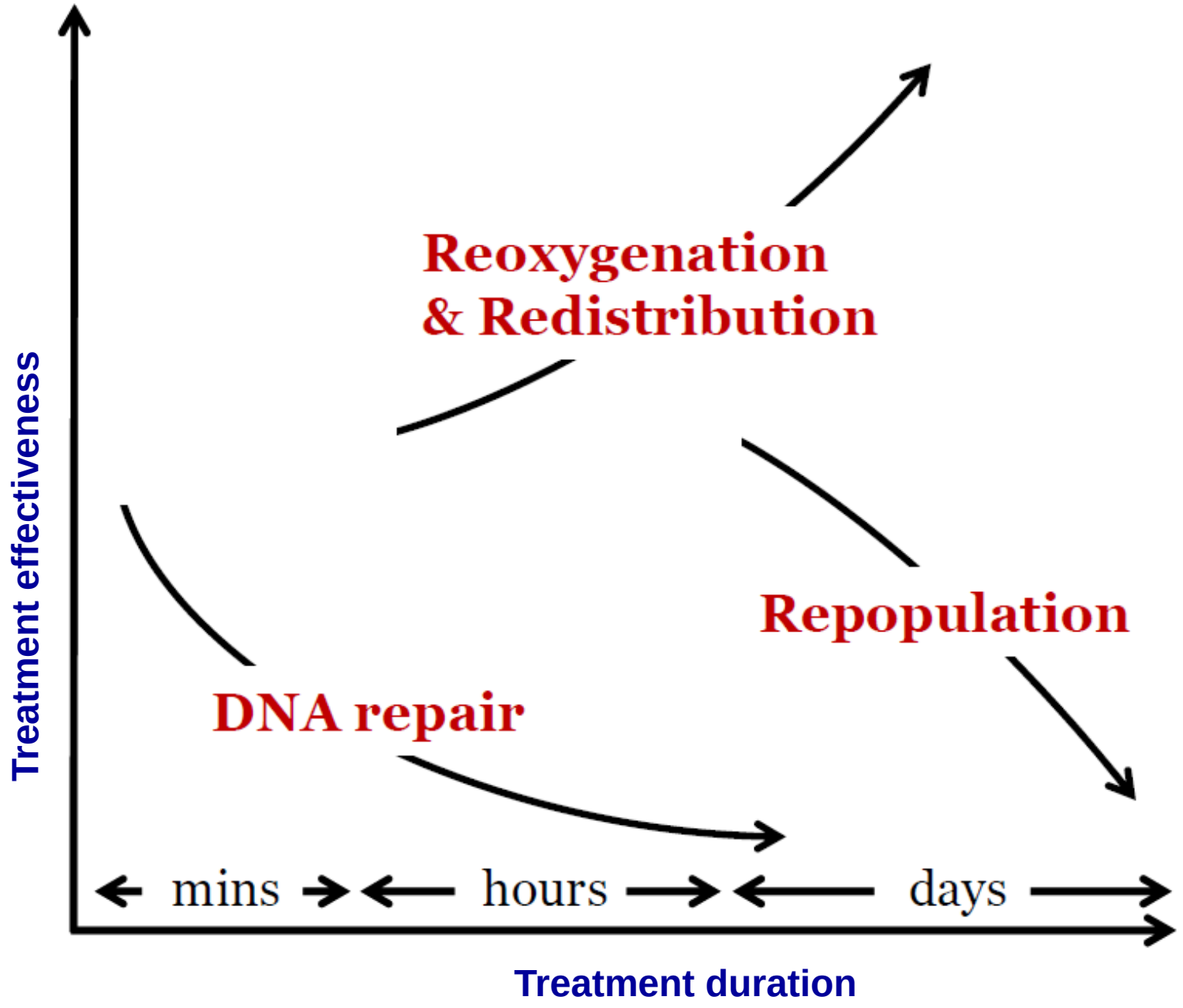


Higher dose is needed **where** tumor has the **highest occupancy** probability

Introduction

The five R's of Radiobiology describe the effects of dose-rate and fractionation on cell survival

1) **Repair**: sub-lethal damage repaired in **min-hour**
2) **Redistribution**: more cells populate M phase after irradiation in **days**
3) **Re-oxygenation**: Hypoxic cells are re-oxygenated after irradiation in **days**
4) **Re-population**: tumor cells proliferation after **3-4 weeks**
5) **Radiosensibility**: intristic radiosensitivity **(α/β)**

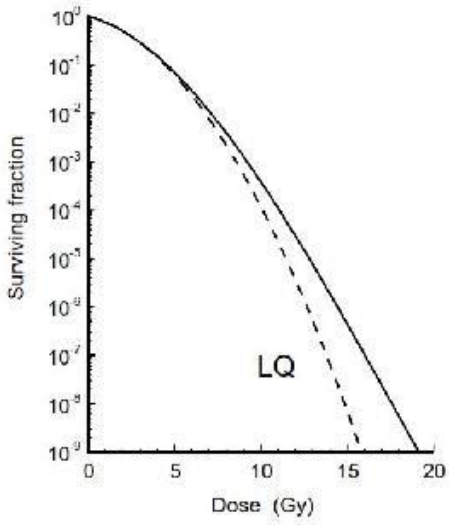

Reoxygenation
& Redistribution
Repopulation
DNA repair
mins
hours
days
Treatment effectiveness
Treatment duration

Consequences for SBRT

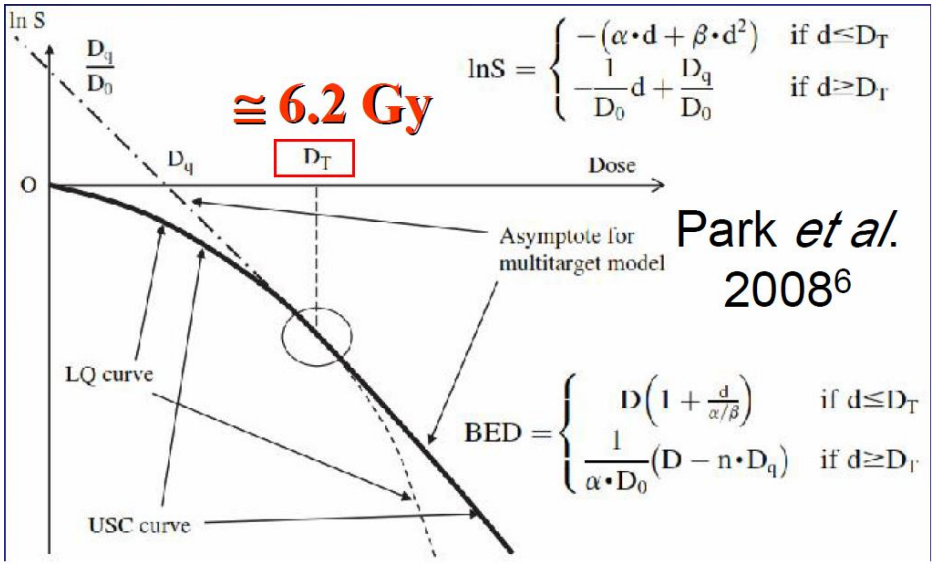
- The dose should be delivered before repair process: **irradiation** time **< 20-25 min**
- Using **more fractions** increases mitotic phase cells fraction: **increases radiosensitivity**
- Using **more fractions** increases well oxygenated cells fraction: **increases radiosensitivity**
- The whole treatment should be concluded before tumor re-population: **treatment** time **< 3 weeks**

Cell killing at high dose per fraction

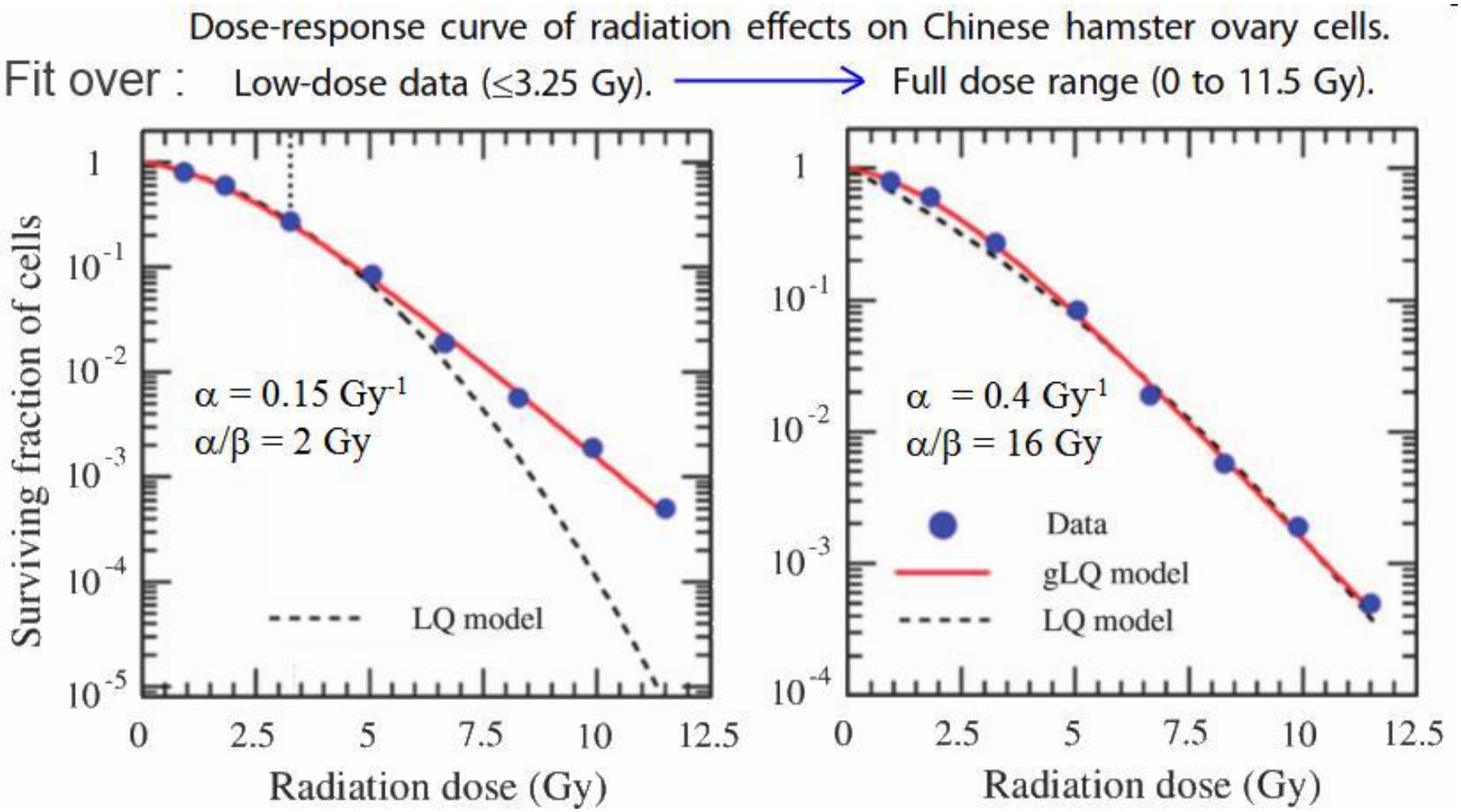
- LQ model is still valid at high dose?



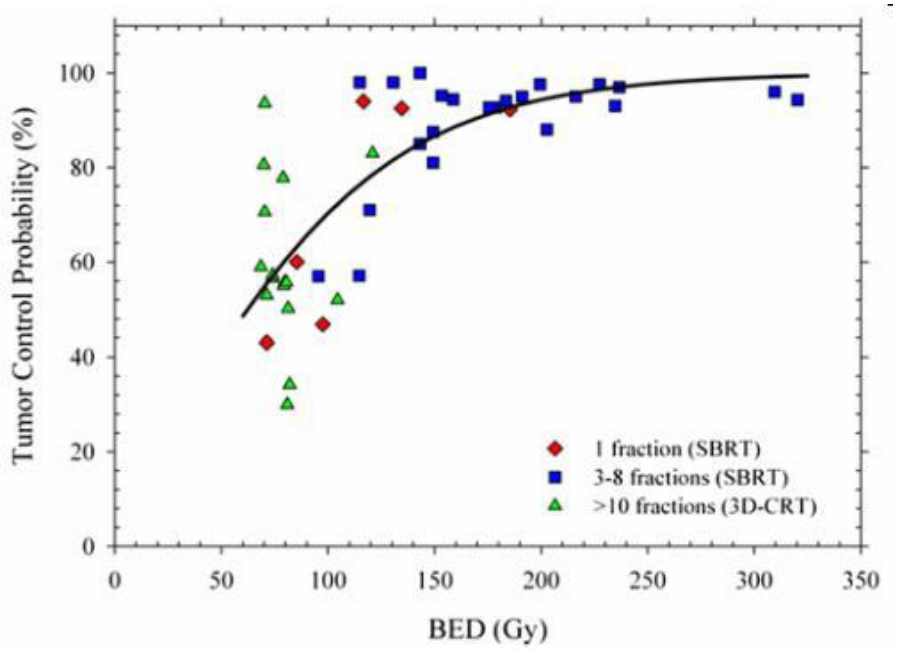
LQ model overestimates the cell killing at high dose

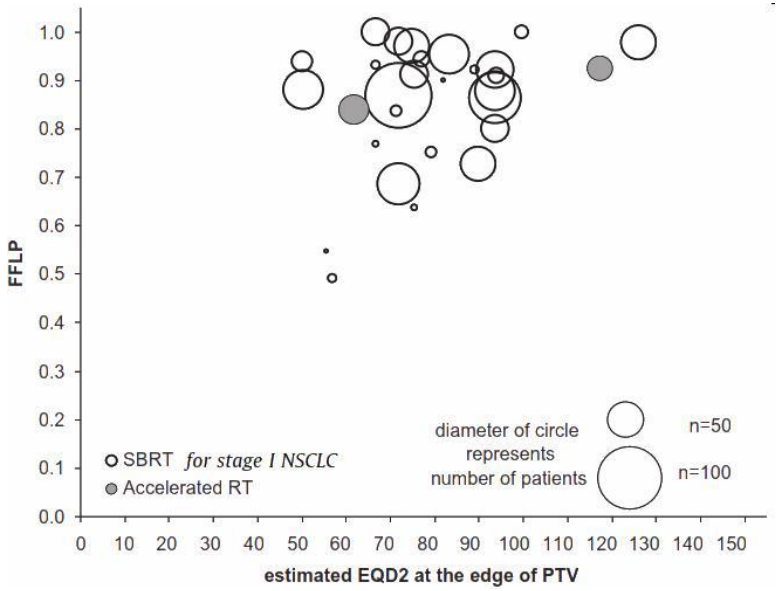


Cell killing at high dose per fraction



Tumor Control Probability Function

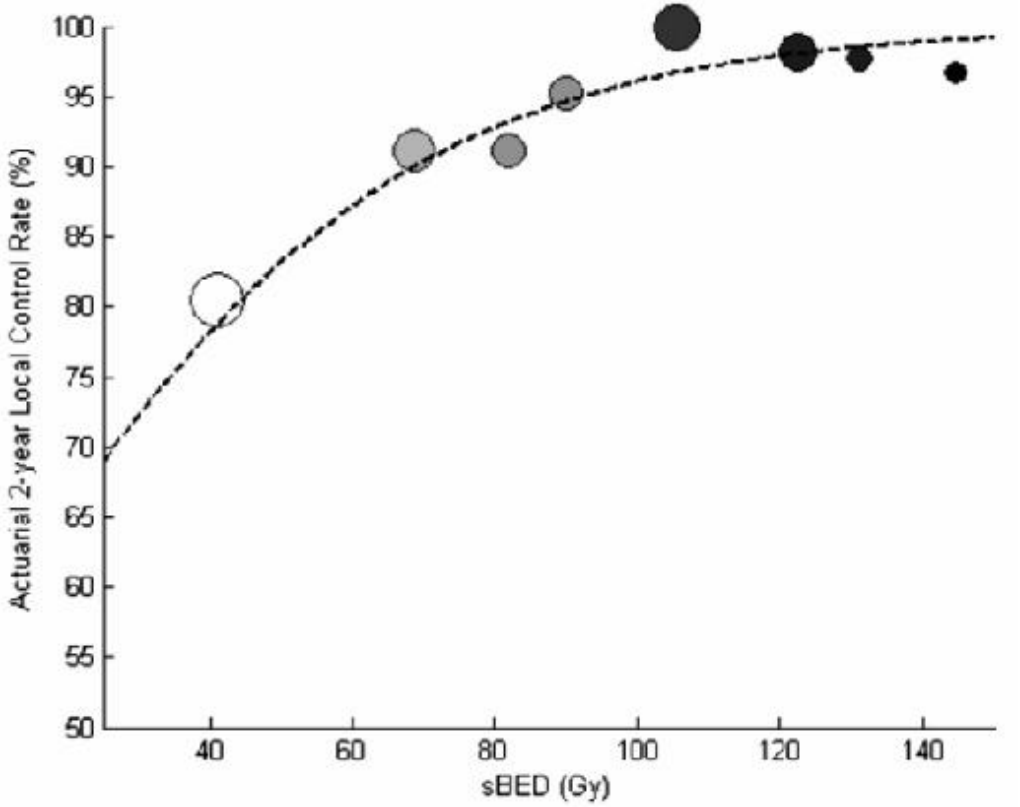




Metha *et al.* 2011:
. 42 studies (1056 pts. 3DCRT + 1640 pts. SBRT)
. LDFS(>2y.) of **Stage I** pts.;
. All fitted together by using **isocenter**-prescription-BED8.6 (BED*iso*)

van Baardwijk *et al.* 2012:
. 15 IPO (990 pts: *d* □ 6 Gy) +2 IPER trials;
. LDFS(3y.) of **Stage I** (66% T1, 34% T2) (>30 m. follow-up)

Tumor Control Probability Function



Ohri *et al.* 2012
IPO only: 482 pts (1998-2010), 3-8 fr. (95%pts), 18.4 m <follow-up>;

- ***Size-adjusted BED*: *sBED = BED10 - c.L***
- *L* = tumor diameter (cm).

Tumor Control Probability Function

The effect of reoxygenation in fractionated SBRT treatment can be included in TCP models: Ruggieri et al. 2013

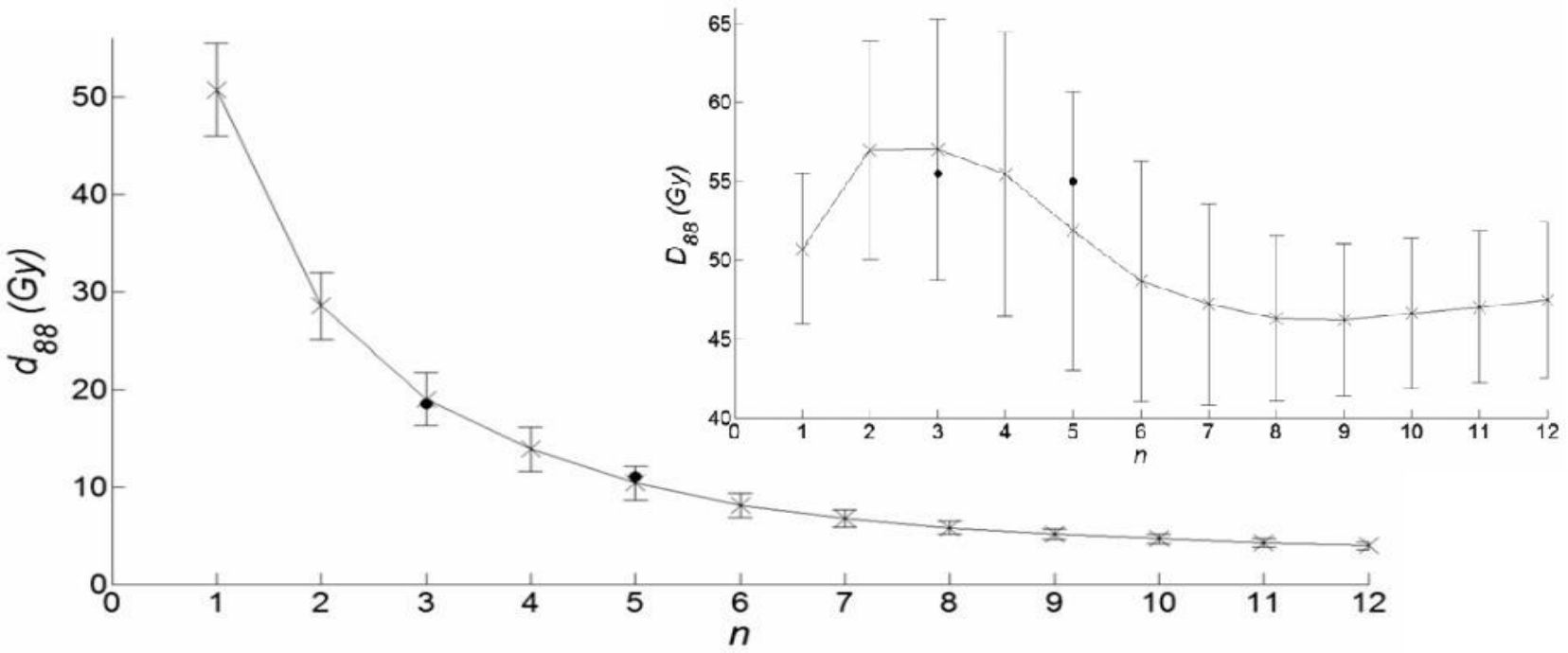


Figure 1. Computed $d_{88} = d_{88}(n)$, for $1 \leqslant n \leqslant 12$, with $(\pm 1\sigma)$ error bars. The two dots for the clinically adopted $d_{88}(n = 3, 5) = (18.5, 11.0)$ Gy values, as described in section 1, are reported for comparison.

TCP: Take home messages:

At the high-dose of SBRT (15-20 Gy) the **LQ** still is the model that **fits the data best**.

The **BED** can be **used** for computing iso-effective schedules but **α/β** ratio is dependent by the dose for fraction: **10 for d < 15**
20 for d >15

A **dose-response** relationship is observed for SBRT of early stage NSCLC with saturation for the PTV-encompassing BED above: **100 Gy_{10}** for small tumours **(<3cm)**, **140 Gy_{10}** for larger tumors **(<7 cm)**.

According to **TCP modelling which includes tumor hypoxia, the optimal *n* value in lung SBRT** results shifted from the current 3-fractions reference schedule towards **5-10 fractions**

How to use in practice

- Fractionization increases TCP
- **Iso TCP** schedules for **lung cancer**:

1) 18 Gy* 3
2) 10 Gy* 5
3) 7.5Gy * 8 (6x8 taking in to account re-oxygenation models)

- Use of **inhomogeneous dose** distribution **increases TCP** if re-oxygenation is taken in to account
- **More dose** is needed where the **tumor** has the highest **occupancy** probability.

Normal tissue complications in SBRT

- Low rate of complications but:

i) Unexpected **fatal complications** in central lung tumor were reported

ii) **Carotid blowout** syndrome (fatal) after SBRT for recurrent head and neck treatment.

iii) **Chest wall pain** is a rather common complication of lung SBRT:

- Severe enough to need medical attention
- Occasional rib fracture

These adverse events are **very rare** in **conventionally fractionated** treatments

Normal tissue complications in SBRT

- Starting point for **Normal tissue dose constraints** was **Timmermann 2008**

- **Not validated** by long-term follow-up
- Constraints are derived in some cases by **toxicity observation**, in some cases from conversions from broader experience using **mathematical models**.

Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
SINGLE-FRACTION TREATMENT				
Optic pathway	<0.2	8	10	Neuritis
Cochlea			12	Hearing loss
Brainstem	<1	10	15	Cranial neuropathy
Spinal cord	<0.25	10	14	Myelitis
	<1.2	7		
Cauda equina	<5	14	16	Neuritis
Sacral plexus	<3	14.4	16	Neuropathy
Esophagus*	<5	14.5	19	Stenosis/fistula
Ipsilateral brachial plexus	<3	14.4	16	Neuropathy
Heart/pericardium	<15	16	22	Pericarditis
Great vessels	<10	31	37	Aneurysm
Trachea and ipsilateral bronchus*	<4	8.8	22	Stenosis/fistula
Skin	<10	14.4	16	Ulceration
Stomach	<10	13	16	Ulceration/fistula
Duodenum*	<5	8.8	16	Ulceration
Jejunum/ileum*	<5	9.8	19	Enteritis/obstruction
Colon*	<20	11	22	Colitis/fistula
Rectum*	<20	11	22	Proctitis/fistula
Bladder wall	<15	8.7	22	Cystitis/fistula
Penile bulb	<3	14	34	Impotence
Femoral heads (right and left)	<10	14		Necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6		Malignant hypertension

Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	7	Basic lung function
Lung (right and left)	1,000	7.4	Pneumonitis
Liver	700	9.1	Basic liver function
Renal cortex (right and left)	200	8.4	Basic renal function

Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
THREE-FRACTION TREATMENT				
Optic pathway	<0.2	15 (5 Gy/fx)	19.5 (6.5 Gy/fx)	Neuritis
Cochlea			20 (6.67 Gy/fx)	Hearing loss
Brainstem	<1	18 (6 Gy/fx)	23 (7.67 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25	18 (6 Gy/fx)	22 (7.33 Gy/fx)	Myelitis
	<1.2	11.1 (3.7 Gy/fx)		
Cauda equina	<5	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	Neuritis
Sacral plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Esophagus*	<5	21 (7 Gy/fx)	27 (9 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Heart/pericardium	<15	24 (8 Gy/fx)	30 (10 Gy/fx)	Pericarditis
Great vessels	<10	39 (13 Gy/fx)	45 (15 Gy/fx)	Aneurysm
Trachea and ipsilateral bronchus*	<4	15 (5 Gy/fx)	30 (10 Gy/fx)	Stenosis/fistula
Skin	<10	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Stomach	<10	21 (7 Gy/fx)	24 (8 Gy/fx)	Ulceration/fistula
Duodenum*	<5	15 (5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Jejunum/ileum*	<5	16.2 (5.4 Gy/fx)	27 (9 Gy/fx)	Enteritis/obstruction
Colon*	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Colitis/fistula
Rectum*	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Proctitis/fistula
Bladder wall	<15	15 (5 Gy/fx)	30 (10 Gy/fx)	Cystitis/fistula
Penile bulb	<3	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	Impotence
Femoral heads (right and left)	<10	21.9 (7.3 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	18.6 (6.2 Gy/fx)		Malignant hypertension

Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	10.5 (3.5 Gy/fx)	Basic lung function
Lung (right and left)	1,000	11.4 (3.8 Gy/fx)	Pneumonitis
Liver	700	17.1 (5.7 Gy/fx)	Basic liver function
Renal cortex (right and left)	200	14.4 (4.8 Gy/fx)	Basic renal function

Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
FIVE-FRACTION TREATMENT				
Optic pathway	<0.2	20 (4 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			27.5 (5.5 Gy/fx)	Hearing loss
Brainstem	<1	26 (5.2 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25	22.5 (4.5 Gy/fx)	30 (6 Gy/fx)	Myelitis
	<1.2	13.5 (2.7 Gy/fx)		
Cauda equina	<5	30 (6 Gy/fx)	34 (6.4 Gy/fx)	Neuritis
Sacral plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus*	<5	27.5 (5.5 Gy/fx)	35 (7 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Heart/pericardium	<15	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10	47 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and ipsilateral bronchus*	<4	18 (3.6 Gy/fx)	38 (7.6 Gy/fx)	Stenosis/fistula
Skin	<10	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Stomach	<10	28 (5.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula
Duodenum*	<5	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Jejunum/ileum*	<5	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	enteritis/obstruction
Colon*	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	colitis/fistula
Rectum*	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	proctitis/fistula
Bladder wall	<15	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	cystitis/fistula
Penile bulb	<3	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10	30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	23 (4.6 Gy/fx)		Malignant hypertension

Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	12.5 (2.5 Gy/fx)	Basic lung function
Lung (right and left)	1000	13.5 (2.7 Gy/fx)	Pneumonitis
Liver	700	21 (4.2 Gy/fx)	Basic liver function
Renal cortex (right and left)	200	17.5 (3.5 Gy/fx)	Basic renal function

*Avoid circumferential irradiation.

Normal tissue complications in SBRT

2010 – Report AAPM TG-101

- Reports a table summary of **suggested dose constraints** for various critical organs for one, three, five fractions treatments.
- **Serial tissues**: volume-dose constraints are in terms of **maximum tissue volume** that should receive a **dose ≥** indicated **threshold**.
- Parallel tissues: volume-dose constraints are in terms of **minimum tissue volume** that should receive a **dose ≤** indicated **threshold**.

Serial tissue	Max critical volume above threshold	One fraction		Three fractions		Five fractions		End point (≥Grade3)
		Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	
Optic pathway	<0.2 cc	8	10	15.3 (5.1 Gy/fx)	17.4 (5.8 Gy/fx)	23 (4.6 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			9		17.1 (5.7 Gy/fx)		25 (5 Gy/fx)	Hearing loss
Brainstem (not medulla)	<0.5 cc	10	15	18 (6 Gy/fx)	23.1 (7.7 Gy/fx)	23 (4.6 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord and medulla	<0.35 cc	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
	<1.2 cc	7		12.3 (4.1 Gy/fx)		14.5 (2.9 Gy/fx)		
Spinal cord subvolume (5–6 mm above and below level treated per Ryu)	<10% of subvolume	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
Cauda equina	<5 cc	14	16	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuritis
Sacral plexus	<5 cc	14.4	16	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus[b]	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Stenosis/fistula
Brachial plexus	<3 cc	14	17.5	20.4 (6.8 Gy/fx)	24 (8 Gy/fx)	27 (5.4 Gy/fx)	30.5 (6.1 Gy/fx)	Neuropathy
Heart/pericardium	<15 cc	16	22	24 (8 Gy/fx)	30 (10 Gy/fx)	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10 cc	31	37	39 (13 Gy/fx)	45 (15 Gy/fx)	47 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and large bronchus[b]	<4 cc	10.5	20.2	15 (5 Gy/fx)	30 (10 Gy/fx)	16.5 (3.3 Gy/fx)	40 (8 Gy/fx)	Stenosis/fistula
Bronchus-smaller airways	<0.5 cc	12.4	13.3	18.9 (6.3 Gy/fx)	23.1 (7.7 Gy/fx)	21 (4.2 Gy/fx)	33 (6.6 Gy/fx)	Stenosis with atelectasis
Rib	<1 cc	22	30	28.8 (9.6 Gy/fx)	36.9 (12.3 Gy/fx)	35 (7 Gy/fx)	43 (8.6 Gy/fx)	Pain or fracture
	<30 cc			30.0 (10.0 Gy/fx)				
Skin	<10 cc	23	26	30 (10 Gy/fx)	33 (11 Gy/fx)	36.5 (7.3 Gy/fx)	39.5 (7.9 Gy/fx)	Ulceration
Stomach	<10 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula
Duodenum[b]	<5 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
	<10 cc	9		11.4 (3.8 Gy/fx)		12.5 (2.5 Gy/fx)		
Jejunum/ileum[b]	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Enteritis/ obstruction
Colon[b]	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Colitis/fistula
Rectum[b]	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Proctitis/fistula
Bladder wall	<15 cc	11.4	18.4	16.8 (5.6 Gy/fx)	28.2 (9.4 Gy/fx)	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	Cystitis/fistula
Penile bulb	<3 cc	14	34	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10 cc	14		21.9 (7.3 Gy/fx)		30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6	18.6 (6.2 Gy/fx) →			23 (4.6 Gy/fx)		Malignant hypertension

Parallel tissue	Minimum critical volume below threshold	One fraction		Three fractions		Five fractions		End point (≥Grade 3)
		Threshold dose (Gy)	Max point dose(Gy)[a]	Threshold dose(Gy)	Max point dose(Gy)[a]	Threshold dose(Gy)	Max point dose(Gy)[a]	
Lung (right and left)	1500 cc	7	NA-Parallel tissue	11.6 (2.9 Gy/fx)	NA-Parallel tissue	12.5 (2.5 Gy/fx)	NA-Parallel tissue	Basic lung function
Lung (right and left)	1000 cc	7.4	NA-Parallel tissue	12.4 (3.1 Gy/fx)	NA-Parallel tissue	13.5 (2.7 Gy/fx)	NA-Parallel tissue	Pneumonitis
Liver	700 cc	9.1	NA-Parallel tissue	19.2 (4.8 Gy/fx)	NA-Parallel tissue	21 (4.2 Gy/fx)	NA-Parallel tissue	Basic liver function
Renal cortex (right and left)	200 cc	8.4	NA-Parallel tissue	16 (4 Gy/fx)	NA-Parallel tissue	17.5 (3.5 Gy/fx)	NA-Parallel tissue	Basic renal function

[a]"Point" defined as 0.035 cc or less.
[b]Avoid circumferential irradiation.

Normal tissue complications in SBRT

- **QU**antitative **A**nalysis of **N**ormal **T**issue **E**ffects in the **C**linic 2010.

- QUANTEC **meta-analysis** of reported literature about side effects. Statistical and **radiobiologycal functions** were used.

- Most of the available data relate to **conventionally fractionated conformal** irradiation, i.e., not hypofractionated or intensity-modulated approaches

Some constraints for SRS/SBRT are reported in QUANTEC

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1	Partial cord cross-section irradiated
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1	3 fractions, partial cord cross-section irradiated
Cochlea	Whole organ	SRS (single fraction)	Sensory neural hearing loss	Prescription dose ≤14	<25	Serviceable hearing
Liver	Whole liver –GTV	SBRT (hypofraction)	Classic RILD	Mean dose <13	<5	3 fractions, for primary liver cancer
				<18	<5	6 fractions, for primary liver cancer
	Whole liver – GTV	SBRT (hypofraction)	Classic RILD	Mean dose <15	<5	3 fractions, for liver metastases
				<20	<5	6 fractions, for liver metastases
	>700 cc of normal liver	SBRT (hypofraction)	Classic RILD	D_{max} <15	<5	Critical volume based, in 3–5 fractions

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy, SRS = stereotactic radiosurgery, BED = Biologically effective dose, SBRT = stereotactic body radiotherapy, RILD = radiation-induced liver disease, RTOG = Radiation Therapy Oncology Group.

* All data are estimated from the literature summarized in the QUANTEC reviews unless otherwise noted. Clinically, these data should be applied with caution. Clinicians are strongly advised to use the individual QUANTEC articles to check the applicability of these limits to the clinical situation at hand. They largely do not reflect modern IMRT.

† All at standard fractionation (*i.e.*, 1.8–2.0 Gy per daily fraction) unless otherwise noted. Vx is the volume of the organ receiving ≥ x Gy. Dmax = Maximum radiation dose.

‡ Non-TBI.

§ With combined chemotherapy.

‖ Dx = minimum dose received by the "hottest" x% (or x cc's) of the organ.

¶ Severe xerostomia is related to additional factors including the doses to the submandibular glands.

** Estimated by Dr. Eisbruch.

†† Classic Radiation induced liver disease (RILD) involves anicteric hepatomegaly and ascites, typically occurring between 2 weeks and 3 months after therapy. Classic RILD also involves elevated alkaline phosphatase (more than twice the upper limit of normal or baseline value).

‡‡ For optic nerve, the cases of neuropathy in the 55 to 60 Gy range received ≈59 Gy (see optic nerve paper for details). Excludes patients with pituitary tumors where the tolerance may be reduced.

QUANTEC Brain-Optical nerves and Chiasm-Brainstem

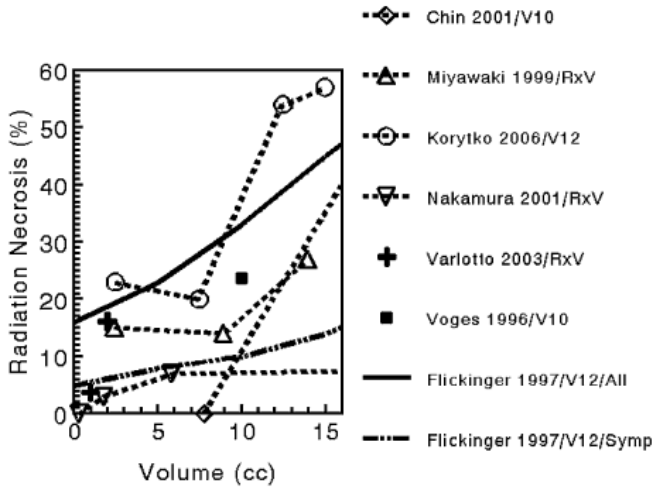


Fig. 1. Relationship between volume receiving high-dose irradiation and incidence of radiation necrosis in single-fraction stereotactic radiosurgery. Studies differed in their completeness of follow-up, definition of volume, and definition of radiation necrosis. Graph based on data presented in Table 1. Volume plotted as a point, representing mid-point of volume range. V_{10} = volume receiving 10 Gy; V_{12} = volume receiving 12 Gy; RxV = treatment volume. Flickinger data is shown for patients with either radiologic or symptomatic evidence of necrosis (marked as "All"), or only those with symptomatic necrosis (Symp). The other authors' data refers to symptomatic necrosis.

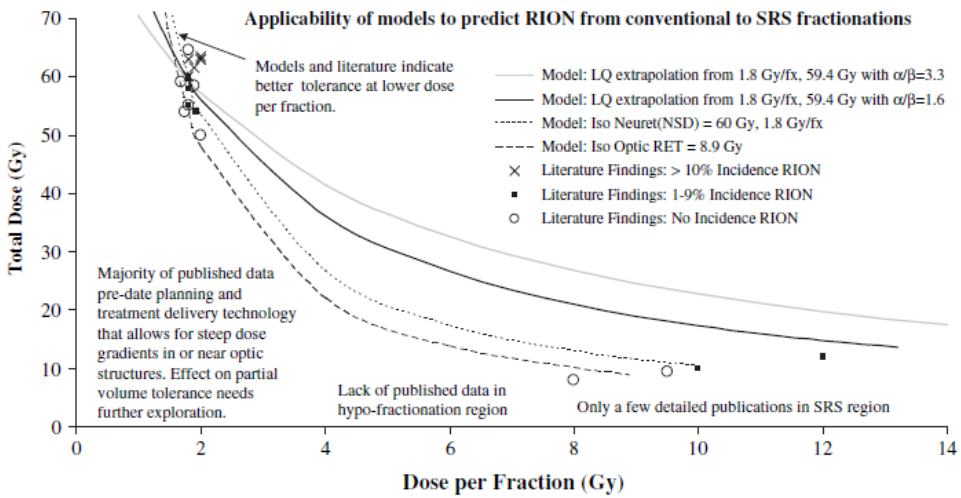


Fig. 2. Isoeffect linear-quadratic model extrapolations and alternative biologically effective threshold models (curves) compared with reported maximum optic nerve/chiasm doses detailing incidence of radiation-induced optic neuropathy (RION) (symbols) for full range of dose per fraction. Linear-quadratic model was unreliable for extrapolating from fractionated (1.8–2.0-Gy/fraction) dose range to single-fraction range. Detailed data needed for low (<1.8 Gy) and hypofractionated regions to better define organ response.

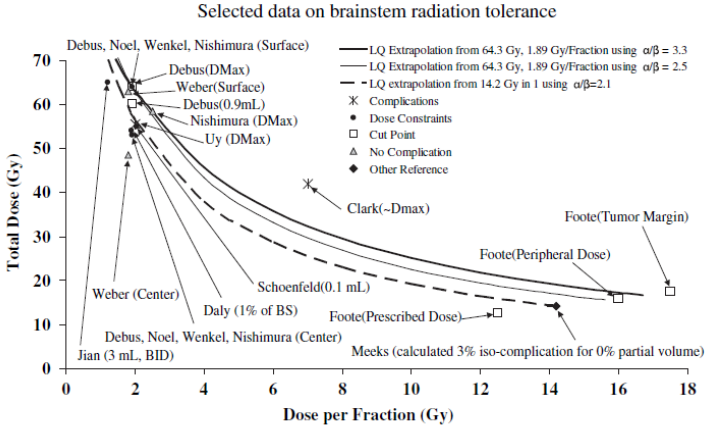


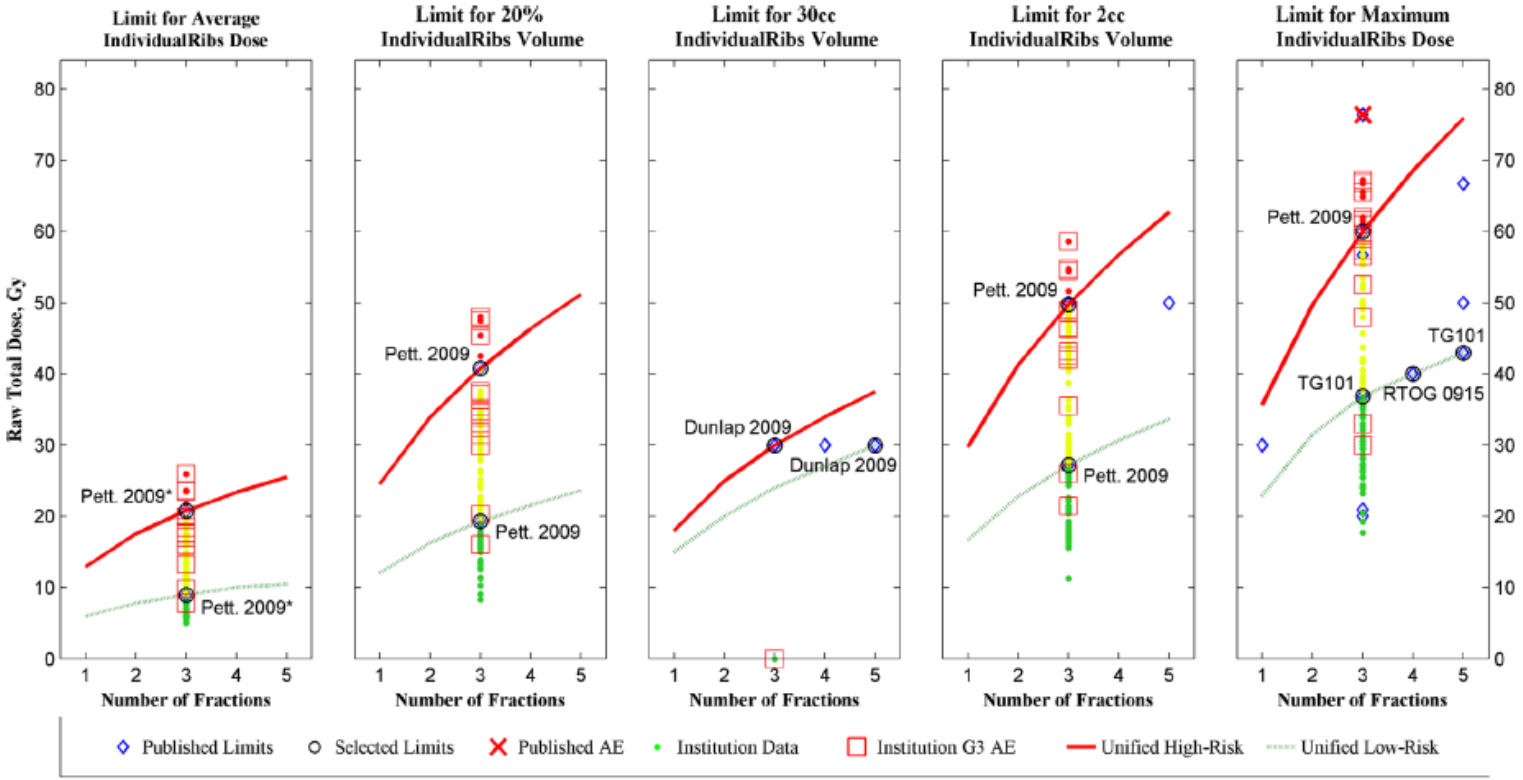
Fig. 1. Comparison of selected data on brainstem tolerance and dose constrains compared to linear quadratic (LQ) model extrapolations. Data points are marked with the corresponding author and dose parameter considered in parenthesis (*e.g.*, surface or maximum dose). Center, 0.9 mL, 0.1 mL, and 3 mL refer to the minimum dose to that hottest volume. Some data were estimated from the cited articles. Cut points illustrate thresholds determined by authors to correlate with significant increase in incidence of brainstem necrosis or neuropathy. Little quantitative data on brainstem doses is available in the dose range of stereotactic radiosurgery and hypofractionation. BID = twice daily; BS = Brain Stem; Dmax = maximum dosage.

- DVH **Risk map**:

2016 Grimm

- Combine **NTCP knowledge** and results (2001 review) and SBRT **dose-tolerance limits** (2008 review from Timmerman).
- DVH Risk Map includes radiation **tolerance limits** as a function of **dose, fractions, volume, risk level** for SRT
- DVH Risk Map can help clinicians to visualize the trends and quantitative values

The DVH Risk Map in the rib fracture case

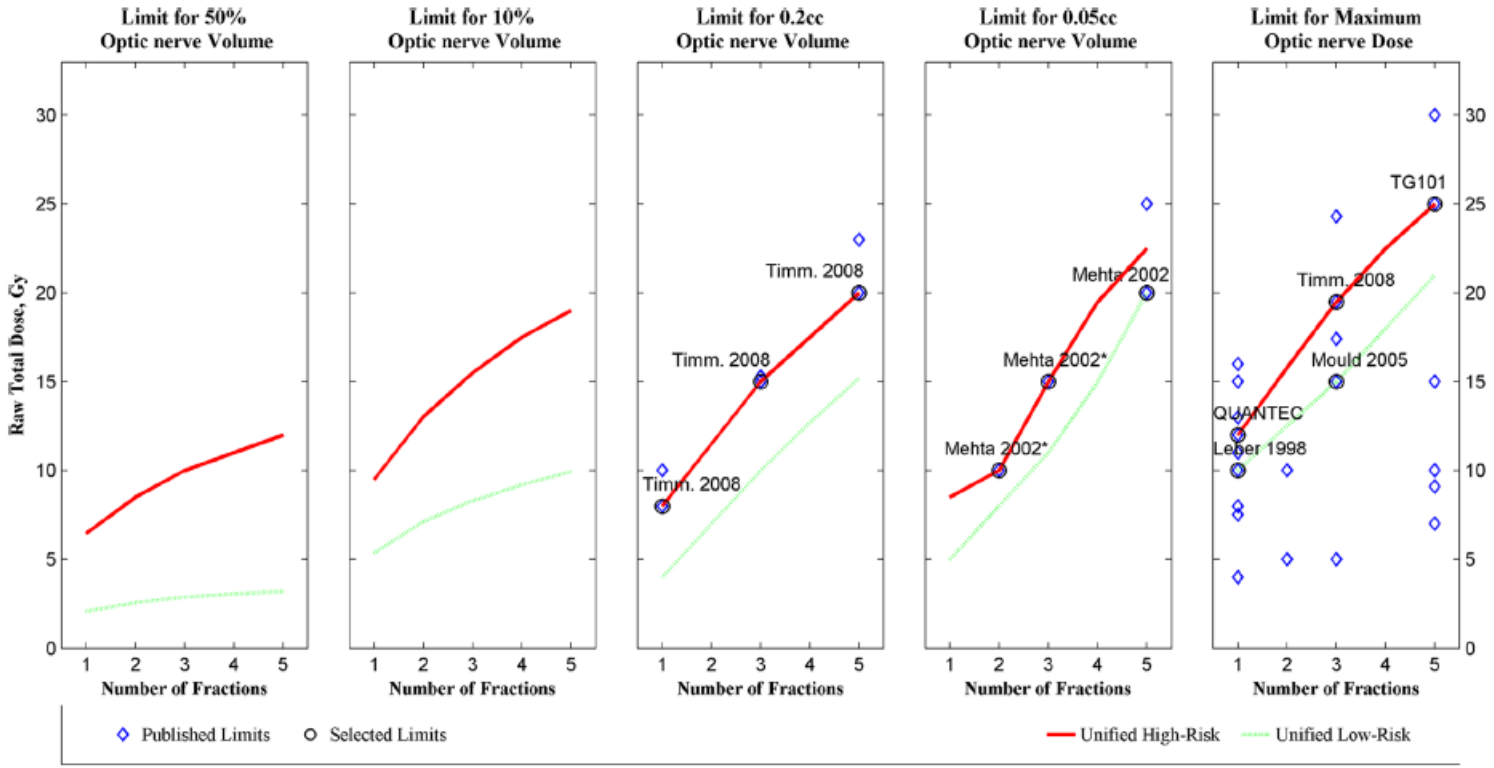


	Low Risk Limits					High Risk Limits				
	Dmean Limit (Gy)	D20% Limit (Gy)	D30cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)	Dmean Limit (Gy)	D20% Limit (Gy)	D30cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*6.0*	*12.1*	*15.0*	*16.7*	*22.9*	*12.9*	*24.6*	*18.0*	*29.8*	*35.7*
2 fx	*7.8, 5.0%*	*16.3, 5.0%*	*20.0*	*22.8, 5.0%*	*31.5, 5.0%*	*17.6, 50.0%*	*33.9, 50.0%*	*25.0*	*41.3, 50.0%*	*49.7, 50.0%*
3 fx	**9.0, 5.0%**	**19.3, 5.0%**	*24.0*	**27.2, 5.0%**	**36.9, 4.5%**	**20.8, 50.0%**	**40.8, 50.0%**	**30.0**	**49.8, 50.0%**	**60.0, 49.9%**
4 fx	*10.0, 5.1%*	*21.6, 5.0%*	*27.0*	*30.7, 5.0%*	**40.0, 3.9%**	*23.4, 50.0%*	*46.4, 50.0%*	*34.0*	*56.8, 50.0%*	*68.6, 50.0%*
5 fx	*10.5*	*23.6*	**30.0**	*33.7*	**43.0**	*25.5*	*51.2*	*37.5*	*62.8*	*76.0*

Next

Figure 5 Full DVH Risk Map for individual ribs, with clinical data and estimates of risk from Pettersson 2009. (Color version

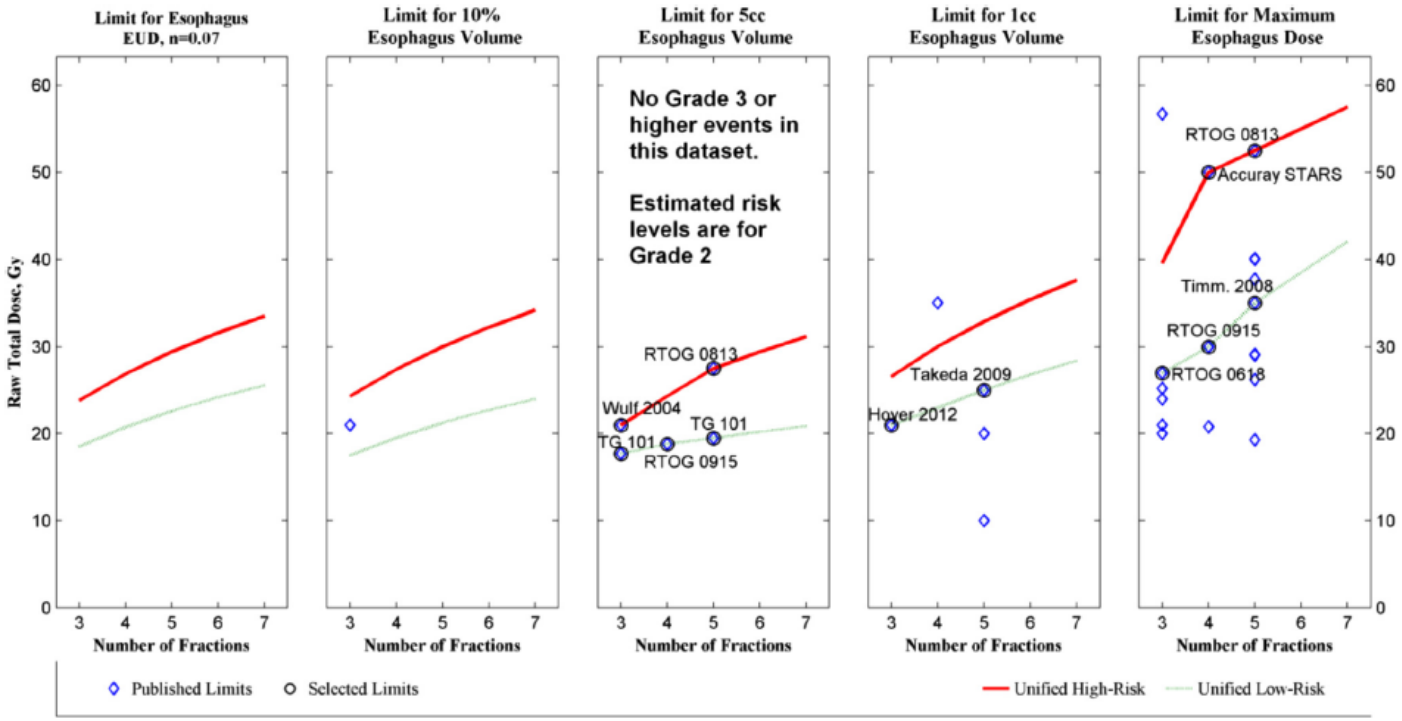
Visual Pathway Dose Tolerance



	Low Risk Limits					High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D0.2cc Limit (Gy)	D0.05cc Limit (Gy)	Dmax Limit (Gy)	D50% Limit (Gy)	D10% Limit (Gy)	D0.2cc Limit (Gy)	D0.05cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*2.1, 0.3%*	*5.4, 0.2%*	*4.0, 0.4%*	*5.0, 0.1%*	**10.0, 0.3%**	*6.5, 1.0%*	*9.5, 1.0%*	**8.0, 1.1%**	*8.5, 0.6%*	**12.0, 0.7%**
2 fx	*2.6, 0.3%*	*7.1, 0.2%*	*7.0, 0.6%*	*8.0, 0.2%*	*12.5, 0.2%*	*8.5, 1.0%*	*13.0, 1.0%*	*11.5, 1.2%*	**10.0, 0.4%**	*15.8, 0.6%*
3 fx	*2.9, 0.3%*	*8.3, 0.2%*	*10.0, 0.7%*	*11.0, 0.3%*	**15.0, 0.2%**	*10.0, 1.0%*	*15.5, 1.0%*	**15.0, 1.5%**	**15.0, 0.8%**	**19.5, 0.7%**
4 fx	*3.1, 0.3%*	*9.2, 0.2%*	*12.7, 0.9%*	*15.0, 0.6%*	*18.0, 0.3%*	*11.0, 1.0%*	*17.5, 1.0%*	*17.5, 1.6%*	*19.5, 1.4%*	*22.5, 0.8%*
5 fx	*3.2, 0.3%*	*9.9, 0.2%*	*15.2, 1.0%*	**20.0, 1.1%**	*21.0, 0.4%*	*12.0, 1.0%*	*19.0, 1.0%*	**20.0, 1.7%**	*22.5, 1.6%*	**25.0, 0.8%**

Figure 3 DVH Risk Map showing published dose tolerance limits organized into high-risk (solid red line) and low-risk (dashed green line) categories. Estimates of risk for each selected limit are shown to the right of each cell in the table. Bold limits in the table indicate published limits, and italicized limits indicate new limits from the trendlines and from modeled estimates of risk. (Color version of figure is available online.)

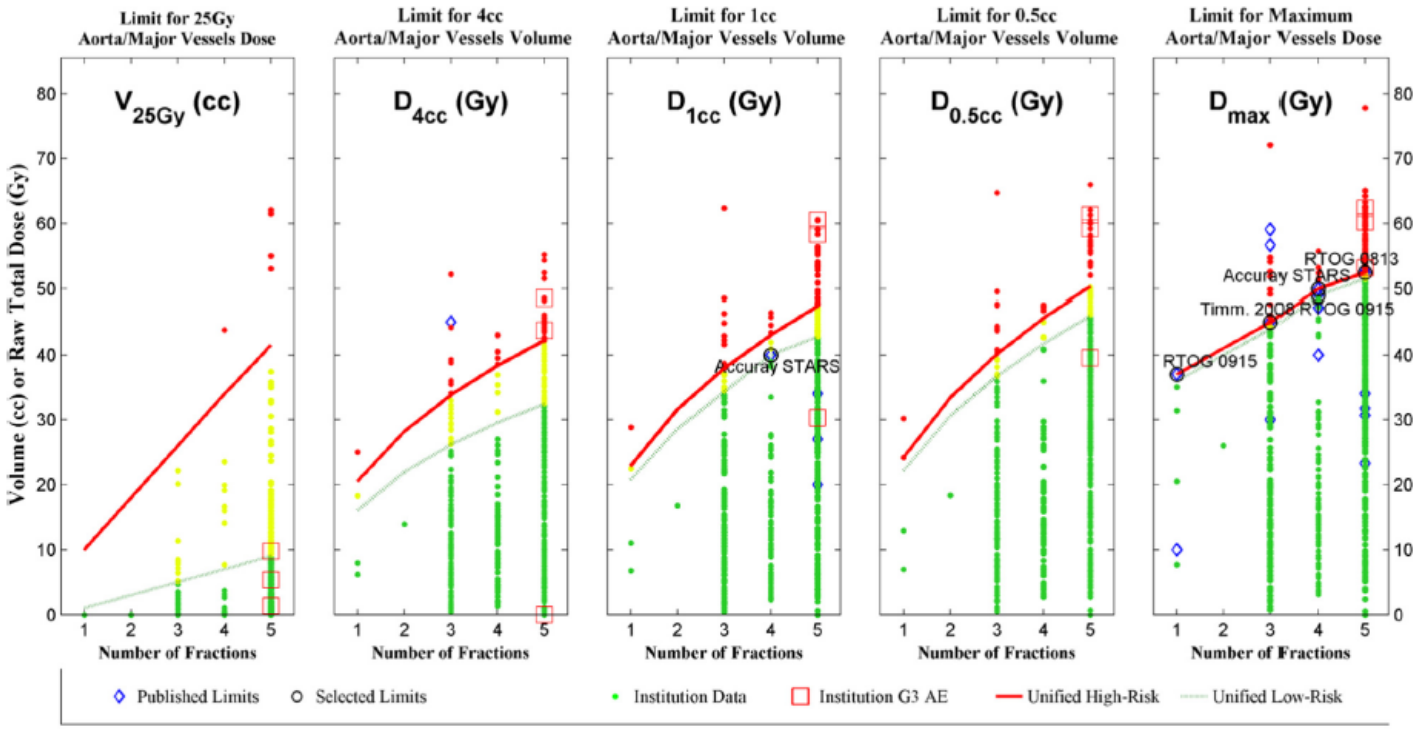
Esophagus Dose Tolerance



	Low Risk Limits					High Risk Limits				
	EUD Limit (Gy)	D10% Limit (Gy)	D5cc Limit (Gy)	D1cc Limit (Gy)	Dmax Limit (Gy)	EUD Limit (Gy)	D10% Limit (Gy)	D5cc Limit (Gy)	D1cc Limit (Gy)	Dmax Limit (Gy)
3 fx	*18.5, 5.0%*	*17.5, 5.0%*	**17.7, 19.7%**	**21.0, 6.9%**	**27.0, 6.3%**	*23.8, 50.0%*	*24.3, 50.0%*	**21.0, 40.6%**	*26.6, 50.0%*	*39.6, >50%*
4 fx	*20.8, 5.0%*	*19.6, 5.0%*	**18.8, 15.5%**	*23.0, 5.2%*	**30.0, 5.3%**	*26.9, 50.0%*	*27.4, 50.0%*	*24.3, 45.0%*	*30.0, 50.0%*	**50.0, >50%**
5 fx	*22.6, 5.0%*	*21.3, 5.0%*	**19.5, 12.5%**	**25.0, 5.0%**	**35.0, 9.8%**	*29.4, 50.0%*	*30.0, 50.0%*	**27.5, >50%**	*32.9, 50.0%*	**52.5, >50%**
6 fx	*24.2, 5.0%*	*22.7, 5.0%*	*20.2, 10.9%*	*26.8, 5.0%*	*38.5, 11.9%*	*31.6, 50.0%*	*32.2, 50.0%*	*29.4, 50.0%*	*35.4, 50.0%*	*55.0, >50%*
7 fx	*25.6, 5.0%*	*24.0, 5.0%*	*20.9, 10.0%*	*28.4, 5.0%*	*42.0, 15.0%*	*33.5, 50.0%*	*34.2, 50.0%*	*31.2, 50.0%*	*37.6, 50.0%*	*57.5, >50%*

Figure 2 DVH Risk Map for grade 2 esophagitis. Published dose-tolerance limits[20] are plotted as blue diamonds, selected dose-tolerance limits are circled and labeled, the high-risk trendline is the red solid line, and the low-risk trendline is the green dashed line. In the tabular portion of the figure, the bolded limits are the selected limits and the italicized limits have been added. The dose-tolerance limit is the number on the left side of each cell, and the corresponding estimated risk level is the number to the right. (Color version of figure is available online.)

Aorta and Major Vessels Dose Tolerance

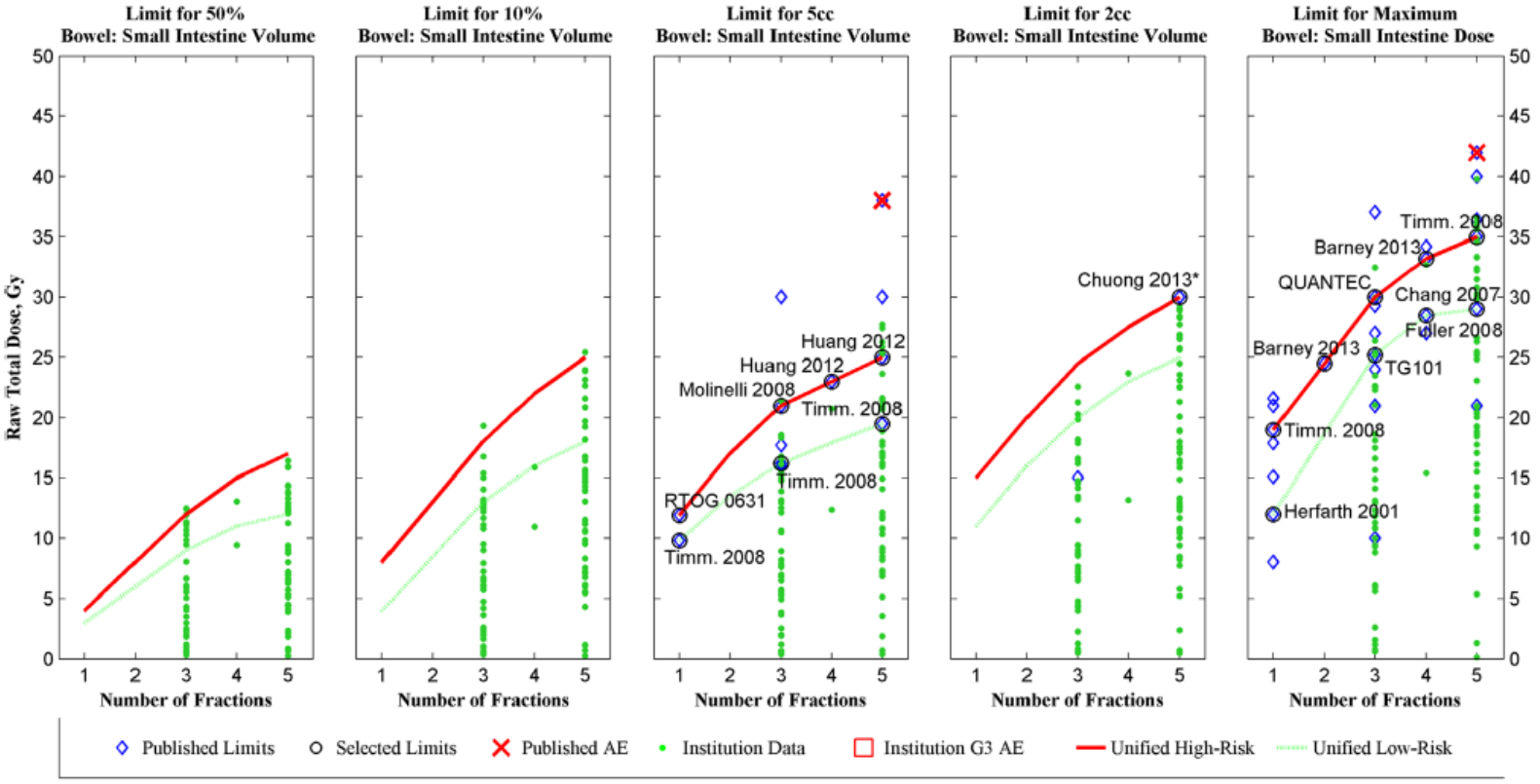


	Low Risk Limits					High Risk Limits				
	V25Gy Limit (cc)	D4cc Limit (Gy)	D1cc Limit (Gy)	D0.5cc Limit (Gy)	Dmax Limit (Gy)	V25Gy Limit (cc)	D4cc Limit (Gy)	D1cc Limit (Gy)	D0.5cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*1.0*	*16.1, 1.0%*	*20.8, 1.0%*	*22.2, 1.0%*	*36.0, 33.8%*	*10.0*	*20.5, 2.0%*	*22.9, 2.0%*	*24.2, 2.0%*	**37.0, 41.9%**
2 fx	*3.0*	*21.9, 1.0%*	*28.6, 1.0%*	*30.6, 1.0%*	*40.0, 4.2%*	*18.0*	*28.2, 2.0%*	*31.6, 2.0%*	*33.4, 2.0%*	*41.0, 5.3%*
3 fx	*5.0*	*26.2, 1.0%*	*34.3, 1.0%*	*36.8, 1.0%*	*44.0, 1.9%*	*26.0*	*33.8, 2.0%*	*37.9, 2.0%*	*40.2, 2.0%*	**45.0, 2.3%**
4 fx	*7.0*	*29.5, 1.0%*	**40.0, 1.2%**	*41.7, 1.0%*	**49.0, 1.5%**	*34.0*	*38.4, 2.0%*	*43.1, 2.0%*	*45.7, 2.0%*	**50.0, 1.8%**
5 fx	*9.0, 0.5%*	*32.4, 1.0%*	*42.8, 1.0%*	*46.0, 1.0%*	*51.5, 1.0%*	*41.5, 1.0%*	*42.2, 2.0%*	*47.5, 2.0%*	*50.4, 2.0%*	**52.5, 1.2%**

Next

Figure 2 DVH Risk Map for aorta tolerance in 1-5 fractions, with estimated risk levels from the model in Figure 1. Data from MDA at CUH are combined with Nishimura 2014 data in this graph, a total of 625 major vessels. Note that units for the leftmost panel are cc whereas the other 4 panels are in units of Gy. In this DVH Risk Map all types of major vessels are averaged together, but all 3 complications in the Nishimura 2014 dataset occurred in the pulmonary artery, hence it may be more radiosensitive than the other major vessels, so these limits might not be applicable to the pulmonary artery. (Color

Small Bowel Dose Tolerance

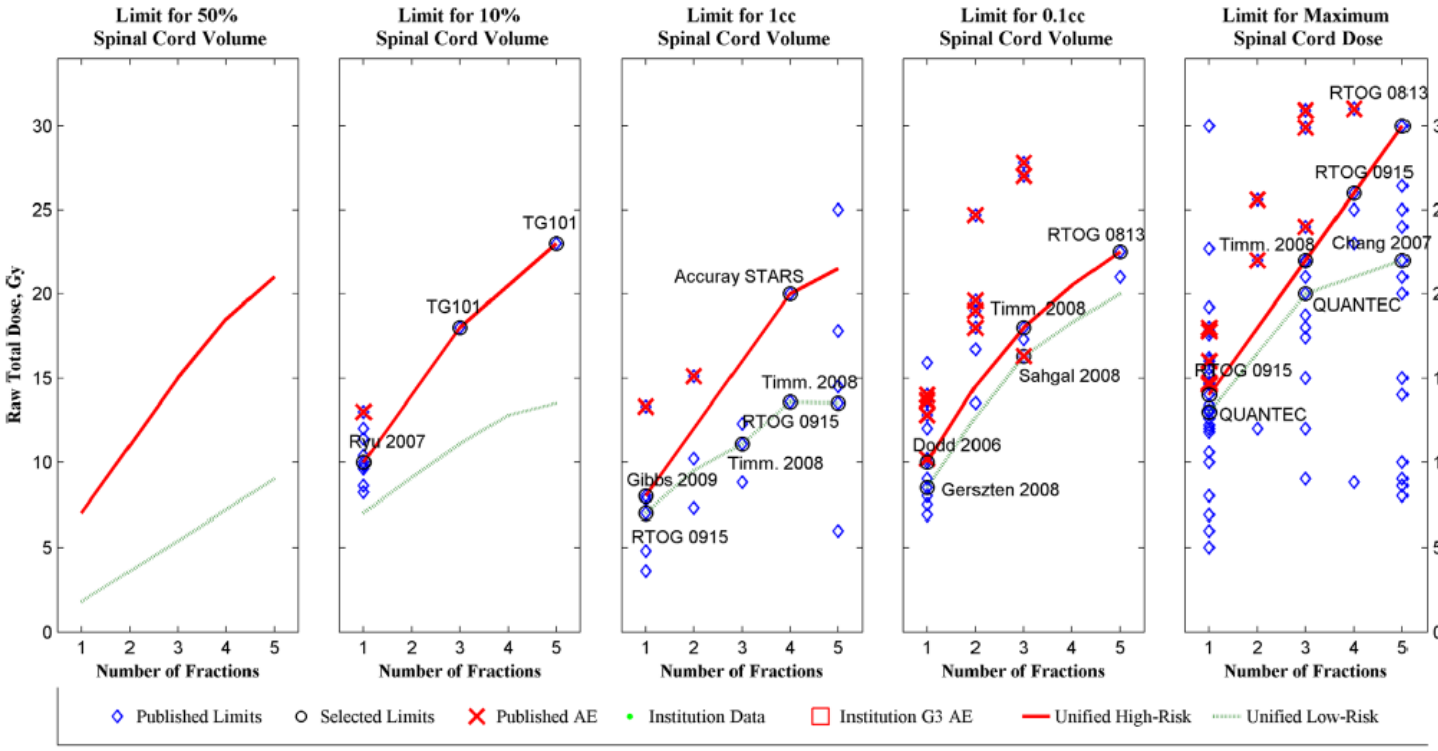


	Low Risk Limits					High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D5cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)	D50% Limit (Gy)	D10% Limit (Gy)	D5cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*3.0*	*4.0*	**9.8, 2.1%**	*11.0, 2.3%*	**12.0, 1.4%**	*4.0*	*8.0*	**11.9, 4.4%**	*15.0, 7.5%*	**19.0, 8.2%**
2 fx	*6.0*	*8.5*	*13.5, 2.3%*	*16.0, 3.0%*	*18.6, 2.3%*	*8.0*	*13.0*	*17.0, 5.5%*	*20.0, 6.9%*	**24.5, 6.4%**
3 fx	*9.0*	*13.0*	**16.2, 2.5%**	*20.0, 3.7%*	**25.2, 3.6%**	*12.0*	*18.0*	**21.0, 6.5%**	*24.5, 7.7%*	**30.0, 7.0%**
4 fx	*11.0*	*16.0*	*17.9, 2.4%*	*23.0, 4.0%*	**28.5, 3.7%**	*15.0*	*22.0*	**23.0, 5.9%**	*27.5, 7.6%*	**33.2, 6.5%**
5 fx	*12.0*	*18.0*	**19.5, 2.4%**	*25.0, 3.9%*	**29.0, 2.8%**	*17.0*	*25.0*	**25.0, 5.8%**	**30.0, 7.5%**	**35.0, 5.6%**

Next

Figure 3 DVH Risk Map for small bowel dose tolerance in 1-5 fractions. (Color version of figure is available online.)

Spinal Cord Dose Tolerance



	Low Risk Limits					High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.1cc Limit (Gy)	Dmax Limit (Gy)	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.1cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*1.8*	*7.0*	**7.0, 0.1%**	**8.5, 0.1%**	**13.0, 0.9%**	*7.0*	**10.0**	**8.0, 0.2%**	**10.0, 0.2%**	**14.0, 1.6%**
2 fx	*3.6*	*9.1*	*9.5, 0.1%*	*12.7, 0.1%*	*16.5, 0.6%*	*11.0*	*14.0*	*12.0, 0.4%*	*14.5, 0.3%*	*18.0, 1.1%*
3 fx	*5.4*	*11.1*	**11.1, 0.1%**	**16.3, 0.2%**	**20.0, 0.7%**	*15.0*	**18.0**	*16.0, 0.9%*	**18.0, 0.4%**	**22.0, 1.3%**
4 fx	*7.2*	*12.8*	**13.6, 0.2%**	*18.3, 0.2%*	*21.0, 0.5%*	*18.5*	*20.5*	**20.0, 2.2%**	*20.5, 0.4%*	**26.0, 1.8%**
5 fx	*9.0*	*13.5*	**13.5, 0.1%**	*20.0, 0.2%*	**22.0, 0.4%**	*21.0*	**23.0**	*21.5, 2.0%*	**22.5, 0.4%**	**30.0, 2.6%**

Figure 3 DVH Risk Map for spinal cord toxicity showing estimated risk level of unified SBRT spinal cord dose tolerance limits for de novo treatments, in terms of raw physical dose (Gy). Bolded limits are published data and italicized limits are interpolated or extrapolated, the blue diamonds correspond to the published dose tolerance limits from the literature review,[8] the circled diamonds with text labels are the selected limits from Appendix A, the red X's are dose-volume points corresponding to published adverse events, the red solid lines are the unified high-risk limits, and the green dashed lines are the unified low-risk limits. In the tabular portion of the figure, within the 1 cc, 0.1 cc and Max Limit cells the number on the left is the dose tolerance limit in Gy, and the number on the right is the corresponding risk level estimated from this dataset. (Color version of figure is available online.)

Radiobiology in planning

- The number of fractions can be used as an optimization parameter to increase the terapeutic ratio.

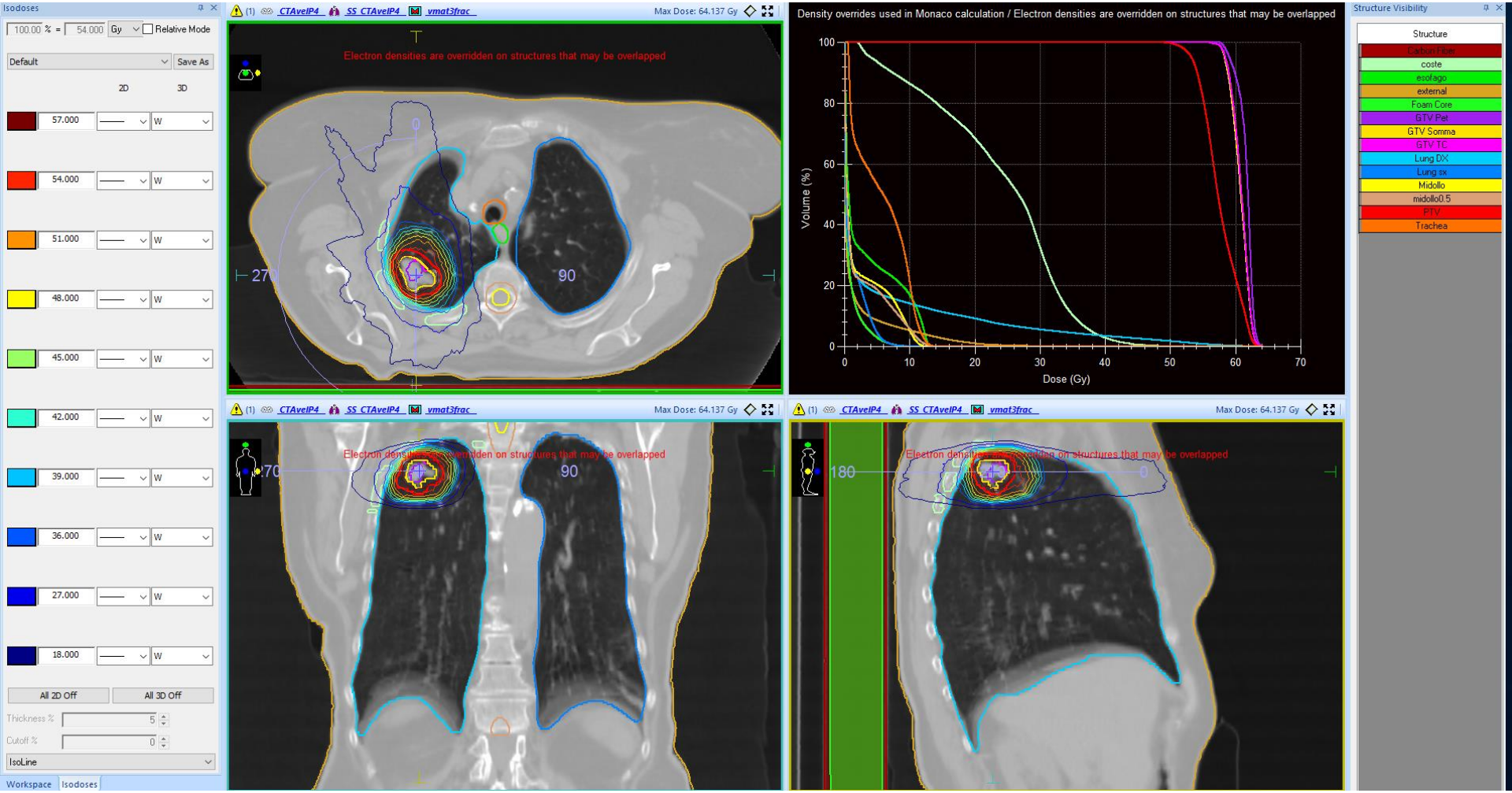
- ES: lung tumor close to ribs

Ribs constraints:

in 3 fractions: **37 Gy D_{max} 28.8 Gy at 1cc** or **27.2 at 2cc**

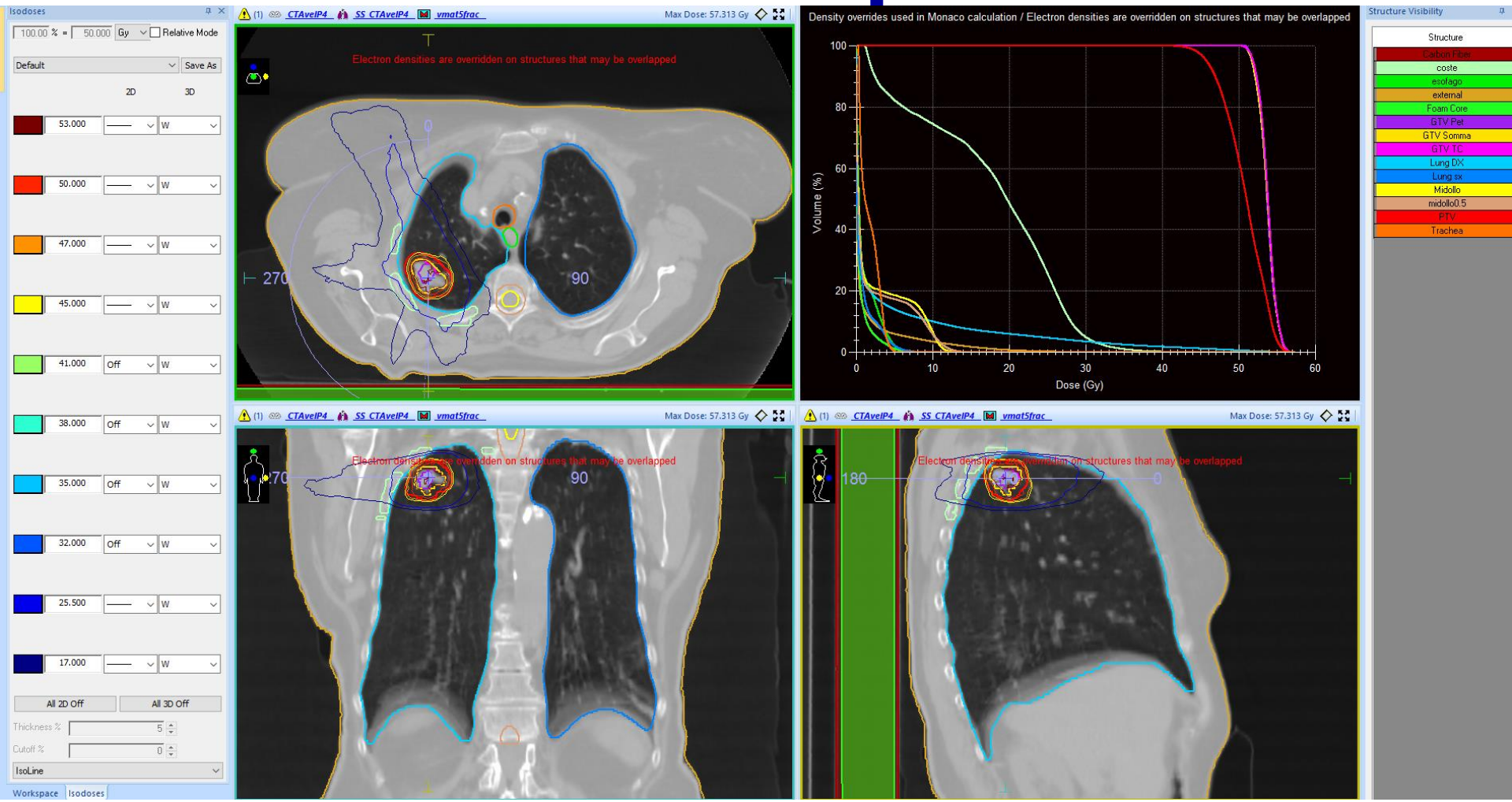
In 5 fractions: **43 Gy Dmax 35 Gy at 1cc** or **33.7 at 2cc**

How to use in practice?



The 3 fractions plan **do not respect** the constraint for ribs fractures

How to use in practice?



The 5 fractions plan **respect** the constraint for ribs fractures but: only **95%** of prescription dose in the PTV and more dose in the ITV

Conclusions

Basic **radiobiologycal concepts** are still **valid** in **SBRT** regime.

Changing the **number of fractions** can be used for **increase terapeutic ratio.**

Inhomogeneous dose inside target increases tumor radiosensitivity **IF** multiple fractions were used.