Re-irradiation in SBRT

Dilemmas, solutions and clinical cases

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Karolinska Univ. Hospital

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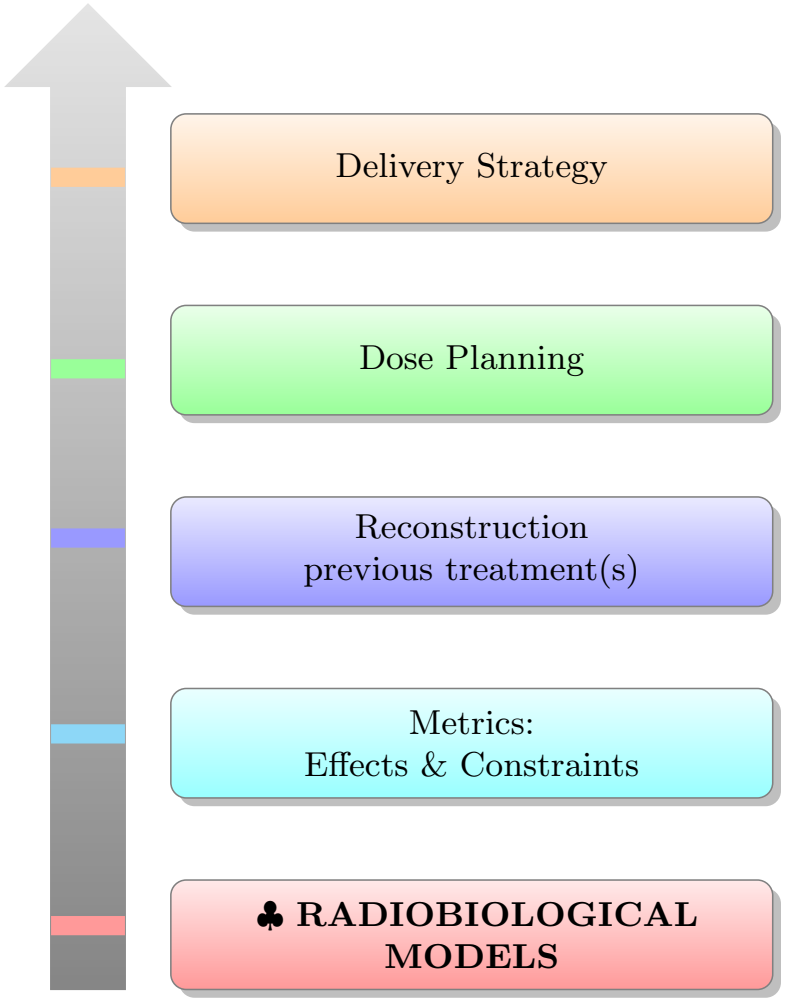

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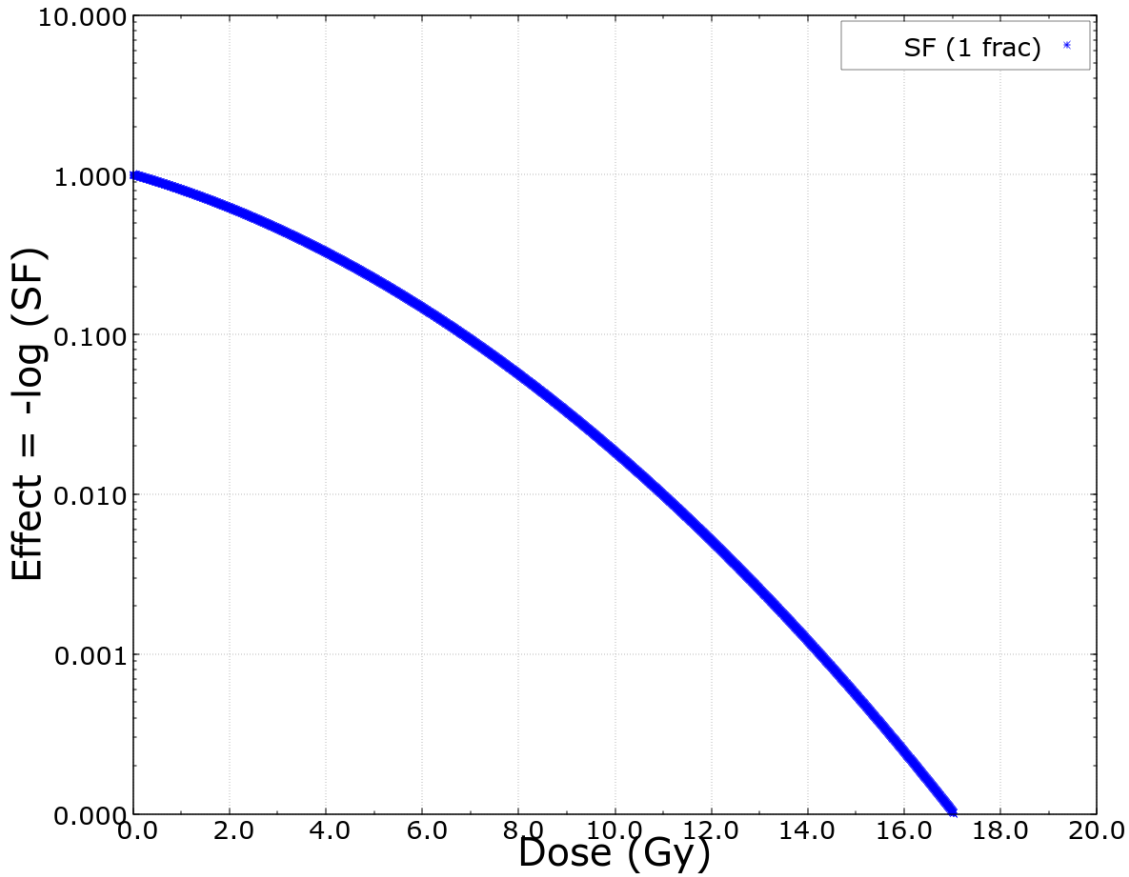
LQ model (brief overview)

LQ $\rightleftarrows$ Survival Fraction (SF) (Cells in vitro)



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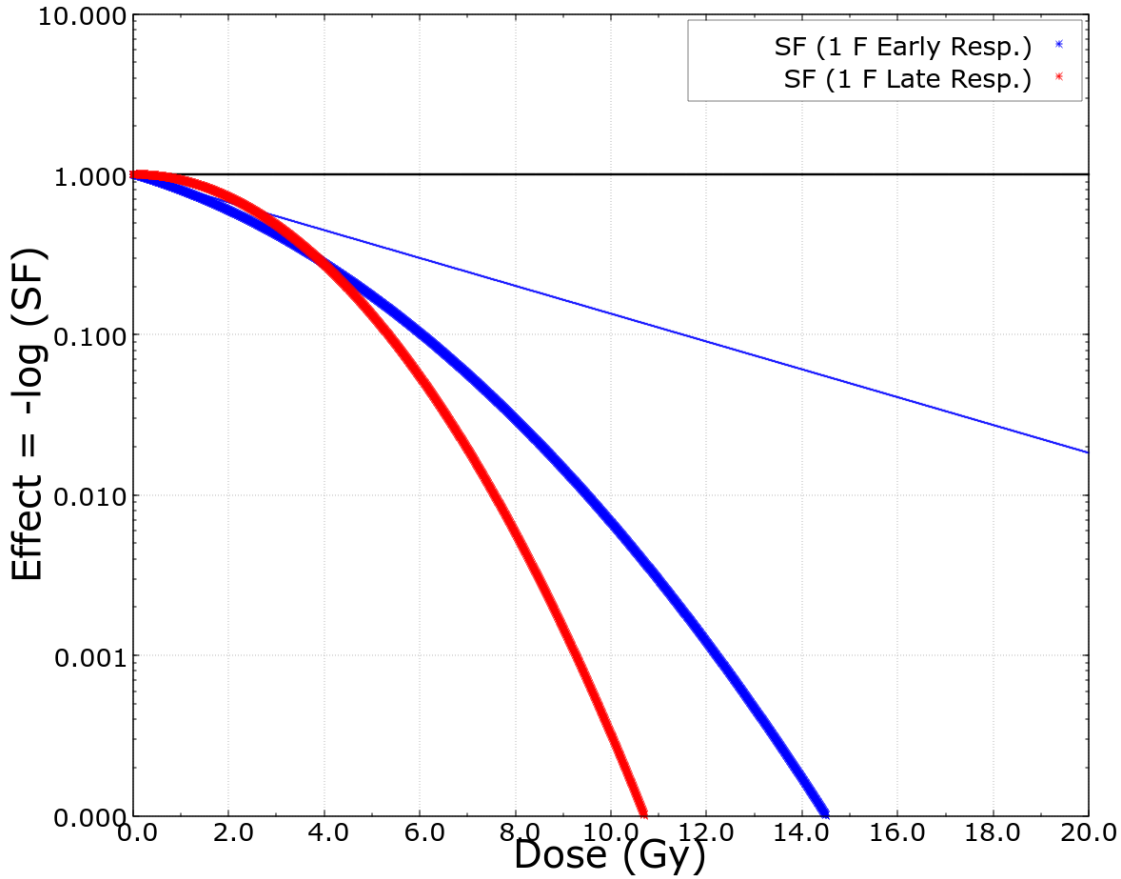

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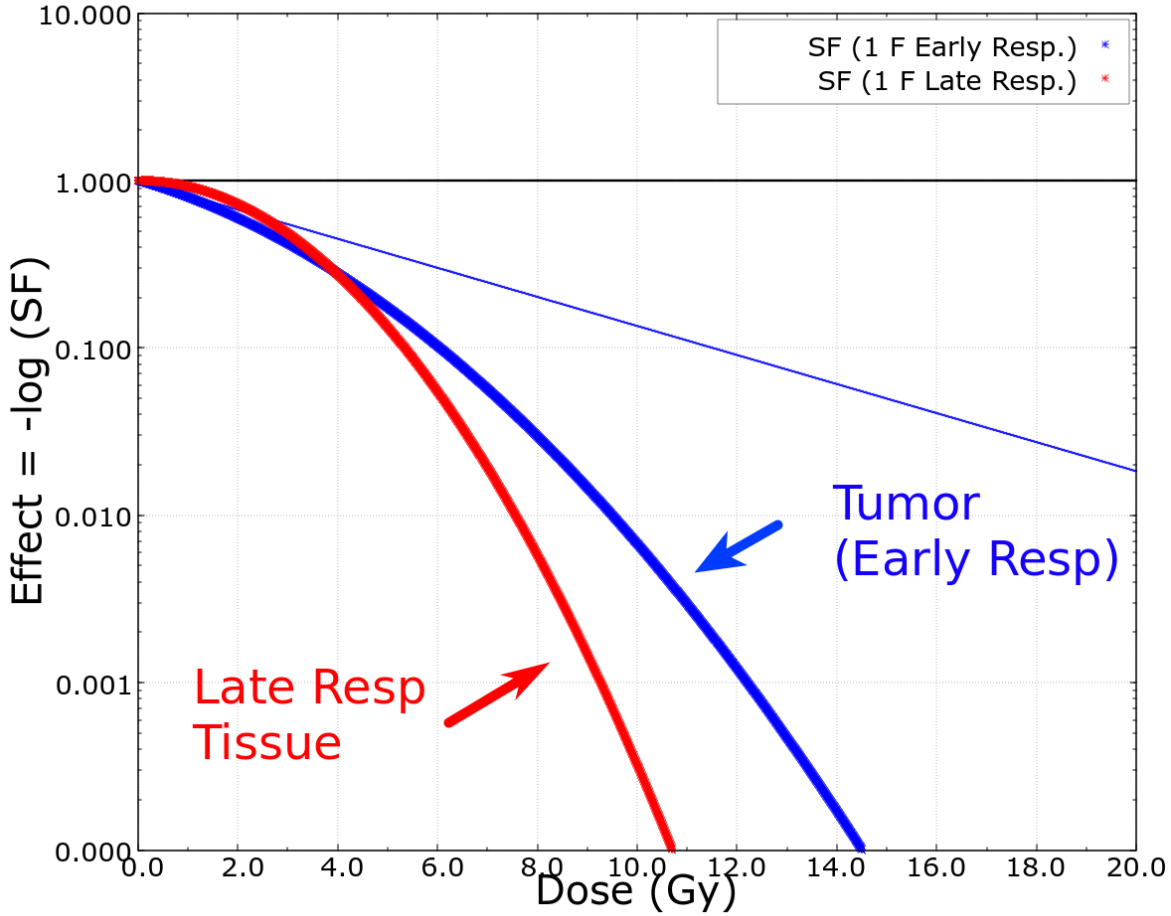

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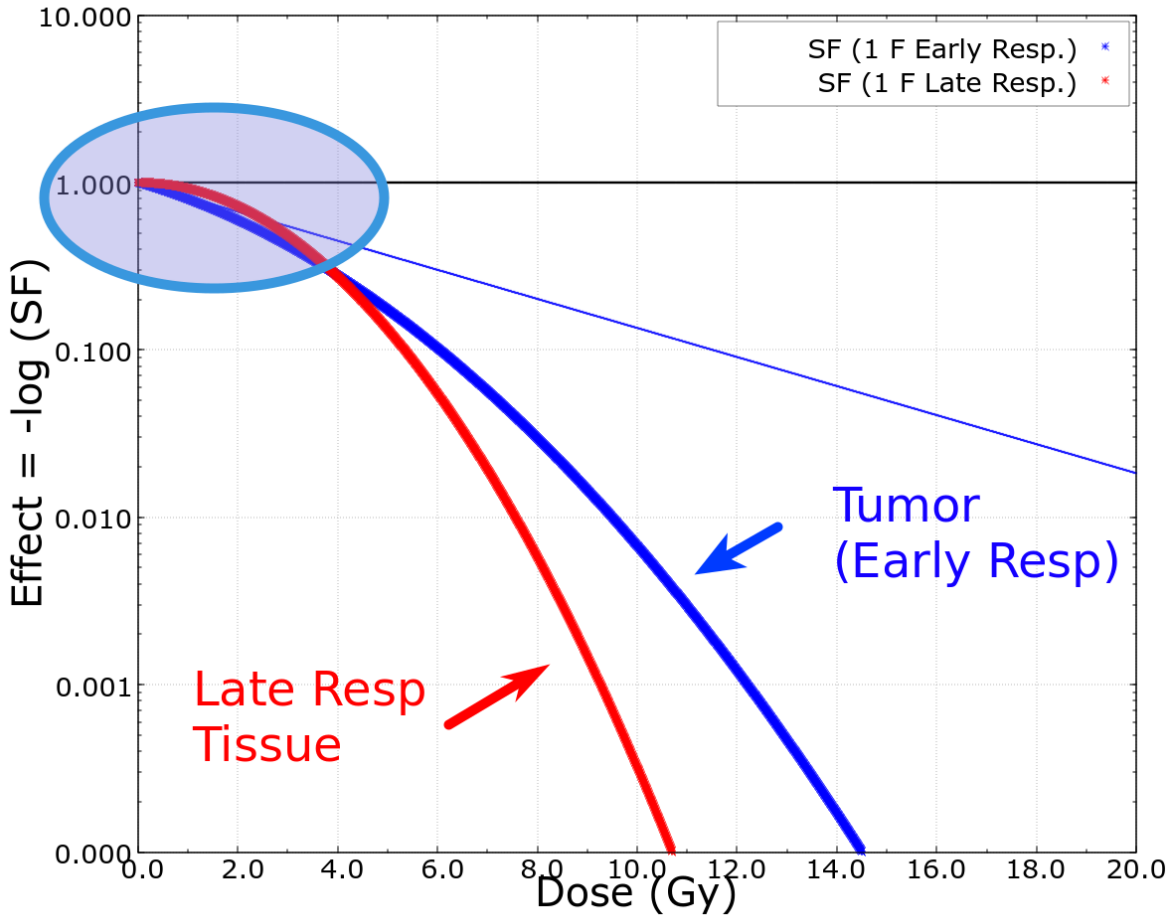

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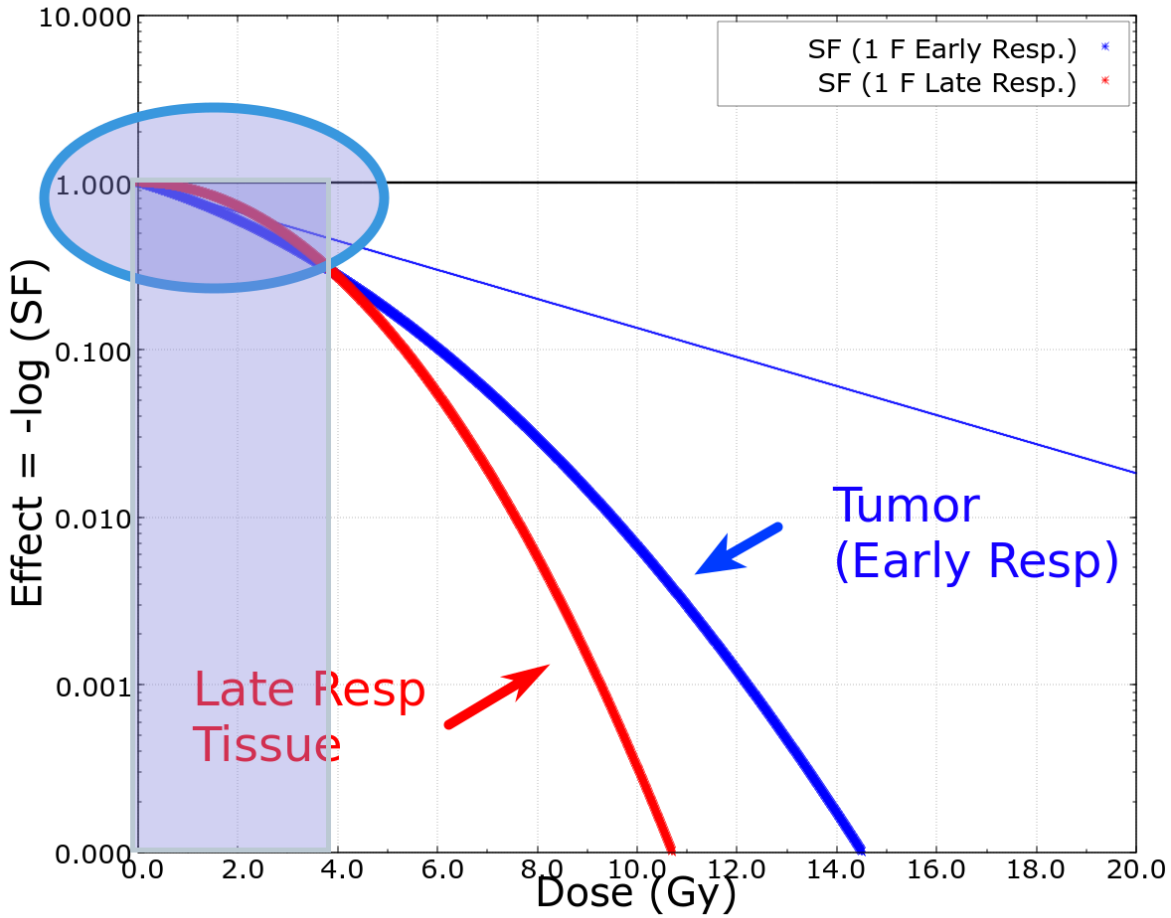

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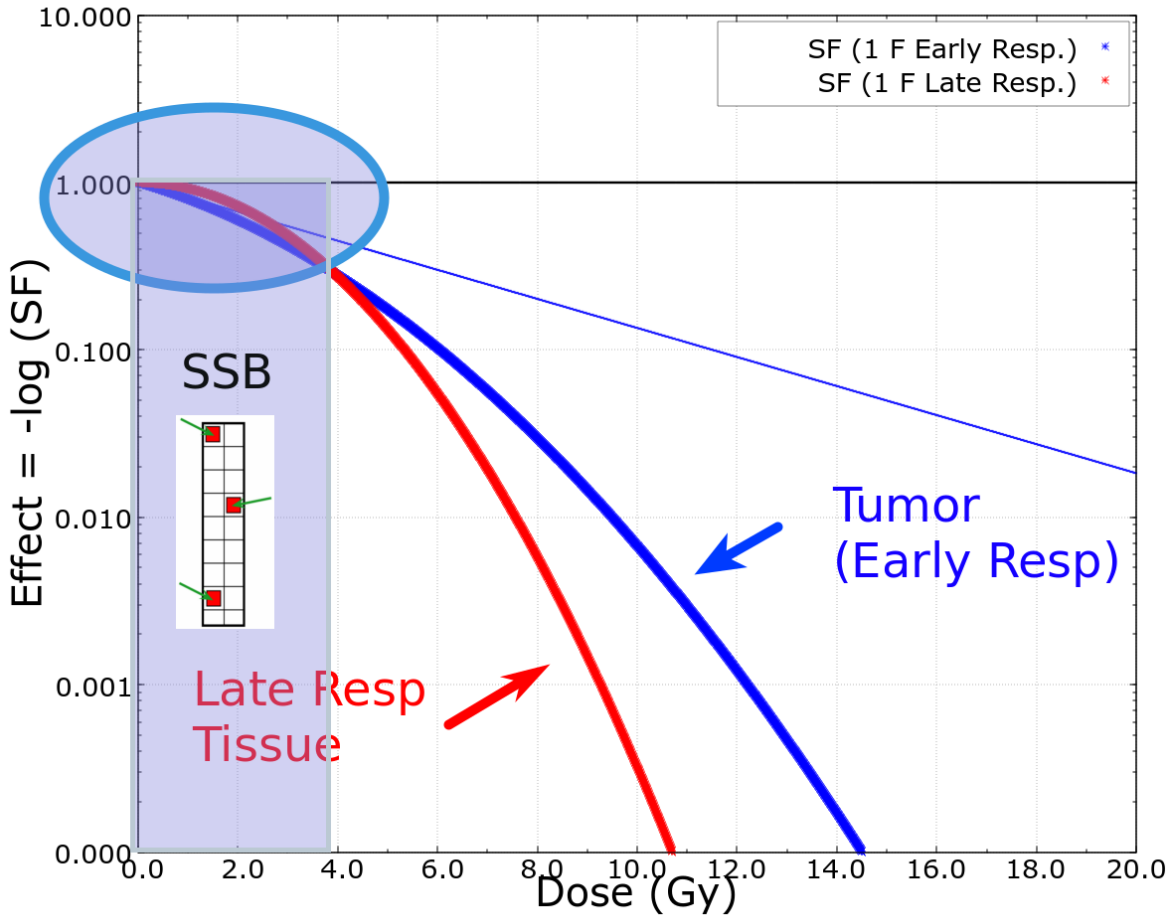

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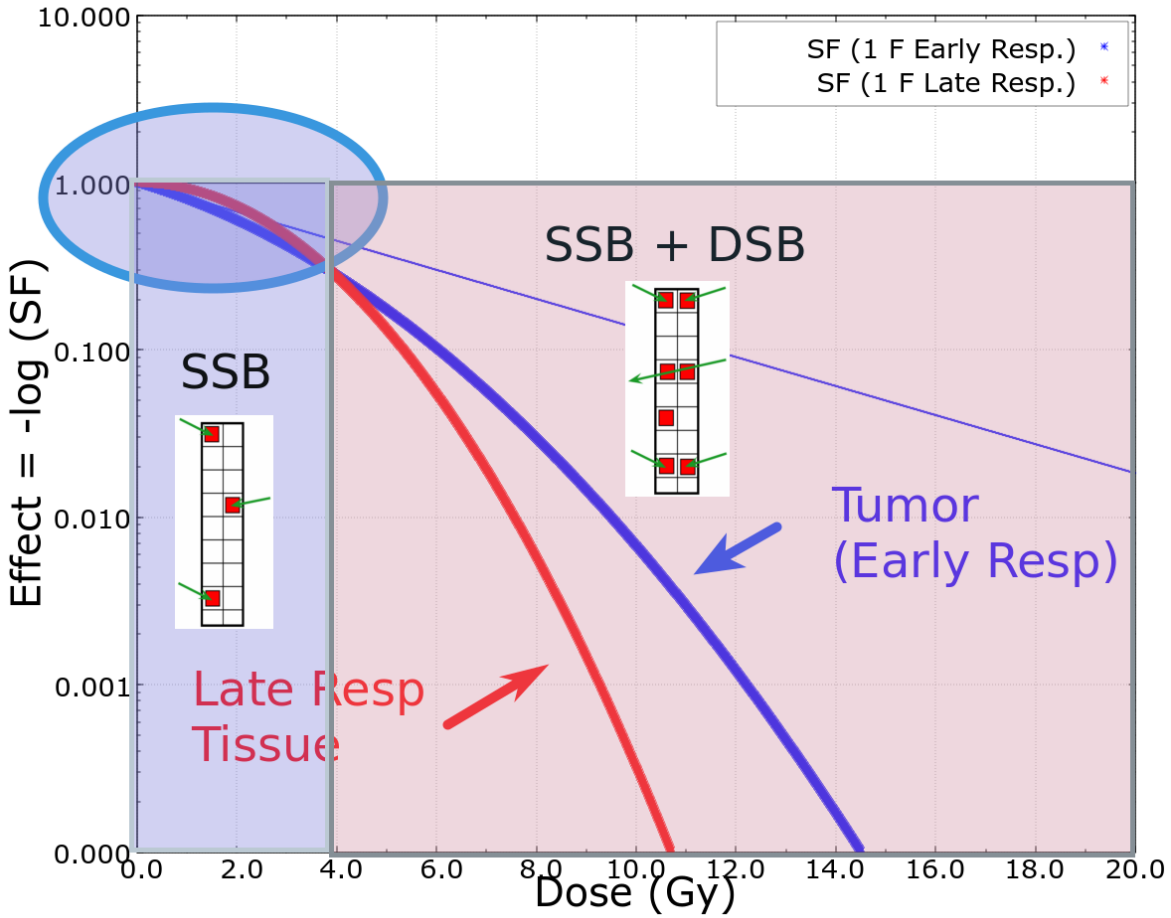

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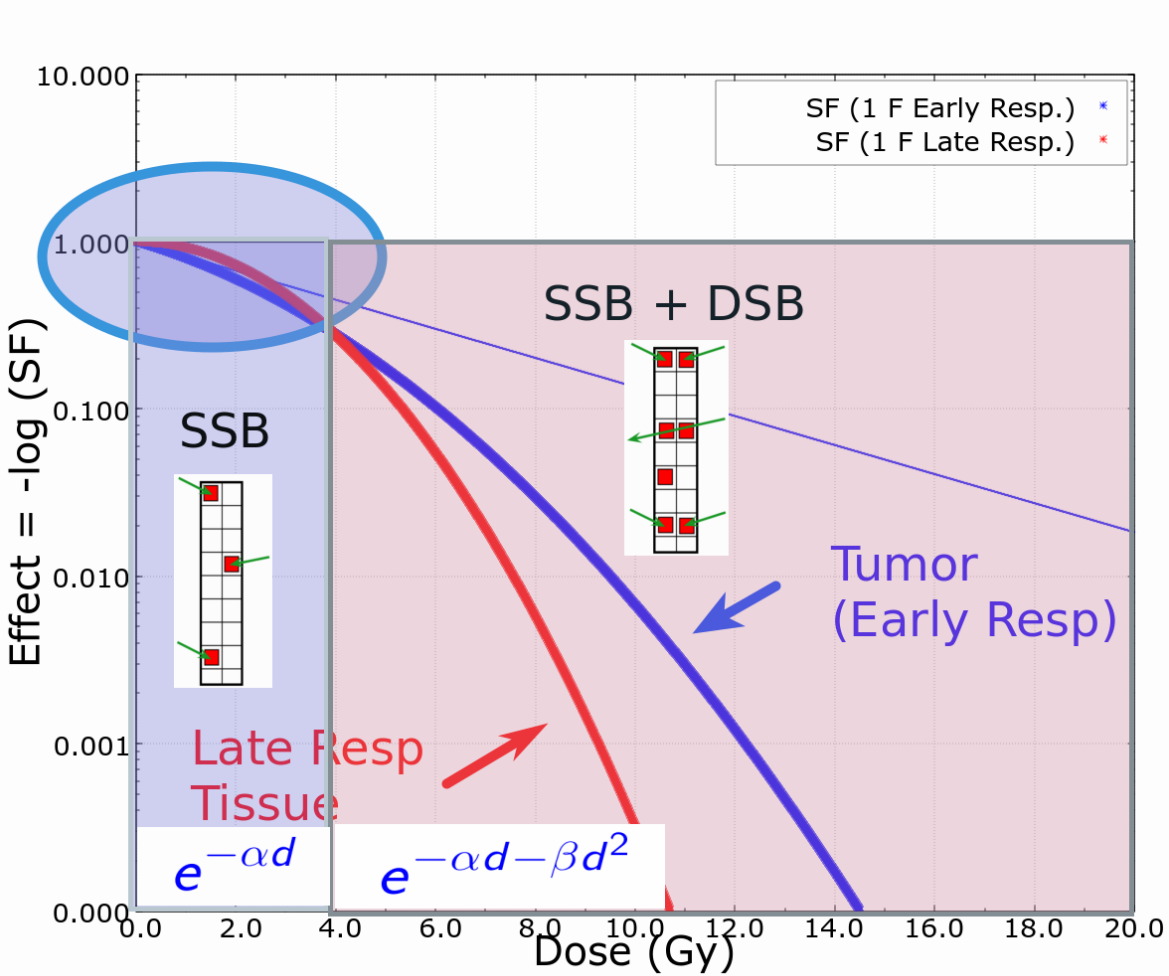

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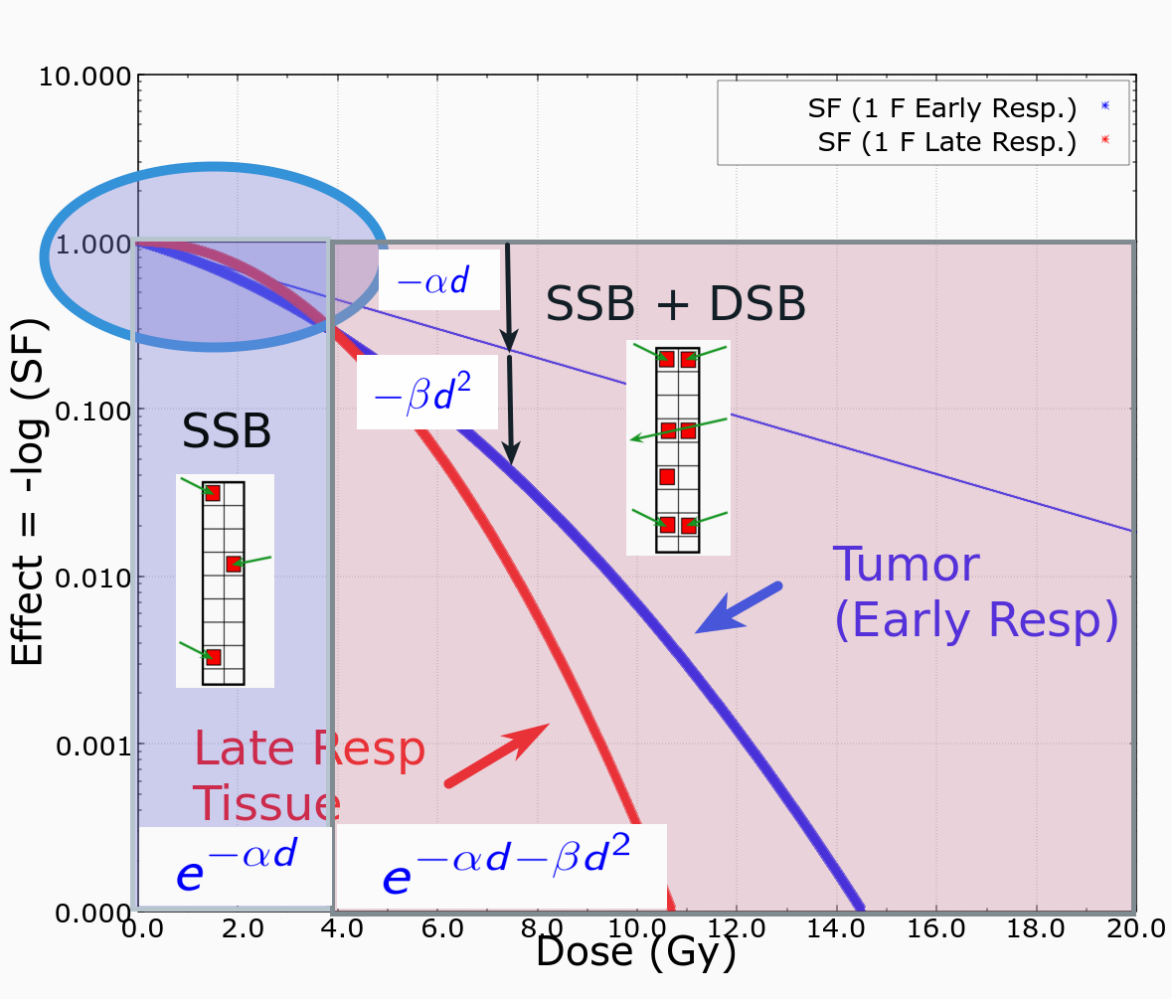

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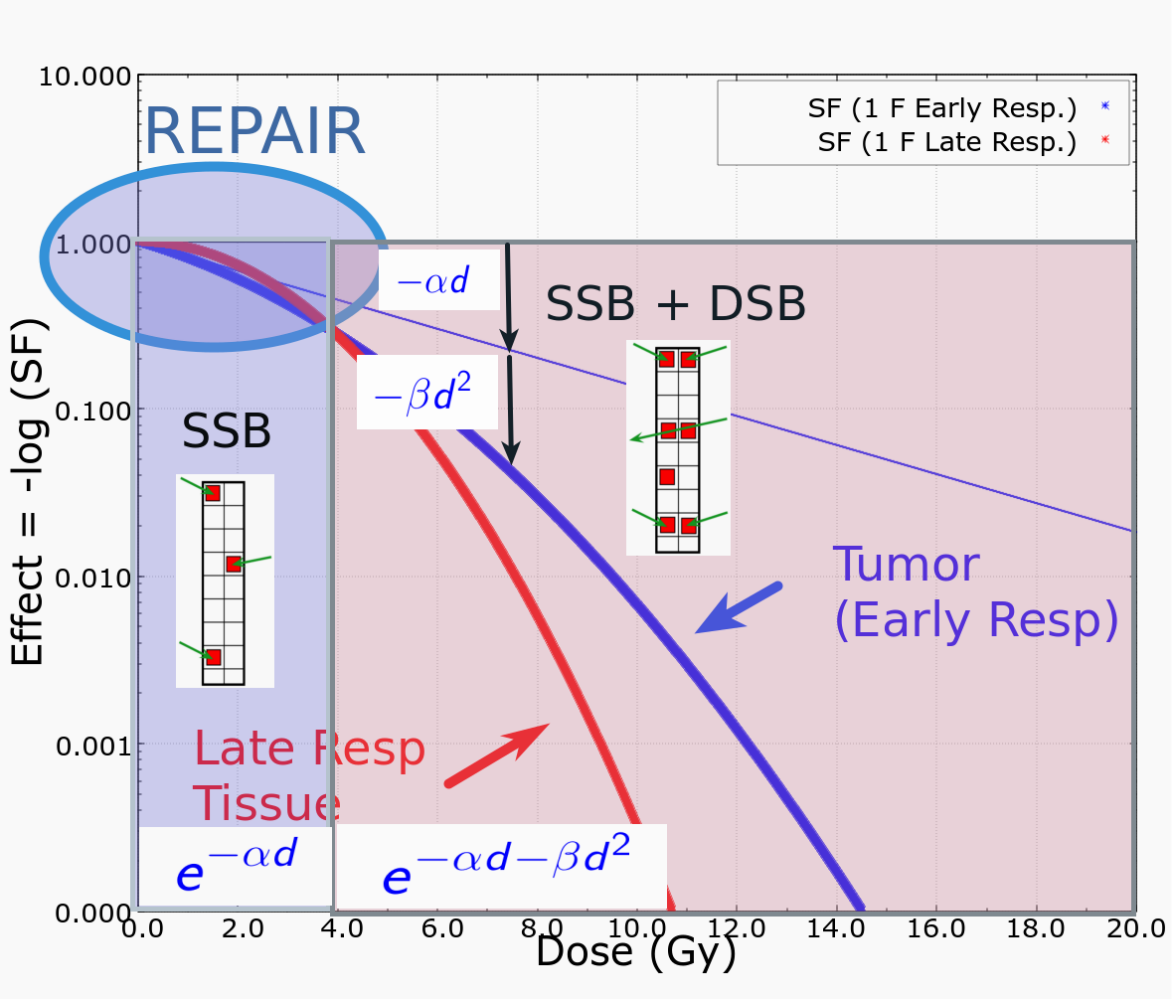

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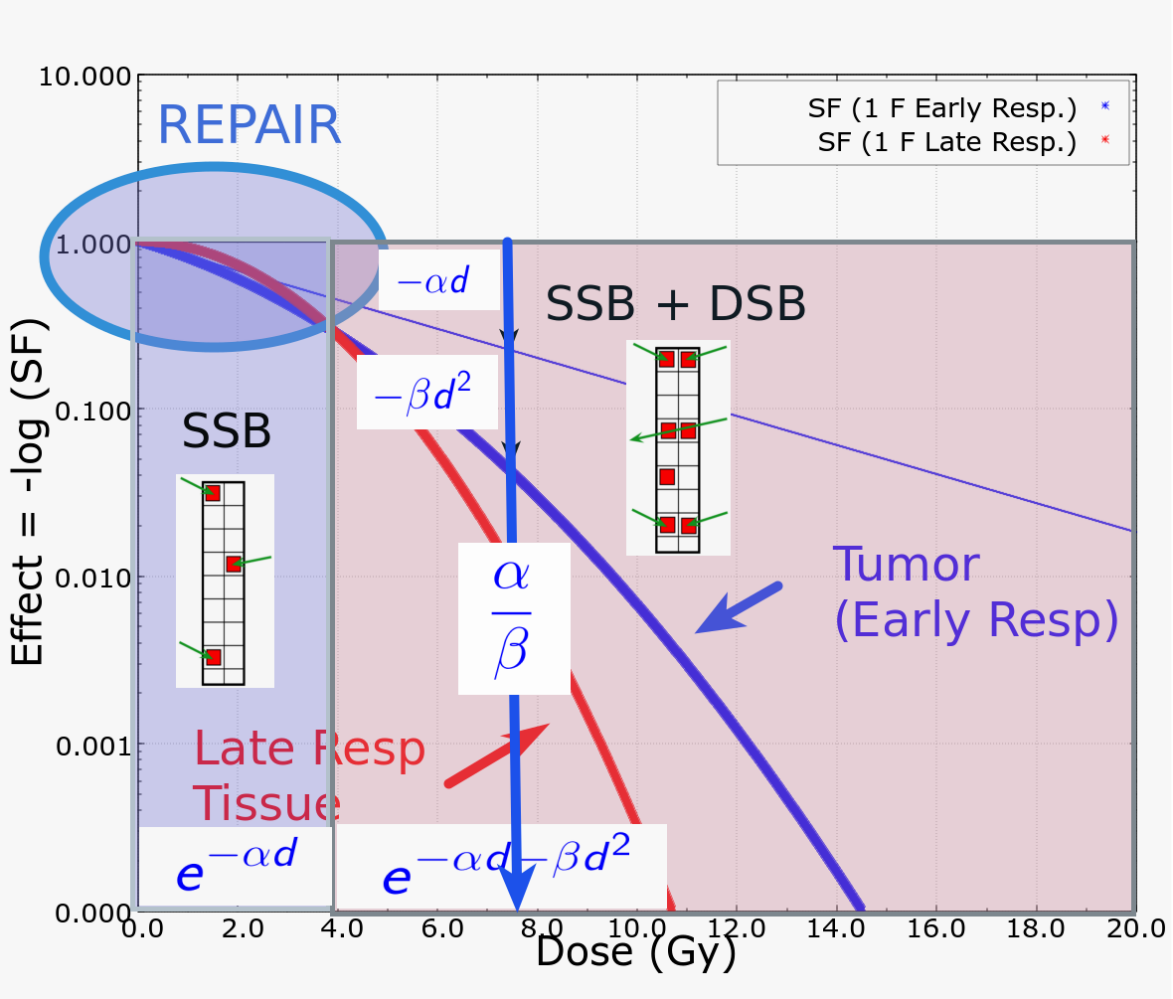

LQ model (brief overview)

LQ $\rightleftarrows$ Survival Fraction (SF) (Cells in vitro)

- Effect $= -log(SF_n)$ (where $SF_n = e^{-nd(\alpha+\beta d)}$)

$$E_{n_2} = n_2 \cdot 2 \cdot \alpha \left(1 + \frac{2}{\frac{\alpha}{\beta}}\right)$$

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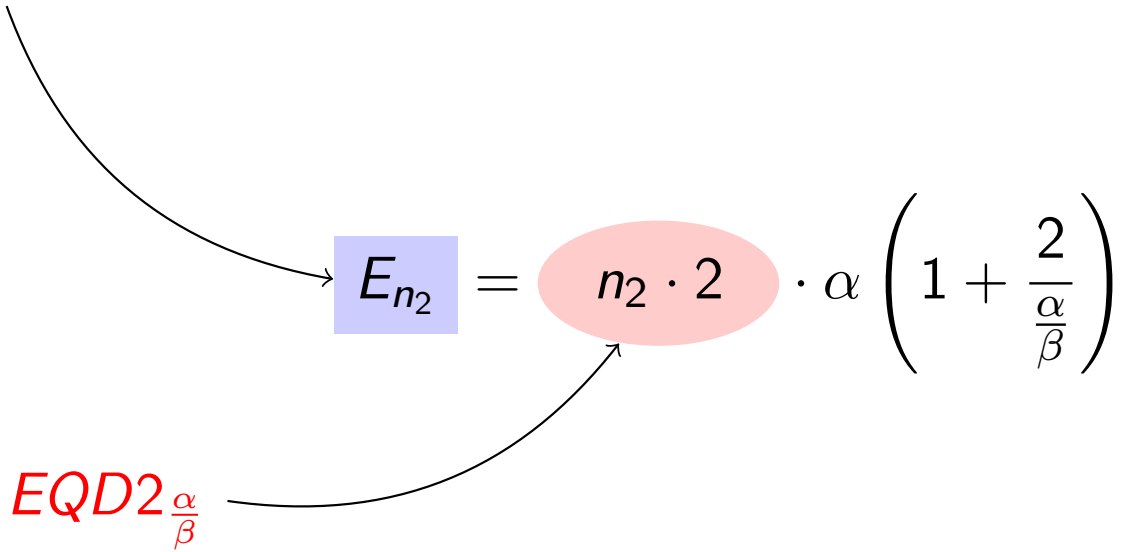

- $EQD2_{\frac{\alpha}{\beta}}$

LQ model (brief overview)

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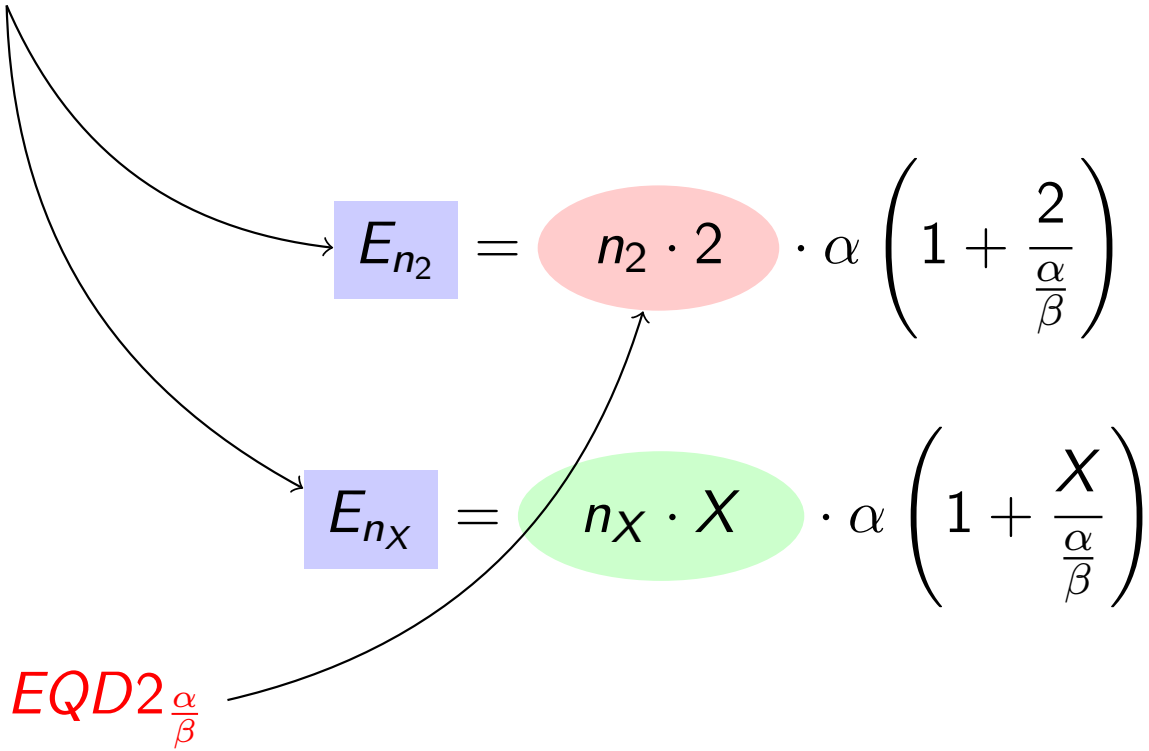

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- $EQD2_{\frac{\alpha}{\beta}}$
- $EQDX_{\frac{\alpha}{\beta}}$

LQ model (brief overview)

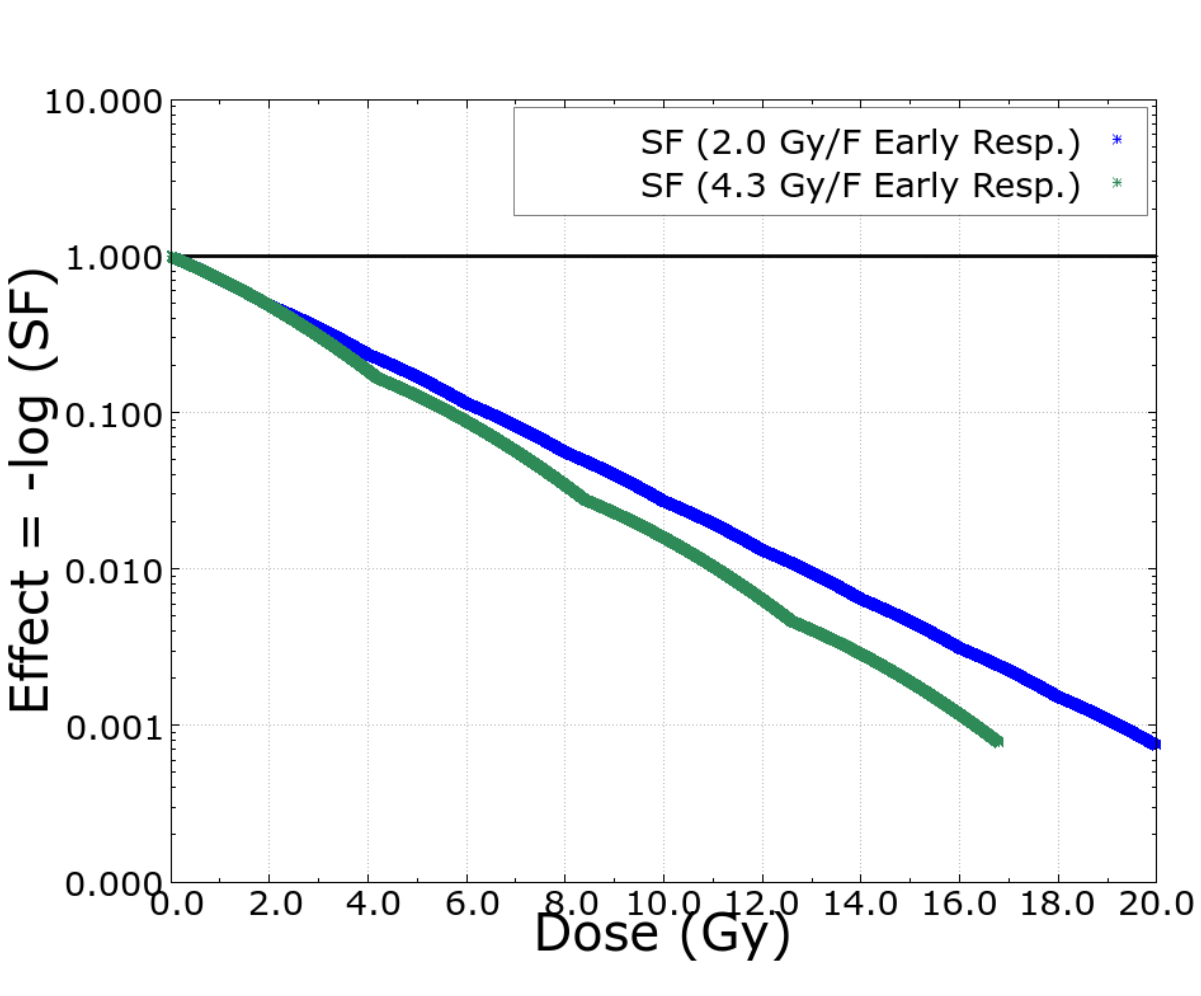
LQ $\rightleftarrows$ Survival Fraction (SF) (Cells in vitro)

- Effect $= -log(SF_n)$ (where $SF_n = exp^{-nd(\alpha+\beta d)}$)

$$E \equiv n_2 \cdot 2 \cdot \alpha \left(1 + \frac{2}{\frac{\alpha}{\beta}}\right) = n_X \cdot X \cdot \alpha \left(1 + \frac{X}{\frac{\alpha}{\beta}}\right)$$

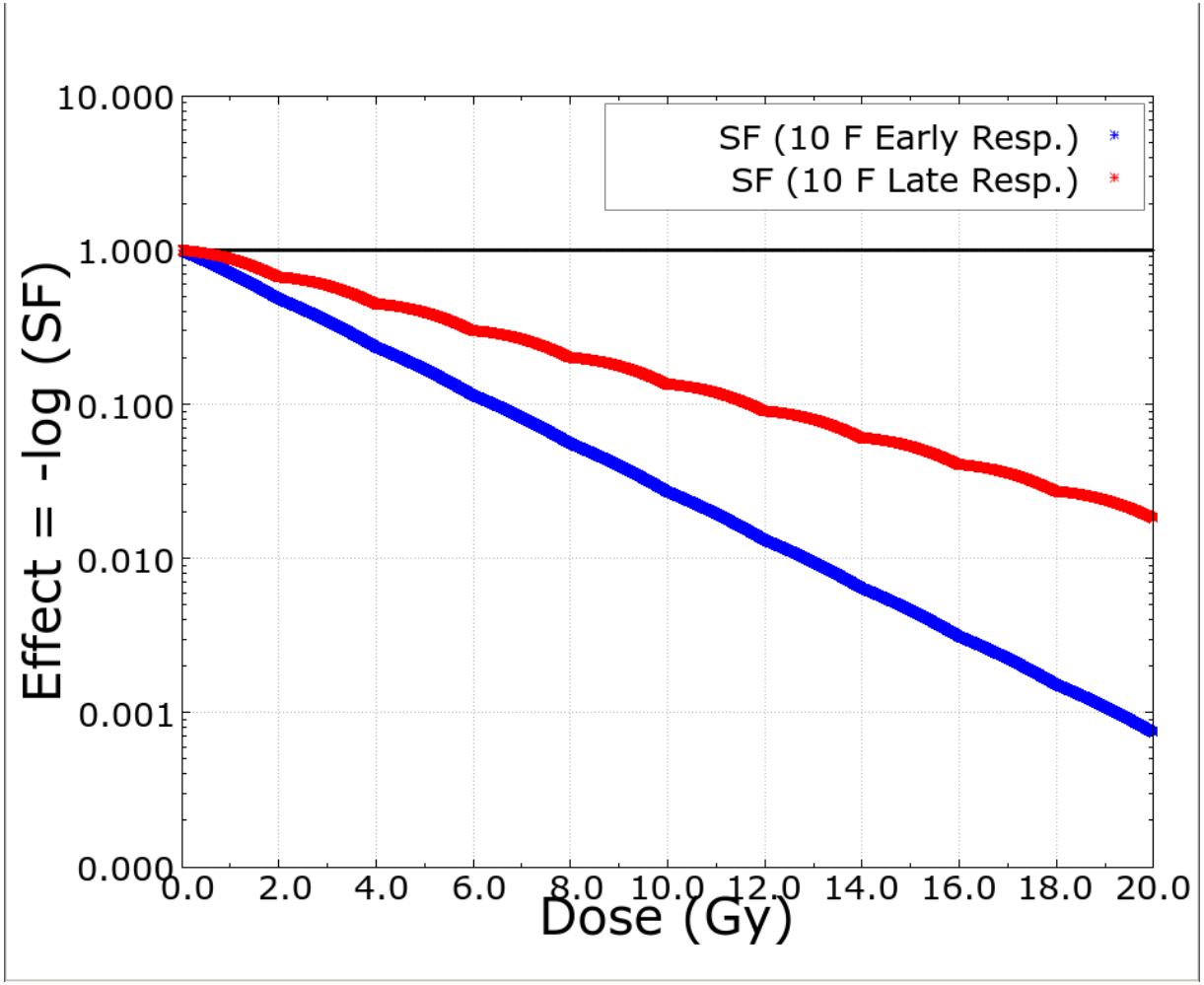
LQ model (brief overview)

LQ $\rightleftarrows$ (SF) (Homegeneous Dose)



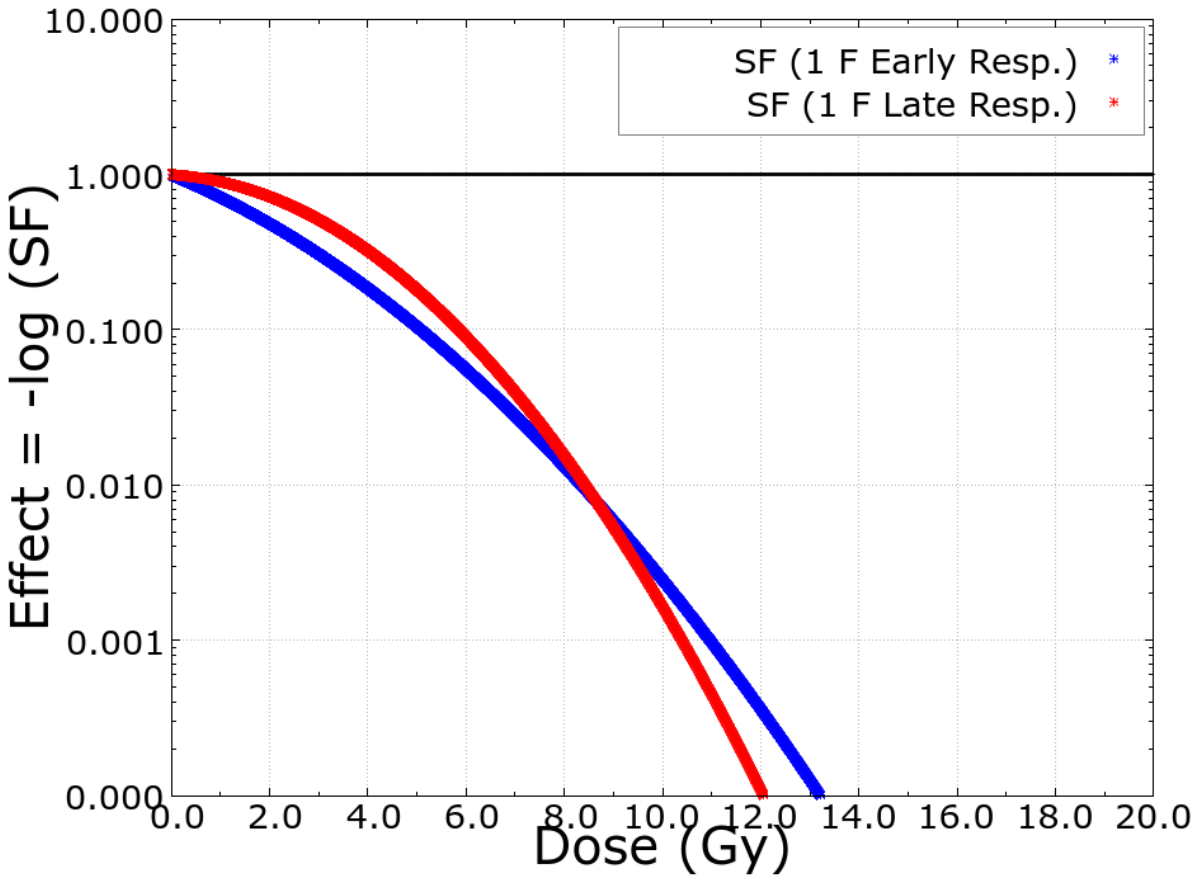
LQ model (brief overview)

LQ $\rightleftarrows$ (SF) (Homegeneous Dose)



LQ model (brief overview)

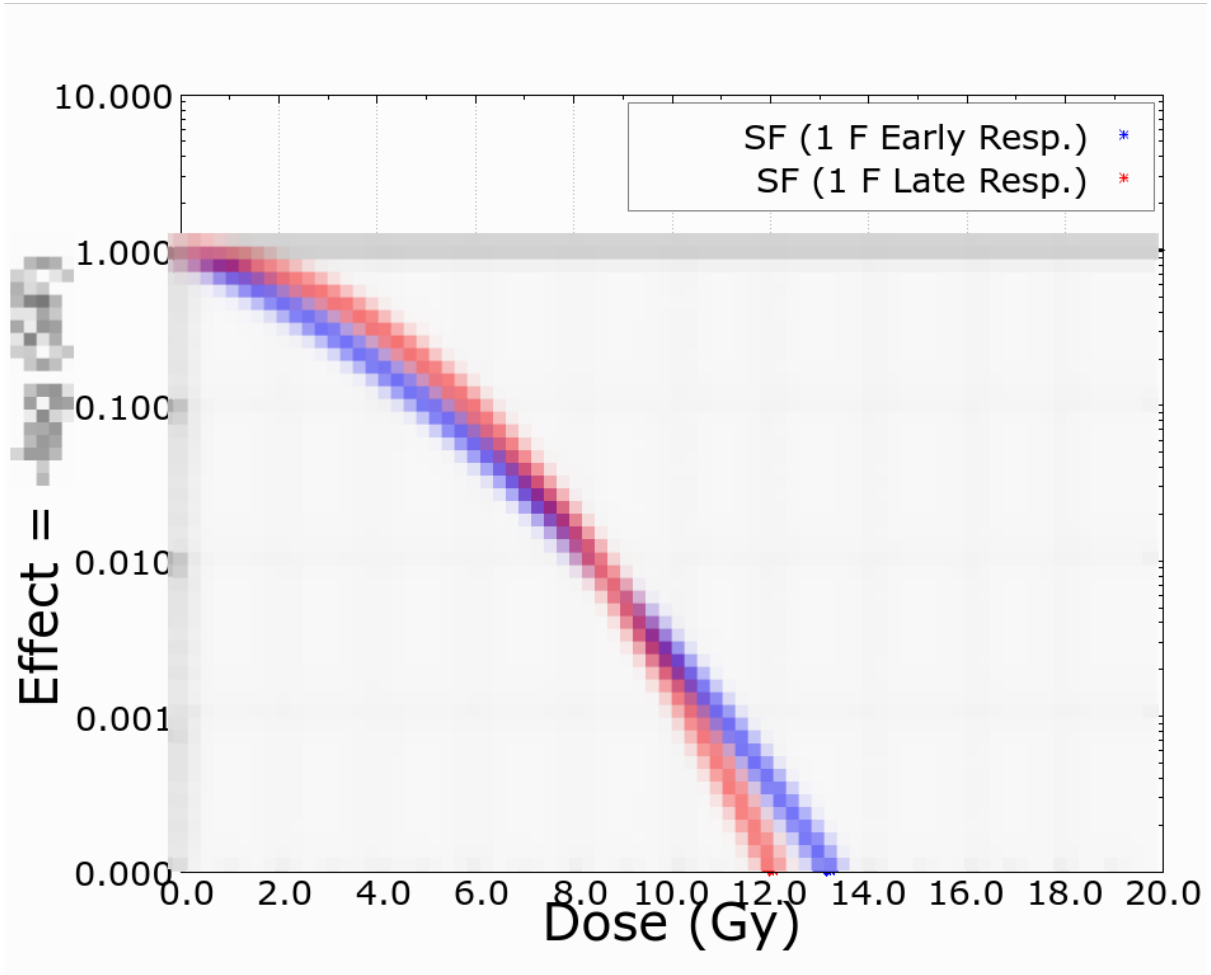
LQ $\rightleftarrows$ (SF) ((Geometrical Sparring Factor (SBRT-SRS)))



LQ model (brief overview)

LQ $\rightleftarrows$ (SF ???) ((Geometrical Sparring Factor (SBRT-SRS)))

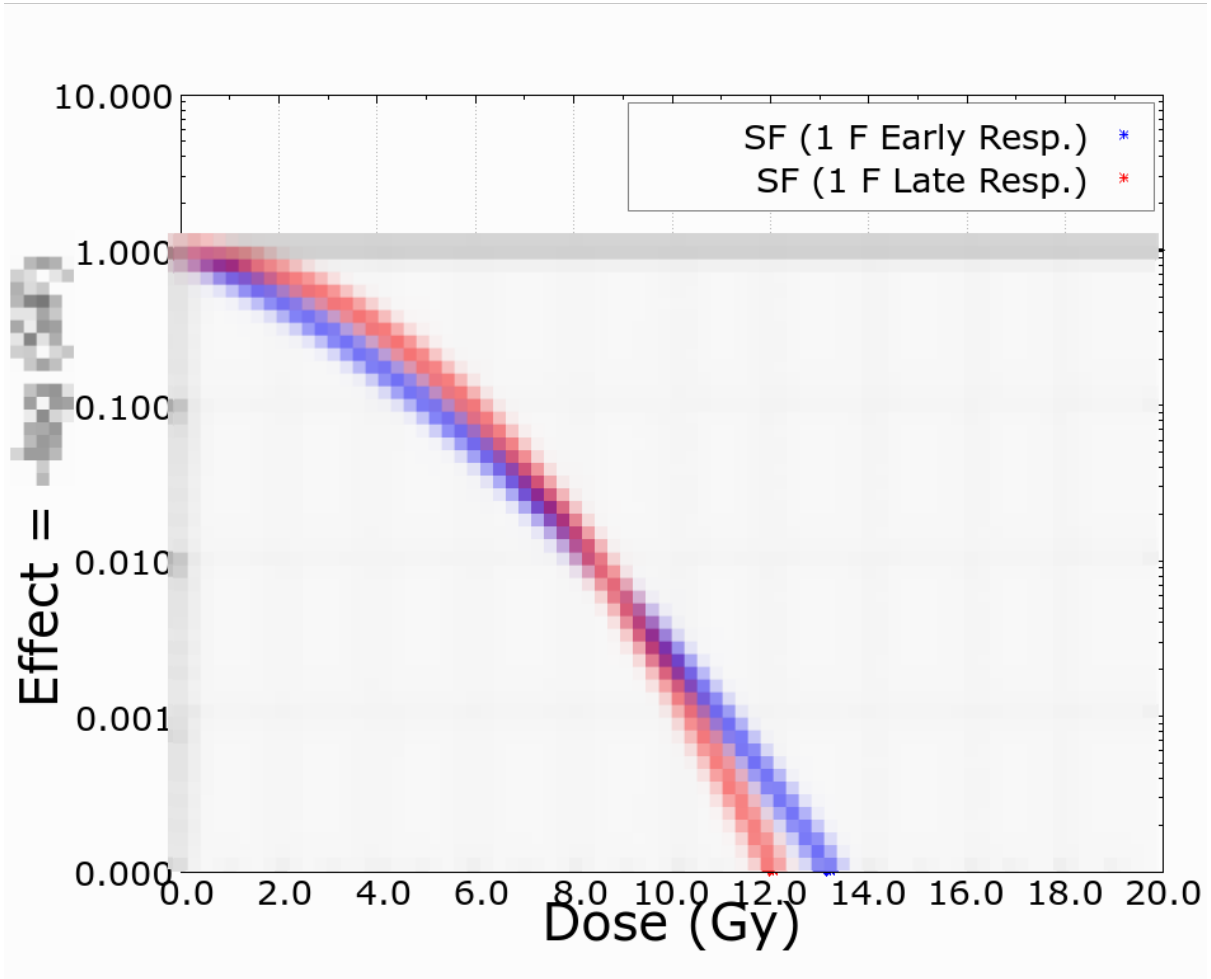
There is a catch is this figure ... What is **EFFECT** ???



LQ model (brief overview)

LQ $\rightleftarrows$ (SF ???) ((Geometrical Sparring Factor (SBRT-SRS)))

We will retake this issue, but first a review of R.B. models

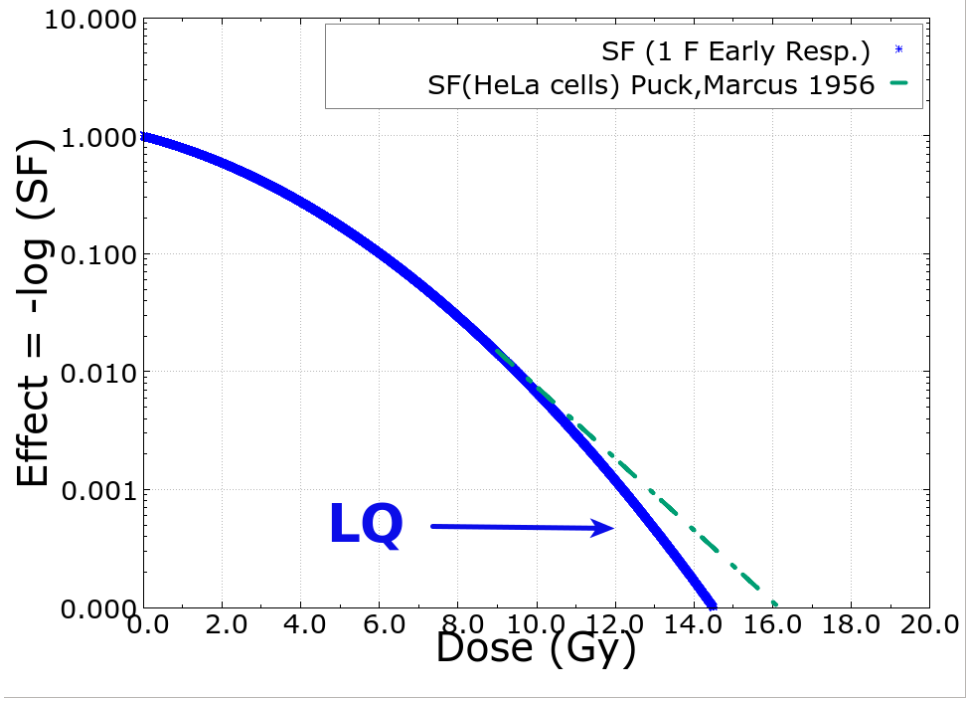


Models (in vitro)

For a number N of clonogenic cells, SF depends on tissue $\frac{\alpha}{\beta}$

$$[SF_n]^{LQ} = e^{-n \cdot d(\alpha + \beta d)}$$

$$TCP = e^{-N \cdot [SF_n]^{LQ}}$$



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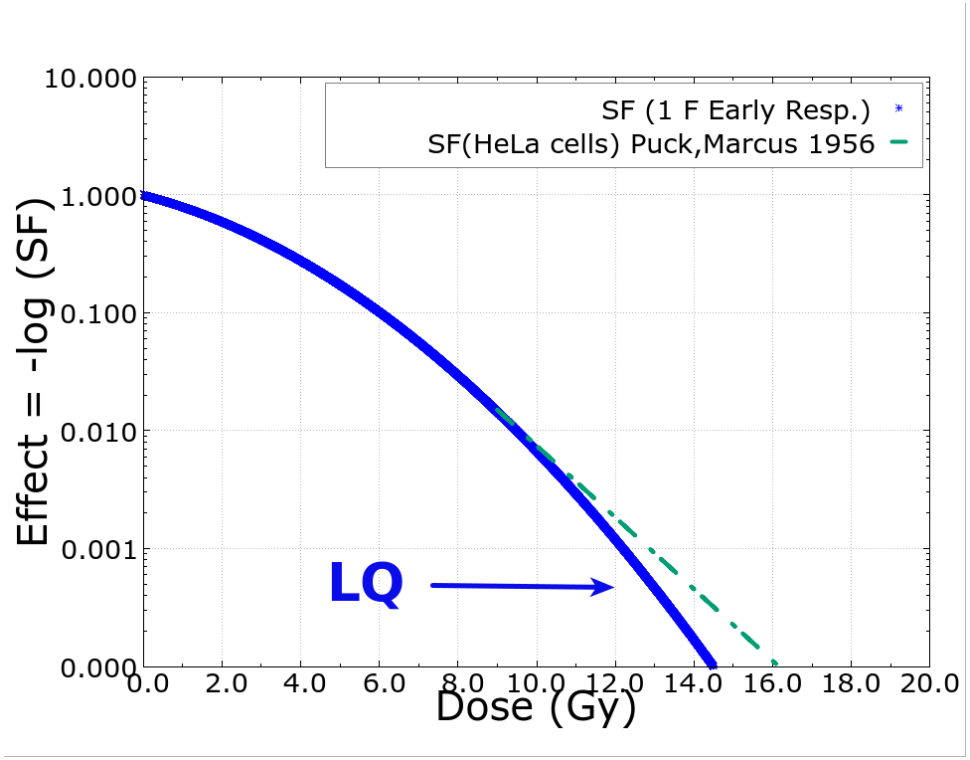
$$[SF_n]^{LQ} = e^{-n \cdot d(\alpha + \beta d)}$$

$$TCP = e^{-N \cdot [SF_n]^{LQ}}$$

Kirkpatrick et al (2008)

- Continuous bending $-\beta d^2$
- Underestimates SF over 10Gy/fr
- i.e. Overestimate rad. mediated cell killing
- **LQ Is Inappropriate** to Model High Dose per Fraction in Raduisurgery



Models (in vitro)

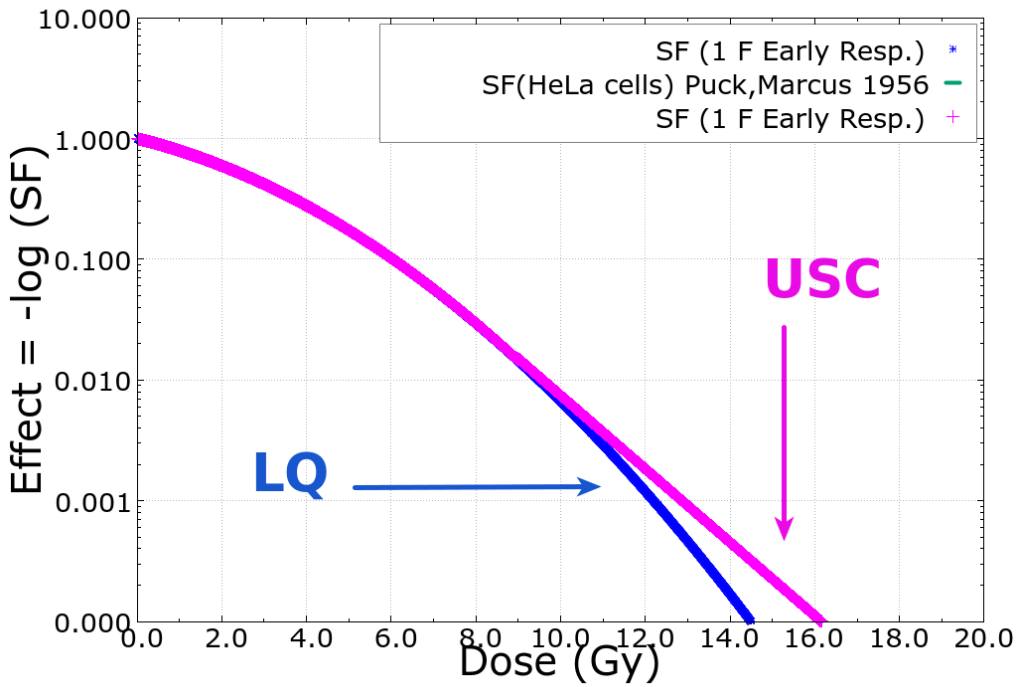
For a number N of clonogenic cells, SF depends on tissue $\frac{\alpha}{\beta}$

$$[SF_n]^{USC} = \begin{cases} -e^{-n \cdot d(\alpha+\beta d)}, & d \leq I \\ \frac{-1}{D_0} \cdot d + \frac{D_q}{D_0}, & d > D \end{cases}$$

$$TCP = e^{-N \cdot [SF_n]^{USC}}$$

Park et al (2008) (USC Model)

- Linearity on d at high dose/frac
- Keeps a mechanistic view (Multi-target)



Models (in vitro)

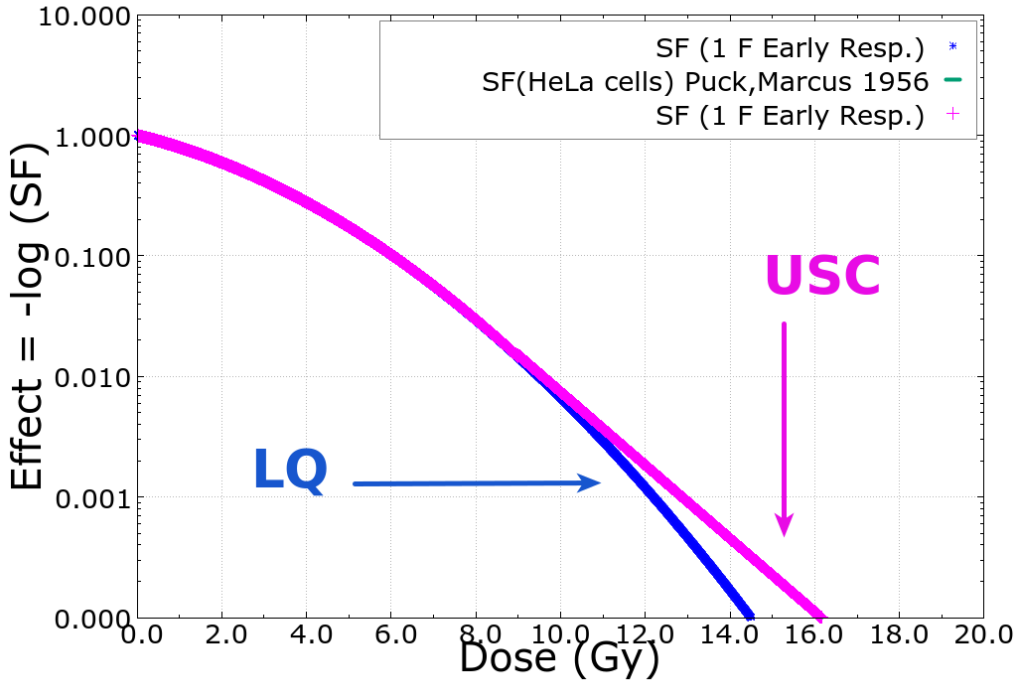
For a number N of clonogenic cells, SF depends on tissue $\frac{\alpha}{\beta}$

Other mechanistic models:

- LQL Linear Quadratic Linear (Guerrero 2004,2010)
- RCR Repair-Conditionally Repair (Lind 2003)
- PLQ Pade Linear Quadratic (Belkic 2013)

$$TCP = e^{-N \cdot [SF_n]^{Model}}$$

- Linearity on d at high dose/frac
- Keep a mechanistic view
- Fit well in-vitro data



LQ critics

ELSEVIER

Seminars in
RADIATION
ONCOLOGY

The Linear-Quadratic Model Is Inappropriate to Model High Dose per Fraction Effects in Radiosurgery

John P. Kirkpatrick, MD, PhD, Jeffrey J. Meyer, MD, and Lawrence B. Marks, MD

The linear-quadratic (LQ) model is widely used to model the effect of total dose and dose per fraction in conventionally fractionated radiotherapy. Much of the data used to generate the model are obtained in vitro at doses well below those used in radiosurgery. Clinically, the LQ model often underestimates tumor control observed at radiosurgical doses. The underlying mechanisms implied by the LQ model do not reflect the vascular and stromal damage produced at the high doses per fraction encountered in radiosurgery and ignore the impact of radioresistant subpopulations of cells. The appropriate modeling of both tumor control and normal tissue toxicity in radiosurgery requires the application of emerging understanding of molecular-, cellular-, and tissue-level effects of high-dose/fraction-ionizing radiation and the role of cancer stem cells.
Semin Radiat Oncol 18:240-243

LQ critics

- (In-vitro) LQ overestimates effect of SRS

Clinical Outcome

A variety of studies suggest that the administration of a single, high dose of radiation in vivo has a much greater effect than that which would be predicted from the LQ model using the coefficients calculated from conventional in vitro dose/fractions. For example, Leith et al[12] calculated the radiation doses required to control metastatic brain lesions using data from in vitro survival curves. They found that the calculated dose required to obtain a high tumor control probability was at least 25 to 35 Gy, which is much greater than that observed to be effective in clinical radiosurgery (eg, doses ≈ 15-20 Gy). Likewise, Kocher et al[13] modeled the effect of radiosurgery in brain metastases and found that the therapeutic effect of radiosurgery on tumor response was far greater than that predicted from the LQ model derived from low-dose/fraction estimates.

LQ critics

- Damage to vascularity above 10 Gy/f (Garcia-Barros et al 2003)

In Vitro Versus In Vivo Effects

Much of the data used to generate survival curves and estimate the model coefficients comes from in vitro cell culture experiments. Notable exceptions include the pioneering studies of irradiated mouse epithelium[3] and jejunal crypt cells.[16] Although some studies have used dose/fractions as high as 16 Gy, the bulk of these data falls well below the doses of 15 to 24 Gy typically used in clinical radiosurgery.[17]

The disconnect between the observed in vivo clinical outcomes and the predictions based on (largely) in vitro cell-survival curves may be related in part to radiation-induced changes in other structures. For example, ionizing radiation can damage supporting tissues such as the microvasculature, a response typically believed to be invoked mostly at high doses per fraction. Garcia-Barros et al[18] and Fuks and Kolesnick[19] have observed that vascular endothelial damage is triggered above 10 Gy per fraction secondary to the activation of acid sphingomyelinase. Pathological studies of resected brain lesions treated originally with radiosurgery show profound changes in the vasculature. Further support for the idea of vascular/stromal damage comes from studies of radiosurgery in arteriovenous malformations.[20-22] Both obliteration of the abnormal vasculature[15] and damage to the surrounding normal tissue[23-25] are rare below single doses of 12 Gy to the involved area but climb steeply with increasing

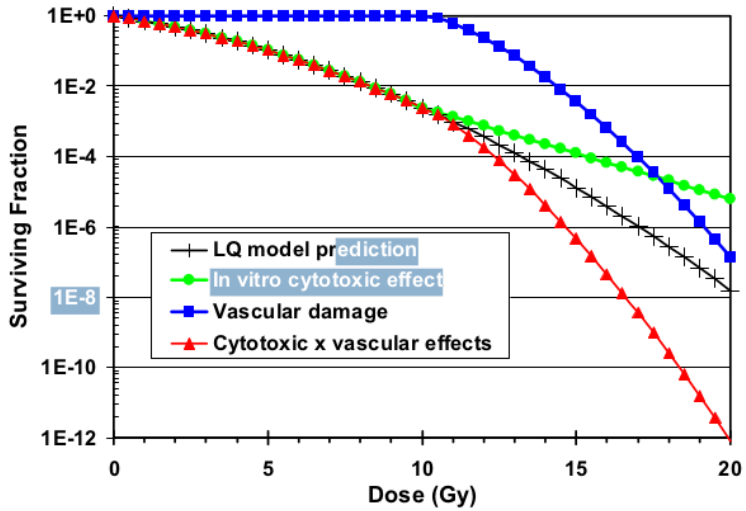


Figure 1 Conceptual cell survival curves. Surviving cell fraction (SF) for the LQ model with $\alpha = 0.3$ Gy^{-1} and $\beta = 0.03$ Gy^{-2} (+), simulated "in vitro cytoxic effect" calculated from the LQ model with $\alpha = 0.3$ Gy^{-1} and $\beta = 0.03$ Gy^{-2} below 10 Gy, the product of SF at 10 Gy and the single exponential model SF = exp(-2α Dose) where $\alpha = 0.3$ Gy^{-1} above 10 Gy (●), vascular damage with a threshold of 10 Gy calculated from SF = exp($-\mu$ [Dose − 10 Gy]$^{1.5}$) with $\mu = 0.5$ Gy^{-1} (■), and the product of the surviving fraction for the in vitro cytoxic effect and vascular damage (▲). (Color version of figure is available online.)

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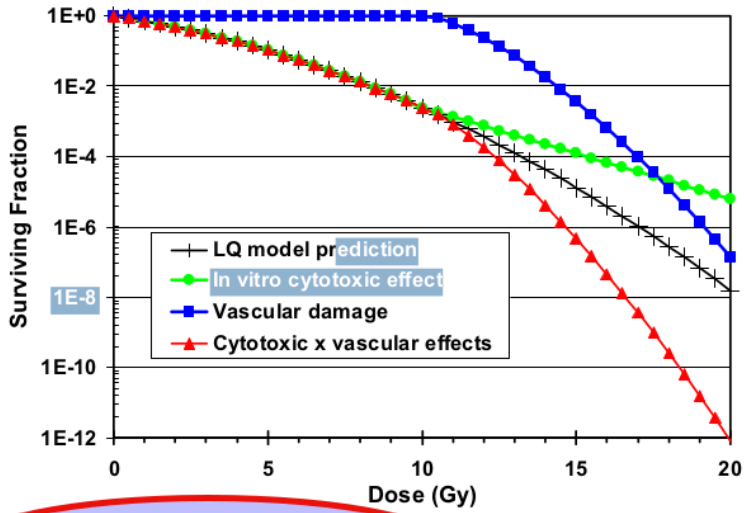

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LQ critics

The (conceptual) CATCH ...: In-vitro survival curves (homogeneous dose levels) vs in-vivo (conceptual) survival curves (inhomogeneuos dose distrib from Radiosurgery)

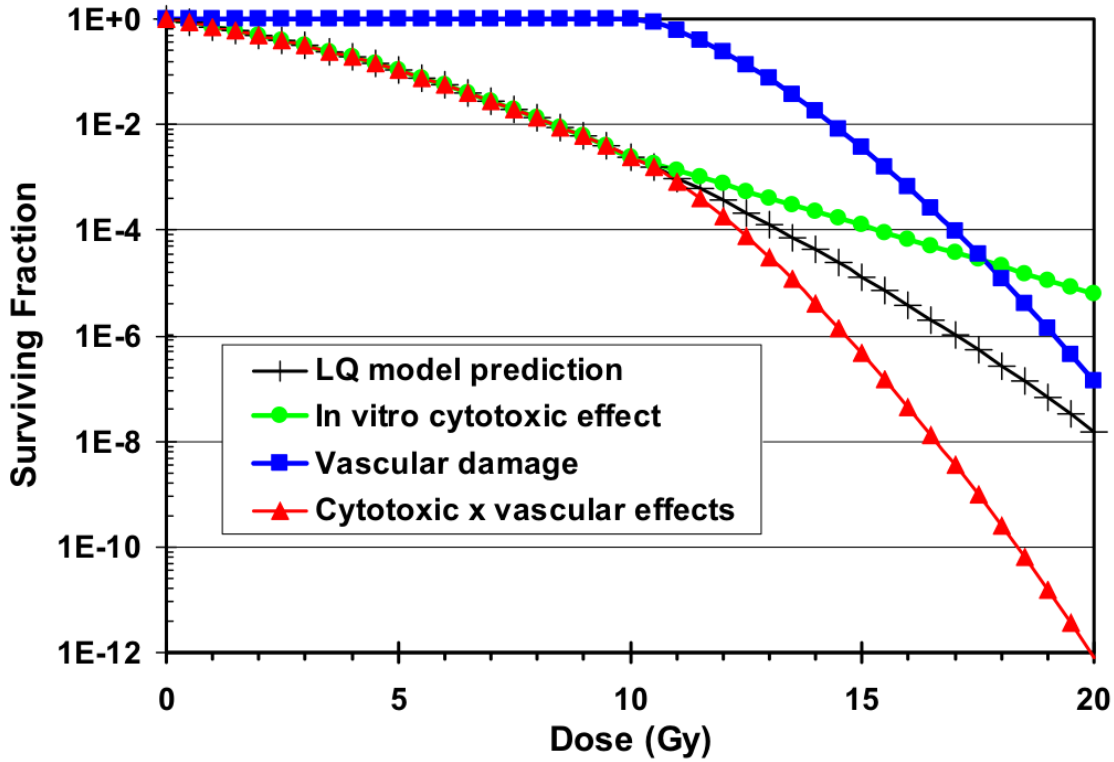

Figure 1 Conceptual cell survival curves. Surviving cell fraction (SF)

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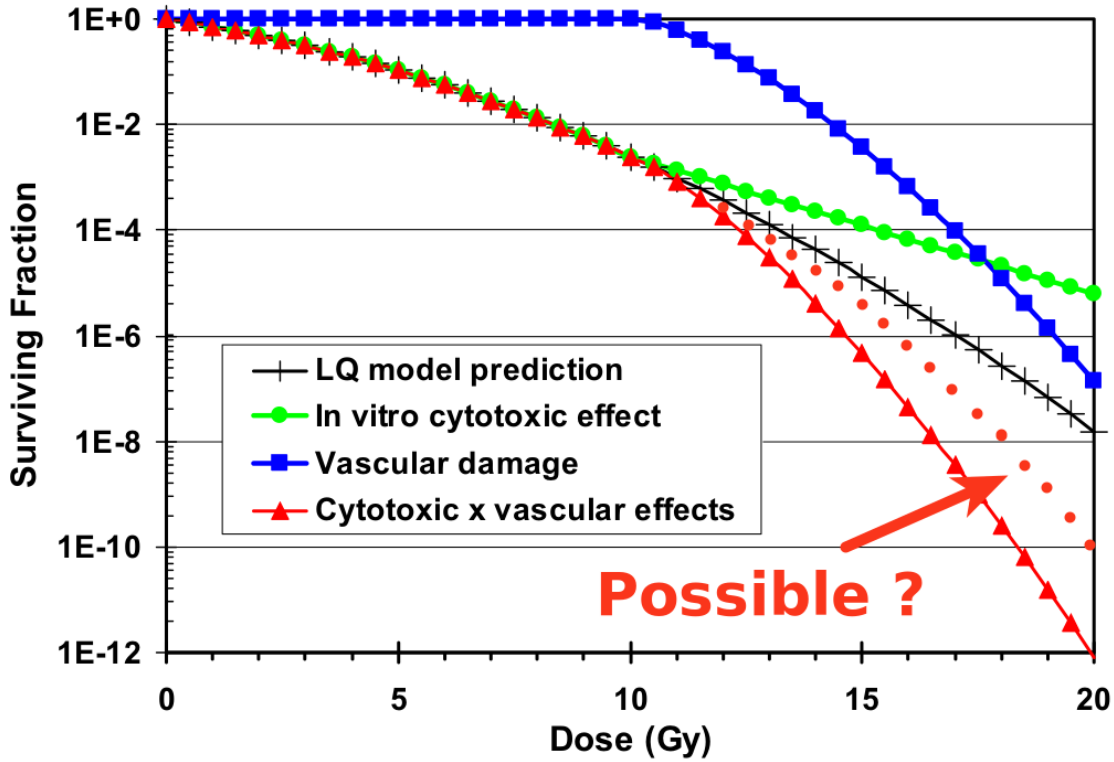

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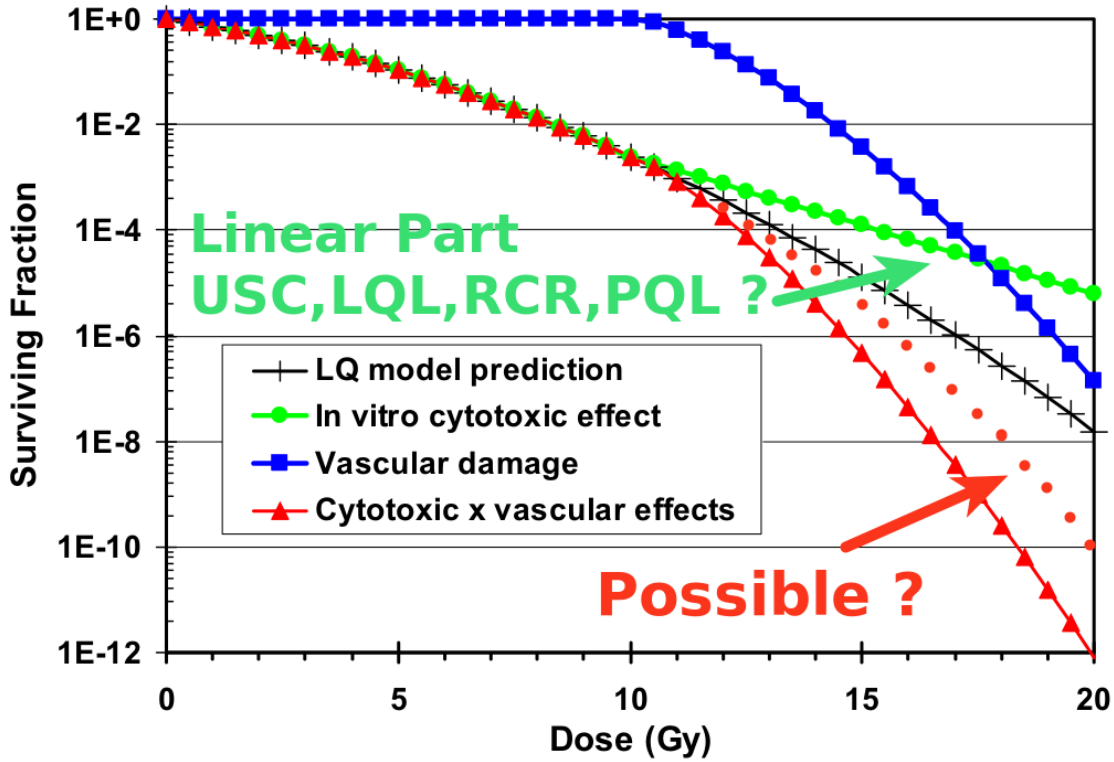

Figure 1 Conceptual cell survival curves. Surviving cell fraction (SF)

LQ critics

Park et al (Review).”Little is known about the vascular changes in human tumors treated with high-dose hypofractionated radiation such as stereotactic body radio- therapy (SBRT) or stereotactic radiosurgery (SRS)”

RADIATION RESEARCH **177**, 311–327 (2012)
0033-7587/12 $15.00

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]

[a] *Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis, Minnesota;* [b] *Department of Microbiology, Center for Advanced Medical Education by BK21 Project, College of Medicine, Inha University, Inchon, Korea;* [c] *Department of Radiation Oncology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; and* [d] *Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden*

LQ critics

H.J.Park et al (Review)."**Denekamp** estimated that one endothelial cell subtends a segment of a tumor volume containing as many as 2000 tumor cells (Fig. 6). Given that blood vessels are serial tissues, sectional damage in a vessel may induce cessation of blood perfusion throughout the affected vessel."

REVIEW

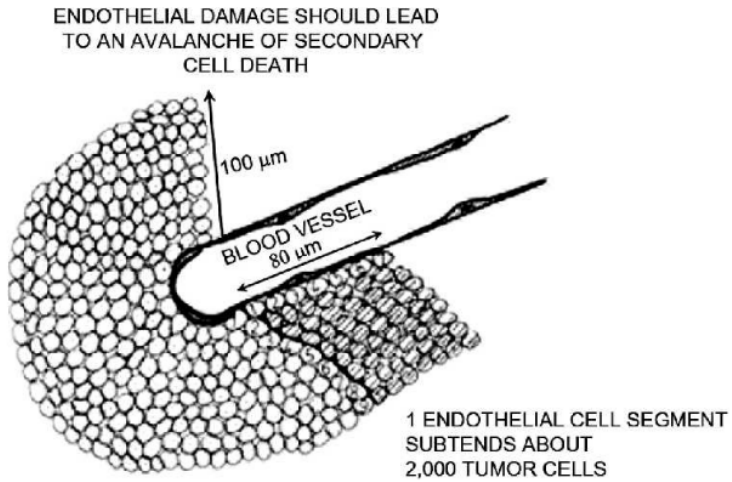

FIG. 6. Schematic illustration of how many tumor cells would be at risk if even a small segment of a capillary is occluded, so that their nutrient supply is completely lost (*94*).

LQ critics

H.J.Park et al (Review). Most studies are Xenografts ...

Human non-small-cell lung cancer (16 patients)	Volumetric perfusion computed tomography	Vascular blood volume and permeability were greater in tumor rim than tumor center. After fractionated irradiation with 9 Gy in 2 fraction, 18 Gy in 4 fraction and 27 Gy in 6 fraction, vascular volume increased significantly in tumor rim and slightly in tumor center. Vascular permeability also increased in tumor rim, but not in tumor center.	NG *et al.* (2007) (*23*)
Human rectal cancer (23 patients)	Perfusion CT imaging	Irradiated with 25 Gy in 5 fraction (5 Gy ' 5) in 1 week. From 3 days after the hypofractionated treatment, trans-endothelial volume constant (K trans) (permeability) slightly increased. The increased vascular permeability may improve the bioavailability of cytotoxic agents in rectal tumors.	Janssen *et al.* (2009) (*24*)
Human melanoma xenograft in athymic nude mice in the flank	Angiography	In 1 week after irradiation with 10.0–15.0 Gy in a single dose, 35–45% of 5–15-μm-diameter vessels were nonfunctional. The doses required for loss of 50% of the functional vessels with diameters of 5–15, 15–25, and 25–35 μm were 16, 21 and 20 Gy, respectively. In spite of early loss of functional vessels, tumors became supervascularized as tumors regressed after 20 or 25 Gy irradiation. Regrowth of irradiated tumors appeared to be preceded by efficient neovascularization.	Solesvik (1984) (*25*)
Human colon tumor xenografts in the flank (s.c.) of athymic mice	^{99m}TcO4-RBC for functional vascular volume and ^{125}I-plasma protein for vascular permeability	Irradiation with 4–16 Gy in a single dose increased the vascular permeability in 24–72 h and decreased the functional vascular volume in 24 h. The increase in vascular permeability by irradiation is potentially valuable to increase monoclonal antibody uptake by tumors.	Kalofonos *et al.* (1990) (*26*)
Human laryngeal squamous cell carcinoma xenografts in nude mice	Histological imaging of endothelial marker for vessels and Hoechst 33342 injection for vascular perfusion	After irradiation with 10 Gy, the number of perfused vessels slightly increased within 1 day, and then significantly decreased at 26 h followed by recovery to control level in 7–11 days. The hypoxic cell fraction decreased at 7 h after irradiation but significantly increased to pre-irradiation levels at 11 days after irradiation.	Bussink *et al.* (2000) (*27*)
Human MA148 ovarian carcinoma xenografts in nude mice, s.c.	Immunohistochemistry for PECAM (CD31-red fluorescence	After irradiation with 5 Gy/week for 4 weeks, the total vessel density decreased by 50%. Irradiation and anginex synergistically reduced the functional vascularity in tumors.	Dings *et al.* (2005) (*28*)
Human A-07 melanoma xenografts in nude mice	Dynamic contrast-enhanced magnetic resonance imaging	At 72 h after 10 Gy irradiation in a single dose, tumor blood perfusion decreased by 40%. However, intratumor mean pO_2 and pO_2 fluctuation were not altered by irradiation with 5 or 10 Gy,	Brurberg (2006) (*29*)

LQ critics

H.J.Park et al (Review). ... or direct small animal experiments.

Tumors and sites	Methods	Vascular changes	(year) (ref.)
Human A549 lung adenocarcinoma xenografts in the hind legs of nude mice, s.c.	Hoechst 33342 for blood perfusion and Dynamic Magnetic Resonance imaging of GD-DTPA for functional vascularization	Analysis with Hoechst 333342 indicated a rich blood vessel perfusion in the peripheral part of the tumors. Irradiation with 20 Gy in a single dose caused no changes in vascular density whereas apoptosis of tumor cells was significant at 10.5 h postirradiation. Blood perfusion, as determined with GD-DTPA imaging increased at 1 h postirradiation. Hypoxic area in the tumors decreased for 30.5 h after irradiation.	Fokas *et al.* (2010) (*30*)
Human U251 glioblastoma xenograft grown s.c. in the back or intracranially (i.c.) in nude mice	Fluorescence imaging of lectin for i.c. tumors and ultrasound analysis of contrast agent for s.c. tumors	Irradiation with 15 Gy in a single dose decreased blood perfusion to 10% of control in i.c. tumors and to 30% of control in s.c. tumors in 2 weeks. In i.c. tumors, CD31-stained cells (endothelial cells) were reduced to 25% of control accompanied by marked increase in hypoxic area (pimonidazole staining). Thereafter, the damaged vasculatures were restored by virtue of vasculogenesis through recruitment of bone marrow-derived cells in both s.c. and i.c. tumors. AMD3100, an inhibitor of vasculogenesis, prevented the recovery of tumor vasculature. Vasculogenesis needs to be blocked for complete control of tumor by radiotherapy.	Kioi *et al.* (2010) (*31*)
Mouse adenocarcinoma of C3H mice in transparent chambers	Transparent chamber. Microsocpic observation	Irradiated with 2,000 or 3,000 R in a single fraction caused pronounced narrowing of microvessels for approximately 1 week. By 2–4 days after irradiation, the circulation was slowed. The retardation of circulation during 2–5 days postirradiation was responsible for tumor cell death. Irradiated vessels were unable to regrow.	Merwin *et al.* (1950) (*32*)
Hamster neurilemmoma in the cheek pouch chambers	Cheek pouch transparent chamber. Microscopic observation	Irradiation with 3,000 R caused variable degrees of edema and extensive reduction in blood flow in 24–30 h, with subsequent restoration toward normalcy accompanied by small focal hemorrhaging. Subsequent tumor growth with neovascularization began in the perimeter of the tumor.	Eddy (1980) (*33*)
Rat R3240 Ac mammary adenocarcinoma in window chambers	Dorsal flap transparent window chamber. Microscopic observation	Irradiation with 5 Gy caused conjoint increase in both vascular density and perfusion during 24–72 h post-irradiation, although the degree of change was variable from one individual to the next. The degree of change in vascular density was inversely related to median pretreatment diameter.	Dewhirst *et al.* (1990) (*34*)
Mouse adenocarcinoma	Histological examination	Irradiated with 2400–2600 R in 1 fraction. Slight dilation of blood	Lasnitzki (1947)

LQ critics

H.J.Park et al (Review). ... SBRT or do you mean SBRT ?.

Human non-small-cell lung cancer (16 patients)	Volumetric perfusion computed tomography	Vascular blood volume and permeability were greater in tumor rim than tumor center. After fractionated irradiation with 9 Gy in 2 fraction, 18 Gy in 4 fraction and 27 Gy in 6 fraction vascular volume increased significantly in tumor rim and slightly in tumor center. Vascular permeability also increased in tumor rim, but not in tumor center.	NG *et al.* (2007) (*23*)

LQ critics

H.J.Park et al (Review). ... Mice and rats ?

Type	Number of Studies
Human Conv (Cervix)	5
Human SBRT (NSCLC)	1
Xenograft	7
Small Animal	19
Total	32

LQ critics

H.J.Park et al (Review). ... Mice and rats ?.

Type	Number of Studies
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Small Animal	19
Total	32

LQ supporters

Published in final edited form as:
Semin Radiat Oncol. 2008 October ; 18(4): 234–239. doi:10.1016/j.semradonc.2008.04.004.

Point: The linear-quadratic model is an appropriate methodology for determining iso-effective doses at large doses per fraction

David J. Brenner, Ph.D., D.Sc.
From the Center for Radiological Research, Columbia University Medical Center, 630 West 168th Street, New York, NY.

Abstract

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, LQ has the following useful properties for predicting isoeffect doses: First, it is a mechanistic, biologically-based model; second, it has sufficiently few parameters to be practical; third, most other mechanistic models of cell killing predict the same fractionation dependencies as does LQ; fourth, it has well documented predictive properties for fractionation/dose-rate effects in the laboratory; fifth, 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 LQ has been applied in the clinic.

LQ supporters

Brenner 2008

- useful properties for **predicting isoeffect** doses
- **mechanistic**, biologically-based model (not mere empirical)
- **few parameters** to be practical
- **validated up to 10 Gy/f** (experimentally and theoretically)
- evidence that it can work up to 18 Gy/f (2008)
- widely **used in clinical setting**

LQ supporters

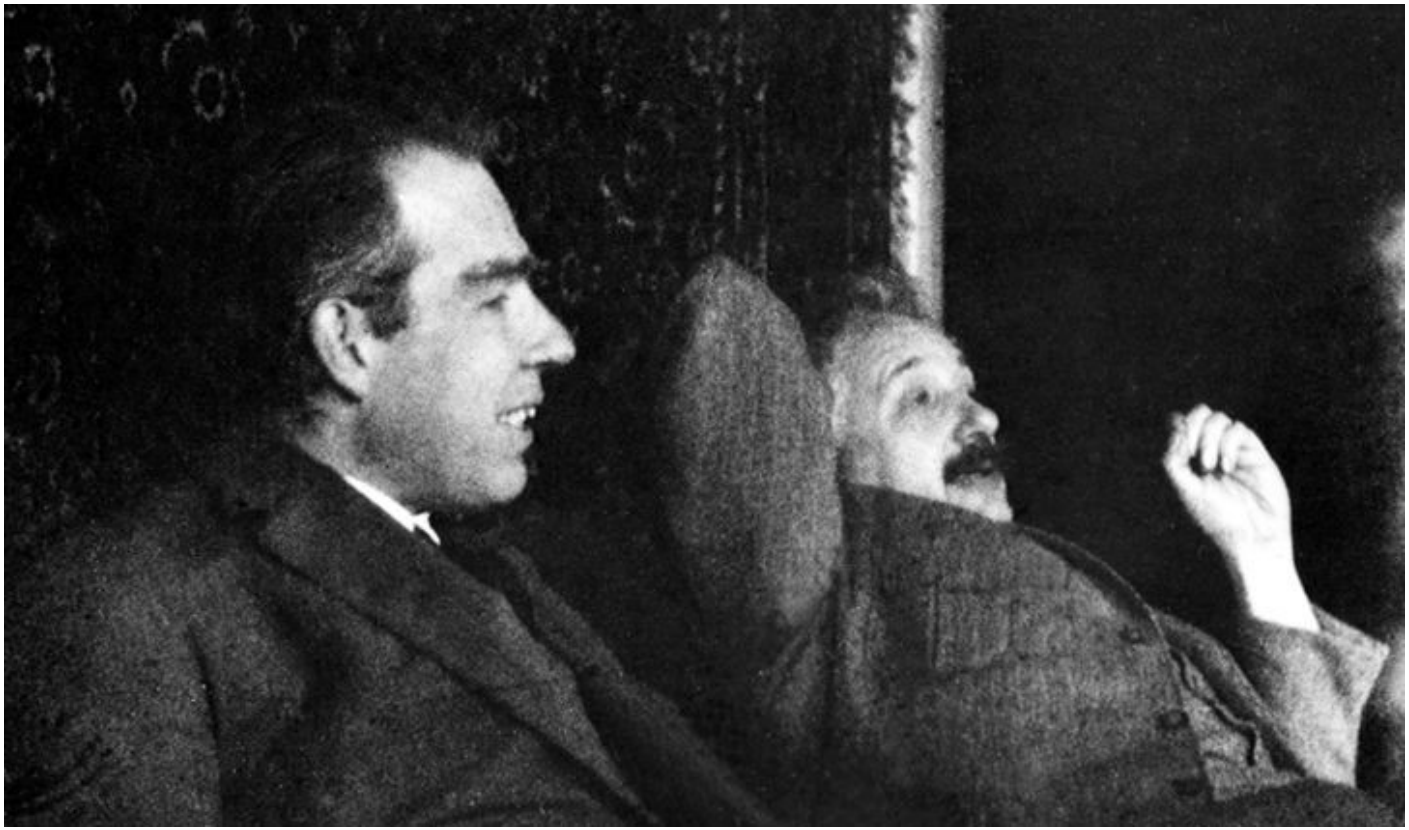
Brenner 2008

$$[SF_n]^{LQ} = e^{-n \cdot d(\alpha + G\beta d)}$$

- DSBs repaired with rate constant $\lambda = \frac{ln2}{T_{0.5}}$
- $G(\lambda, t) \in [0, 1]$ is the (protracted) repair time factor

LQ for SRS and SBRT (YES or NO)

Heated debate going on



LQ for SRS and SBRT (YES or NO)

Heated debate going on

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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Colin G. Orton, Ph.D., Moderator

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OVERVIEW

The linear-quadratic (LQ) model is frequently used for modeling the effects of radiotherapy at low and medium doses per fraction for which it appears to fit clinical data reasonably well. It has also been used at the very high doses per fraction encountered in stereotactic radiosurgery, but some have questioned such use because there are little clinical data to demonstrate that the model is accurate at such high doses. This is the proposition debated in this month's Point/Counterpoint.

Arguing for the Proposition is John P. Kirkpatrick, M.D., Ph.D. Dr. Kirkpatrick is an Associate Professor at the Department of Radiation Oncology, Duke University Medical Center. He has a Ph.D. in Chemical Engineering from Rice University, Houston, and an M.D. degree from the University of Texas Health Science Center, San Antonio, TX.

Arguing against the Proposition is David J. Brenner, Ph.D., D.Sc. Dr. Brenner is a Professor of Radiation Oncology and Public Health at the Columbia University Medical Center. He focuses on developing models for the carcinogenic effects of ionizing radiation on living systems at the chromosomal, cellular, tissue, and organism levels. He divides his research time roughly equally between the effects of high doses of ionizing radiation (related to radiation therapy) and the effects of low doses of radiation (related to radiological, environmental, and occupational exposures). When not involved in radiation matters, he supports the Liverpool Football Club.

FOR THE PROPOSITION: John P. Kirkpatrick, M.D., Ph.D.

LQ for SRS and SBRT (YES or NO)

Kirkpatrick

- LQ assumes **homogeneous cell pop** (tissue **microenvironment ?**)
- **Local hypoxia** in most tumors (reduced radioresponsiveness)
- Parameters derived from **in-vitro** and **small-animal** experiments

Brenner

- Varing **radiosensitivity will be included**
- Hypoxia ? **Fractionate** then, allow reoxygenation. Hypoxia can be modelled in LQ
- Those give a **first approximation** of DSB damage-repair mechanics at different dose rates (Low and high)

LQ for SRS and SBRT (YES or NO)

Kirkpatrick (SRS 1F)

- LQ assumes **homogeneous cell pop** (tissue **microenvironment ?**)
- **Local hypoxia** in most tumors (reduced radioresponsiveness)
- Parameters derived from **in-vitro** and **small-animal** experiments

Brenner (SRS F$\geq$ 2, SBRT)

- Varing **radiosensitivity will be included**
- Hypoxia ? **Fractionate** then, allow reoxygenation. Hypoxia can be modelled in LQ
- Those give a **first approximation** of DSB damage-repair mechanics at different dose rates (Low and high)

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (including heterogeneity)

ELSEVIER

Radiotherapy and Oncology

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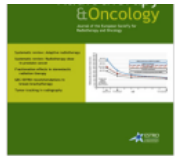

Fractionation effect in stereotactic RT

High-dose and fractionation effects in stereotactic radiation therapy: Analysis of tumor control data from 2965 patients

Igor Shuryak [a], David J. Carlson [b], J. Martin Brown [c], David J. Brenner [a,*]

[a] Center for Radiological Research, Columbia University, New York; [b] Department of Therapeutic Radiology, Yale University School of Medicine, New Haven; and [c] Division of Radiation and Cancer Biology, Department of Radiation Oncology, Stanford University, USA

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Dose

ABSTRACT

Background and purpose: Two aspects of stereotactic radiotherapy (SRT) require clarification: First, are tumoricidal mechanisms at high-doses/fraction the same as at lower doses? Second, is single high-dose SRT treatment advantageous for tumor control (TCP) vs. multi-fraction SRT?
Material and methods: We analyzed published TCP data for lung tumors or brain metastases from 2965 SRT patients, covering a wide range of doses and fraction numbers. We used: (a) a linear-quadratic model (including heterogeneity), which assumes the same mechanisms at all doses, and (b) alternative models with terms describing distinct tumoricidal mechanisms at high doses.
Results: Both for lung and brain data, the LQ model provided a significantly better fit over the entire range of treatment doses than did any of the models requiring extra terms at high doses. Analyzing the data as a function of fractionation (1 fraction *vs.* >1 fraction), there was no significant effect on TCP in the lung data, whereas for brain data multi-fraction SRT was associated with higher TCP than single-fraction treatment.
Conclusion: Our analysis suggests that distinct tumoricidal mechanisms do not determine tumor control at high doses/fraction. In addition, there is evidence suggesting that multi-fraction SRT is superior to single-dose SRT.
 Radiotherapy and Oncology 115 (2015) 327–334

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

$$[\overline{SF_n}]^{LQ} = e^{-n \cdot d(\alpha + \beta d)}$$

- Start with the simple LQ survivall fraction

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

$$[SF_n]^{LQ} = e^{-n \cdot d(\alpha + \beta d)}$$

$$[\overline{SF_n}]^{LQhet} = \int_0^{\infty} pdf\left(a|\alpha, g\right) \cdot [SF_n]^{LQ} \cdot da$$

- radiosensitive heterogeneous pop. of tumor cells (varying α)
- a is a R.V. sampled from a $\Gamma\left(a|, \alpha, g\right)$
- assuming sufficient inter-fraction time for complete DNA damage repair

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

$$TCP = e^{-N\cdot[SF_n]^{LQhet}}$$

$$[\overline{SF_n}]^{LQhet} = \int_0^{\infty} pdf\left(a|\alpha,g\right)\cdot [SF_n]^{LQ}\cdot da$$

- Averaged SF
- $pdf\left(a|\alpha,g\right)$ mean value $= \alpha$
- α (originally mechanistic par.) $\leadsto$ optimized **fitting par.**

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

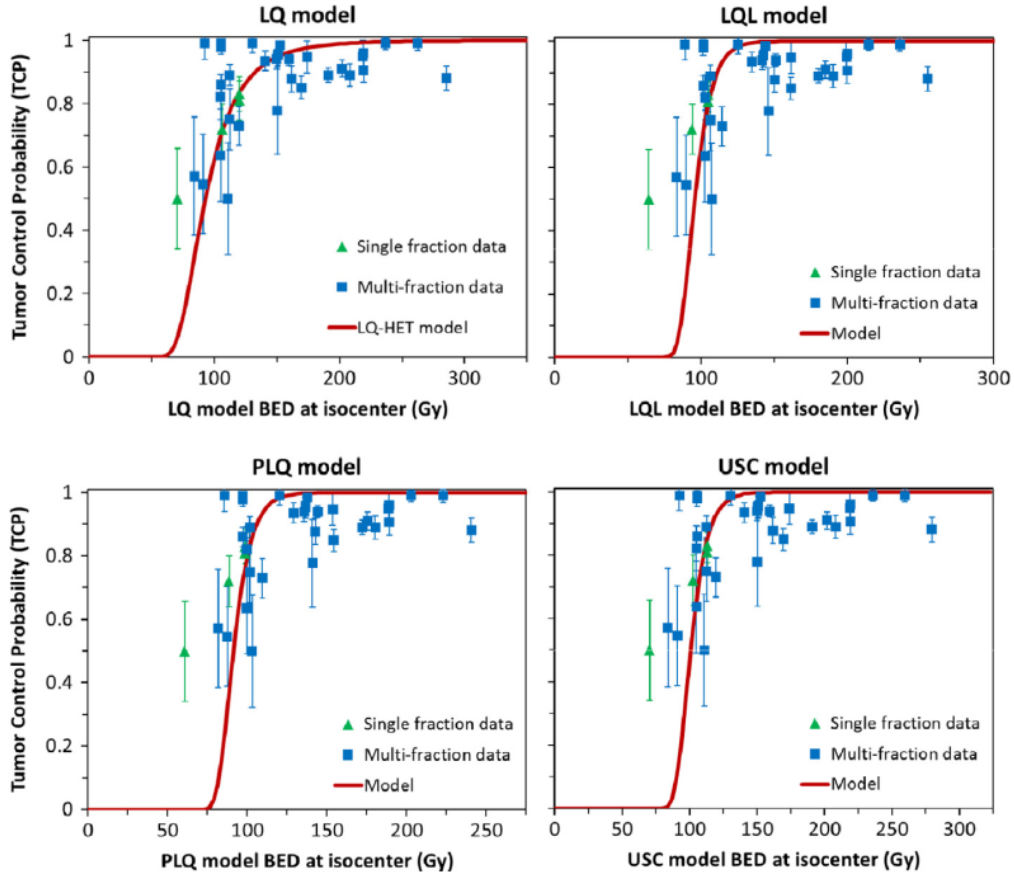


Fig. 1. Best fits to data on early-stage NSCLC from the LQ model with heterogeneous radiosensitivity (LQ), and from the LQL, PLQ and USC models with homogeneous radiosensitivity. In this and the following figures, error bars represent standard errors.

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

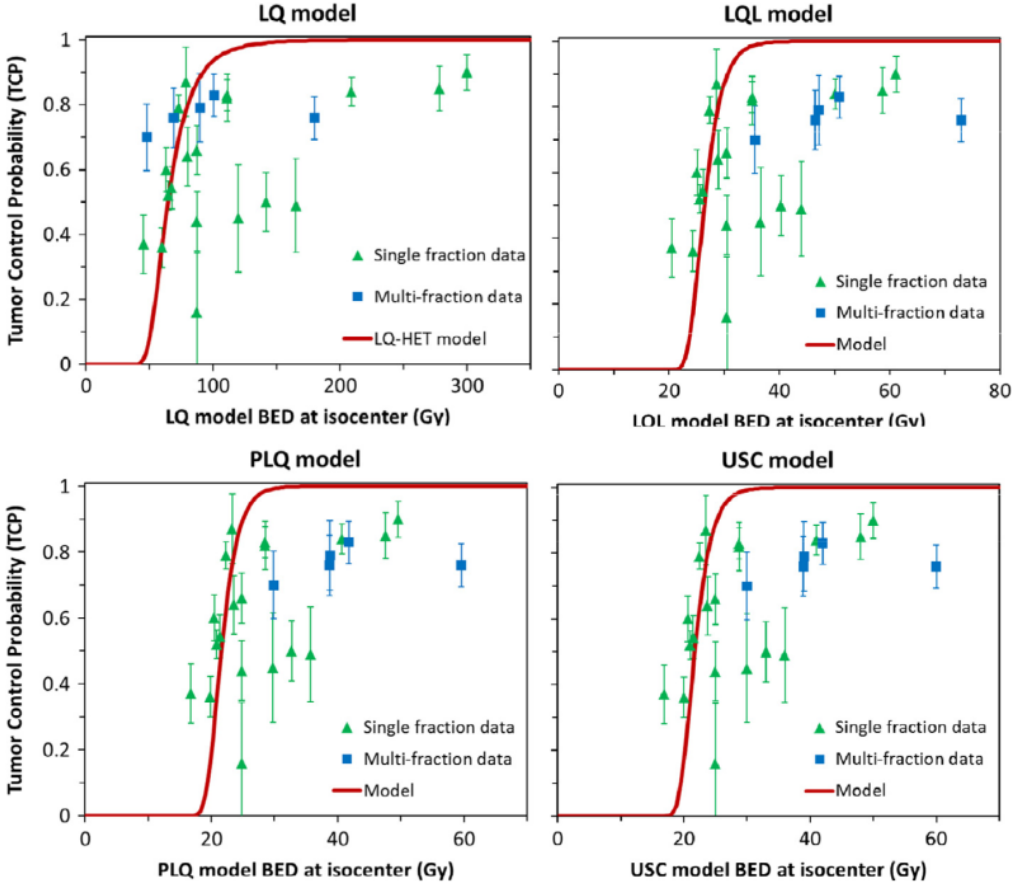


Fig. 2. Best fits to data on brain metastases from the LQ model with heterogeneous radiosensitivity (LQ), and from the LQL, PLQ and USC models with homogeneous radiosensitivity.

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

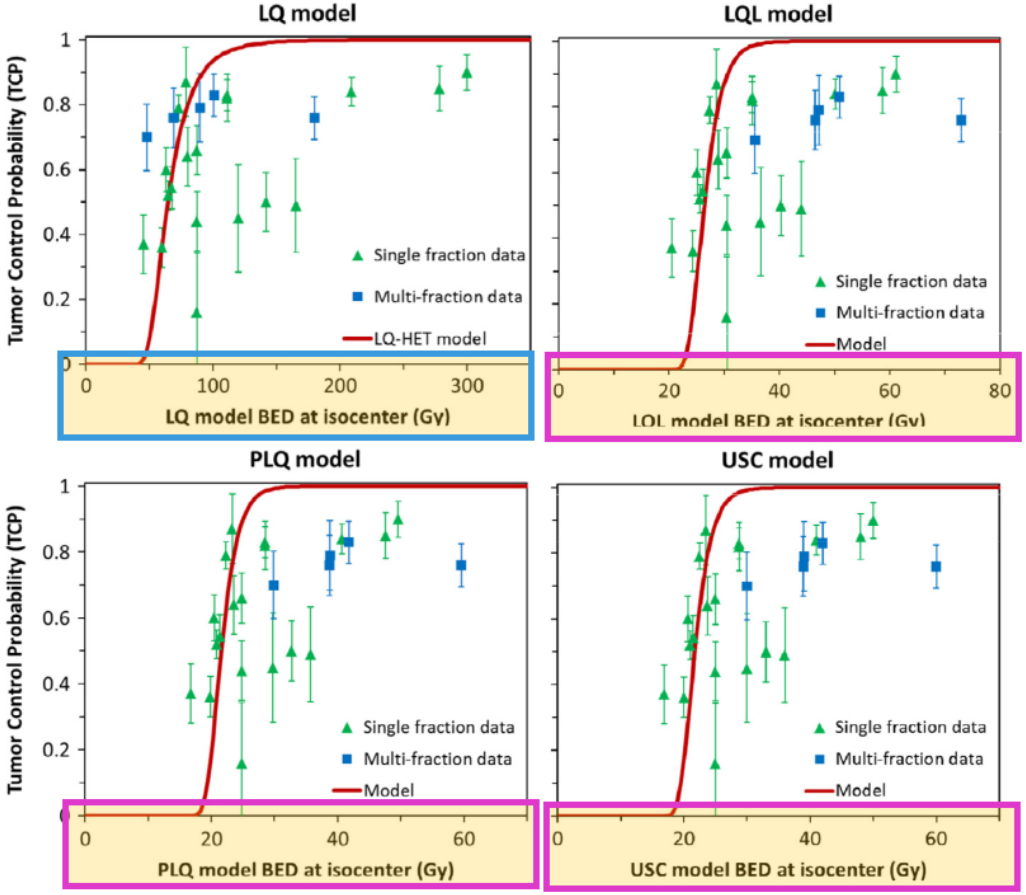


Fig. 2. Best fits to data on brain metastases from the LQ model with heterogeneous radiosensitivity (LQ), and from the LQL, PLQ and USC models with homogeneous radiosensitivity.

LQ for SRS and SBRT (YES or NO)

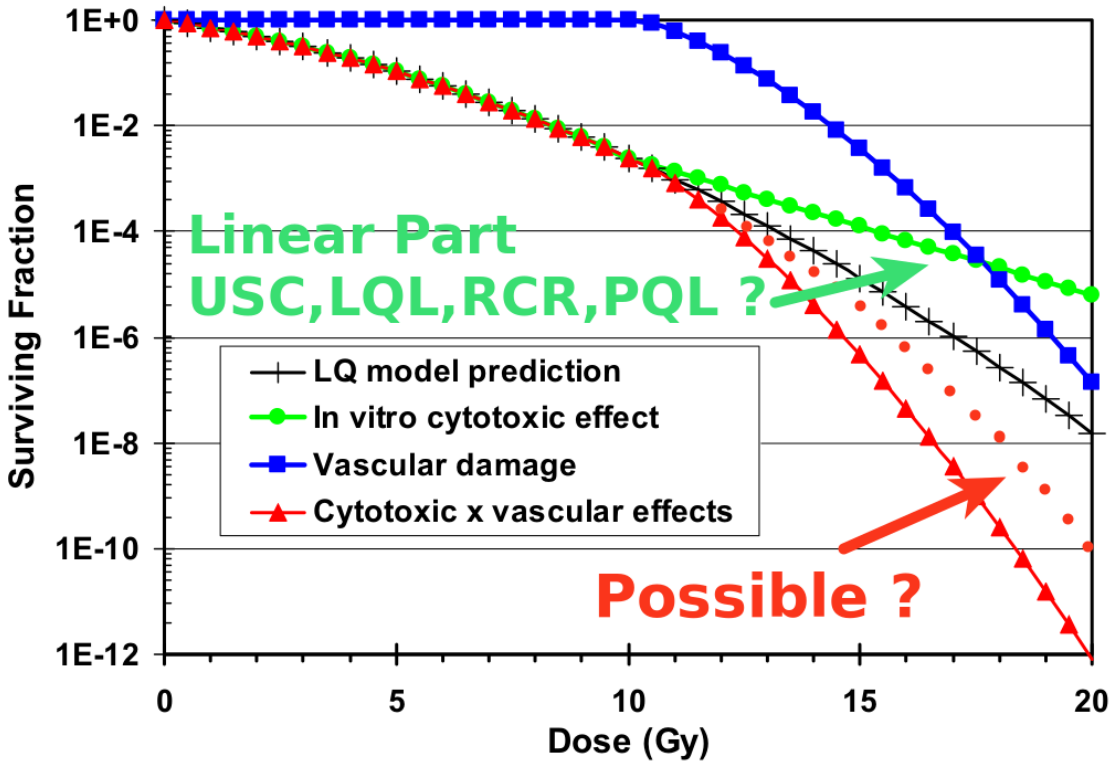
Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

- If damage to vasculature correct ⇒ TCP should show a steep response above 10Gy/f (not see in data)
- USC, RCR and PQL (unique high-dose/f kill mechanisms) fit the data much worse than the heterogeneous LQ formalism which assumes the same mechanisms at all doses
- Based on data multi-fraction brain SRT was pre- dicted to produce slightly better TCPs than single-fraction treat- ments for brain metastases. These conclusions are consistent with expected effects on **hypoxic tumors**, where fractionation allows tumor **reoxygenation between fractions**

LQ for SRS and SBRT (YES or NO)

Shuryak, Brenner 2015. LQ (incl. radiosensitivity heterogeneity)

- Comment: since α and $\frac{\alpha}{\beta}$ are optimized fitting parameters are they (unintended) accounting for the damage of tumor vascularity for high dose/f ?



LQ for SRS and SBRT (YES or NO)

Dörr et al 2017

Review Article

Normal tissue tolerance

Wolfgang Dörr[1], Thomas Herrmann[2], Klaus-Rüdiger Trott[3]

[1]Applied and Translational Radiobiology (ATRAB), Department of Radiotherapy, Medical University of Vienna, Vienna, Austria; [2]Elbeweg 8, 01326 Dresden, Germany; [3]Osterwaldstraße 71, 80805 München, Germany

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Correspondence to: Prof. Dr. Wolfgang Dörr. Applied and Translational Radiobiology (ATRAB), Department of Radiotherapy, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. Email: wolfgang.doerr@meduniwien.ac.at.

Abstract: Effects of radiation exposure are observed in virtually all normal tissues. *Early reactions* occur primarily in turnover tissues (e.g., bone marrow, epidermis, mucosae of the gastrointestinal tract), where proliferative impairment results in progressive hypoplasia and eventually complete loss of functional cells, after a tissue dependent but dose independent latent time. These early radiation reponses are regularly preceded and accompanied by vascular and inflammatory reactions. In contrast, late reactions are based on combined parenchymal, vascular, and connective tissue changes; very late effects are dominated by vascular sequelae. In most instances, a significant involvement of the immune system can also be demonstrated for chronic radiation sequelae, and a contribution of neural changes is discussed. The orchestrated response of all tissue components results in loss of function within the exposed volume. Importantly, latent times of late effects are inversely dependent on dose. Hence modern, highly conformal treatment techniques with relatively low and inhomogeneous doses in the organs at risk (OAR) require very long follow-up intervals with a precise assessment and documentation

LQ for SRS and SBRT (YES or NO)

Dörr et al 2017 (on LQ)

- The LQ model describes the relationship between **total isoeffective doses** and **dose per fraction**
- Estimates of **effectivity/toxicity** after changes in dose per fraction and total dose
- LQ model at the tissue or endpoint level **is not based** on radiobiological mechanisms, such as **target cell survival**
- LQ at **tissue** or **endpoint level** is **mathematical fit of the change of dose effect curves** or the **incidence of treatment adverse effects**, if doses per fraction doses are modified

LQ for SRS and SBRT (YES or NO)

Dörr et al 2017 (on NTCP and QUANTEC)

- NTCP models based on DVH reduction
- NTCP **ignore regional differences in radiation sensitivity**
- **endpoints** and **symptoms** of late radiation damage **do not occur in tissue volumes** **but in specific, sensitive structures**, and that radiation damage to different substructures in the same organ leads to different pathophysiological endpoints
- **Tolerance** doses in EQDx need to be defined **for individual endpoints**, rather than OAR in general
- previous or additional **chemotherapy** may impact on the function of the un-irradiated organ volume.

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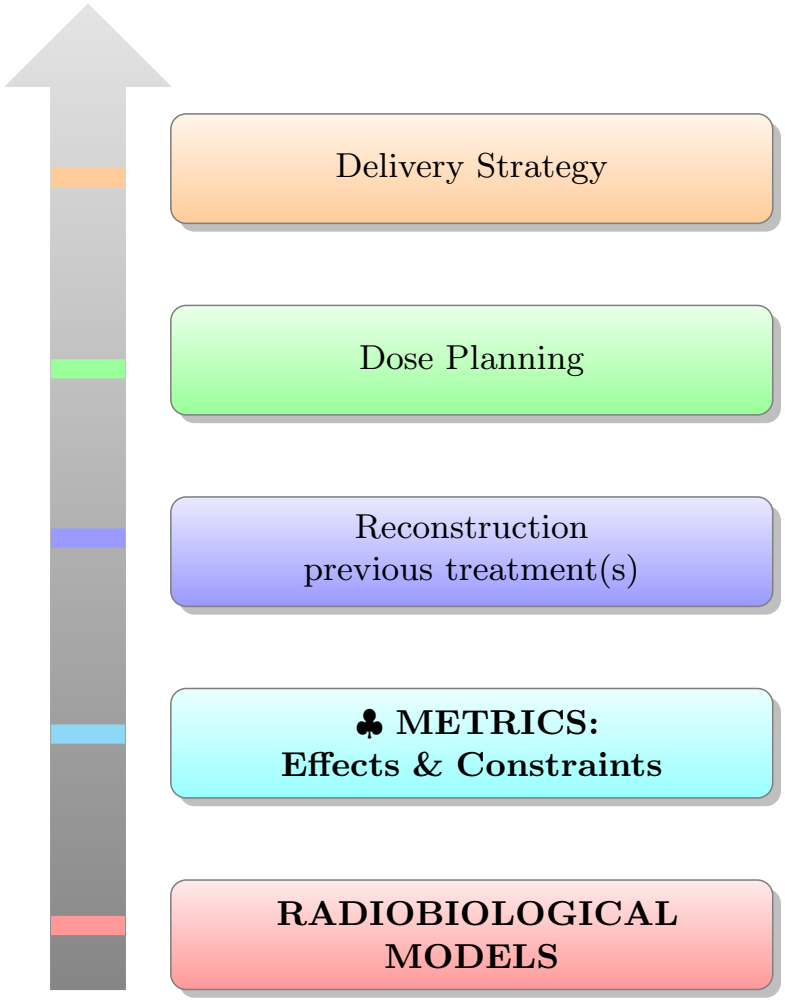

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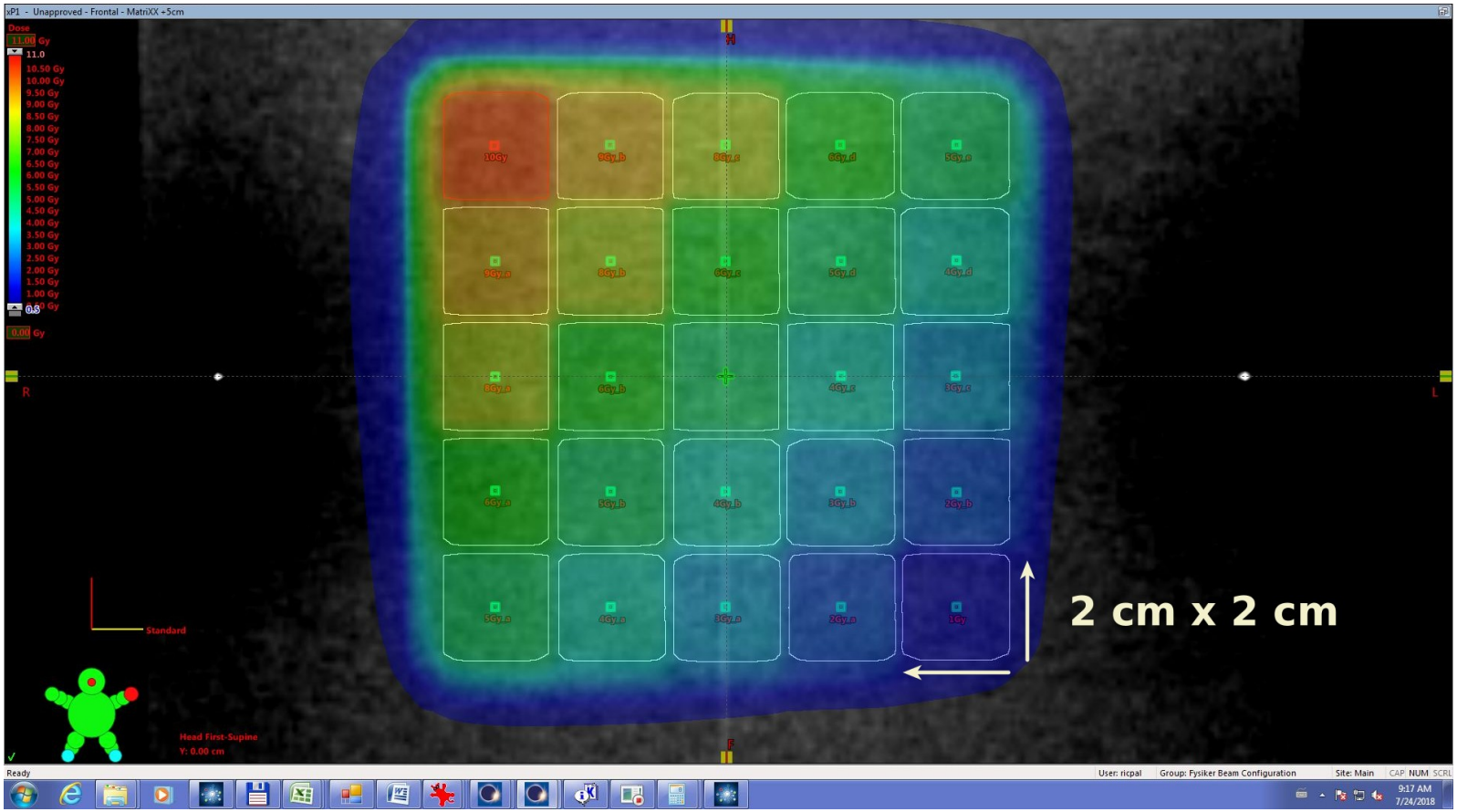
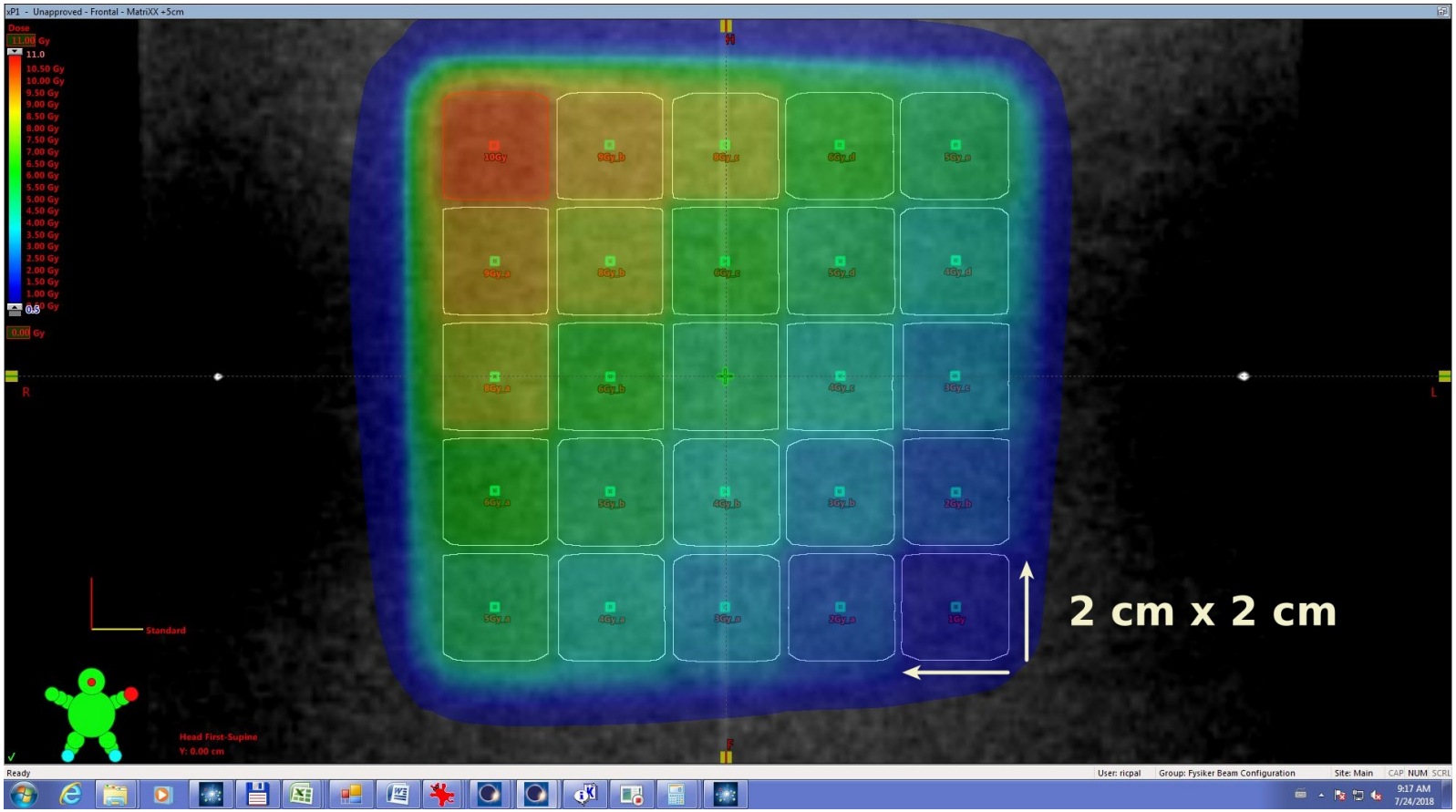
Metrics: Effects, Constraints

Let's make a *gedankenexperiment* now ...



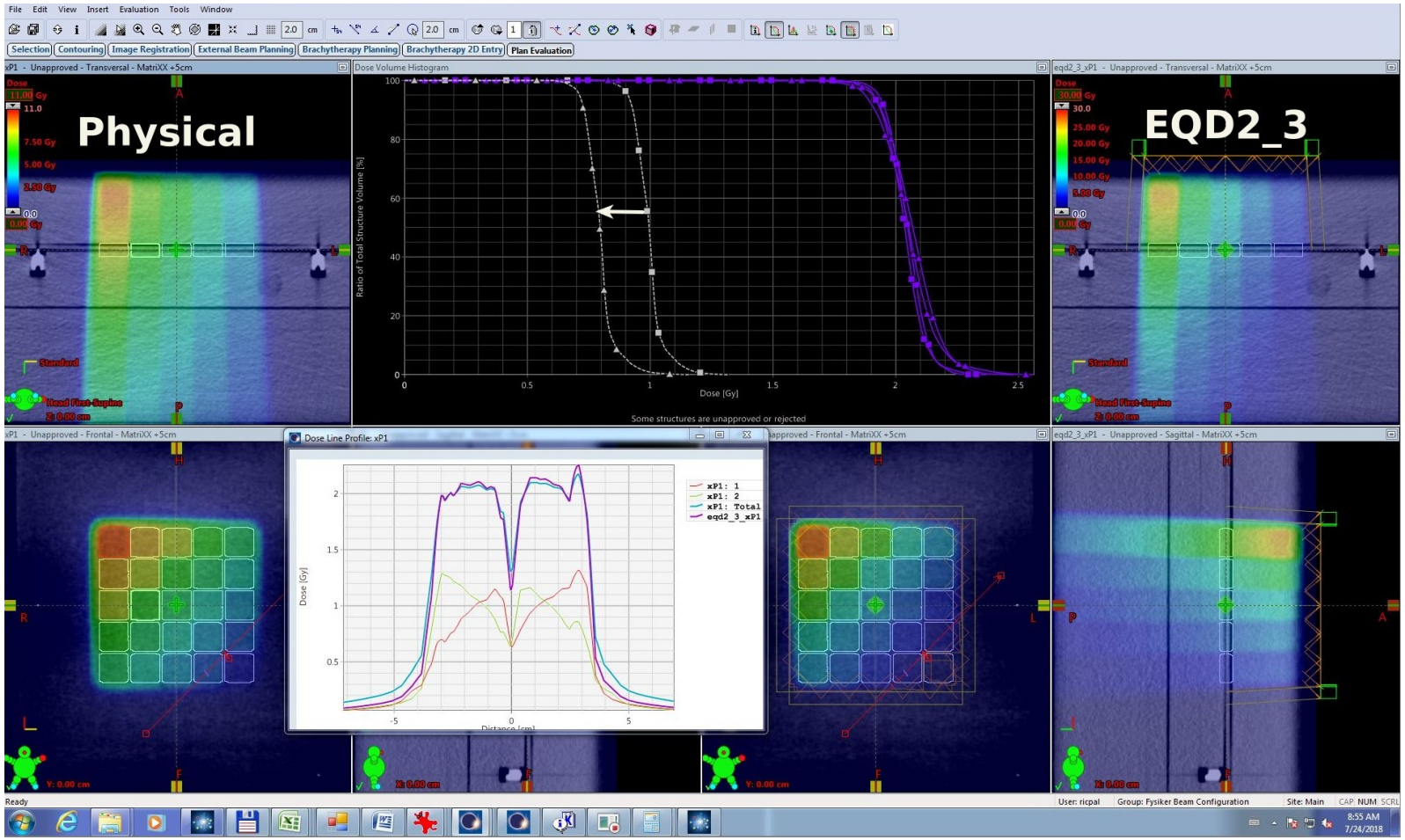
Metrics: Effects, Constraints

Use the TPS to irradiate patches of 2 x 2 cm
homogenouesly and different dose levels (1 - 10 Gy) in 1 fraction



Metrics: Effects, Constraints

$EQD2_3$ dose patch (Petri) represents the SF n_2 2Gy/f
$\equiv$ SF physical dose administed in 1 frac.



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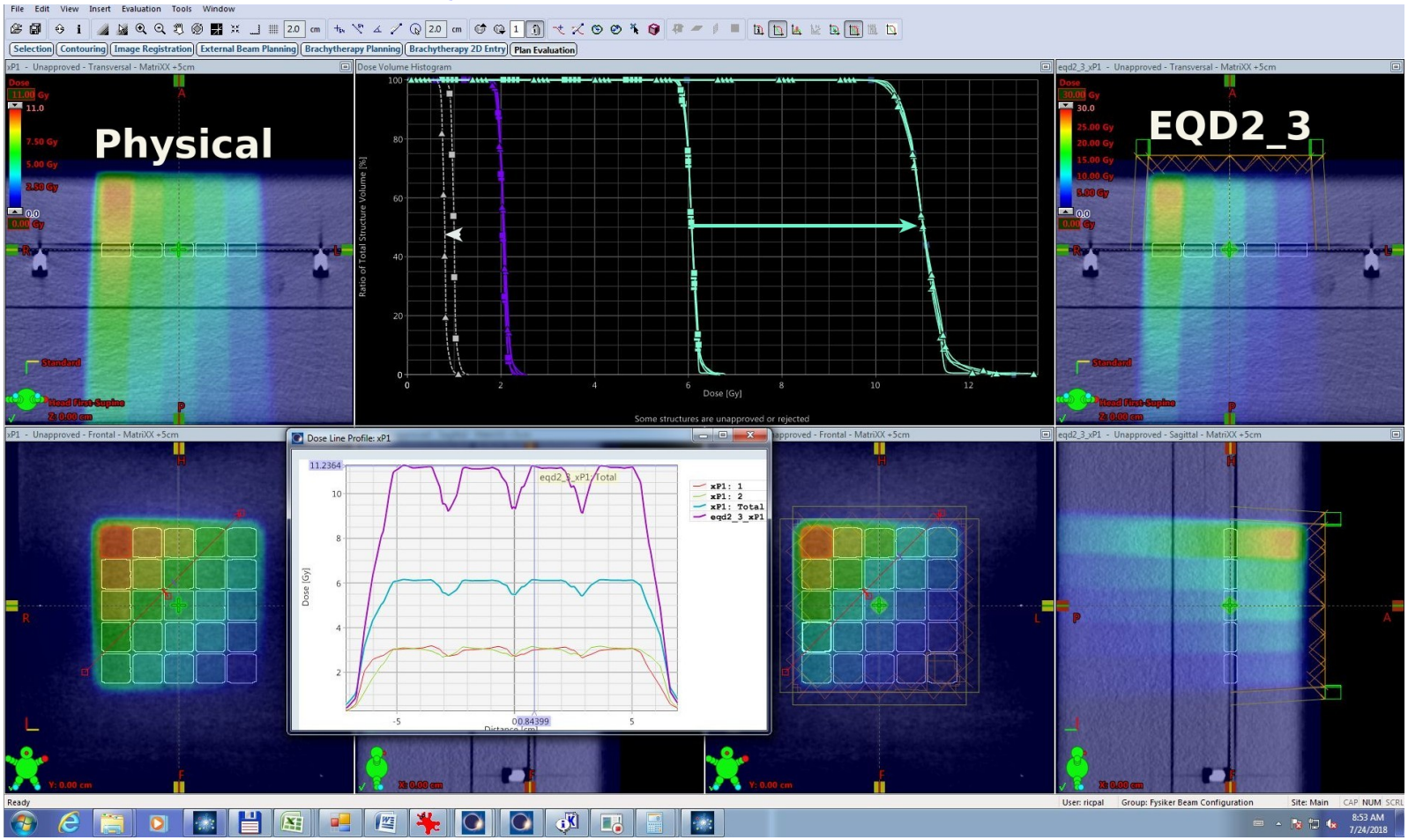

Metrics: Effects, Constraints

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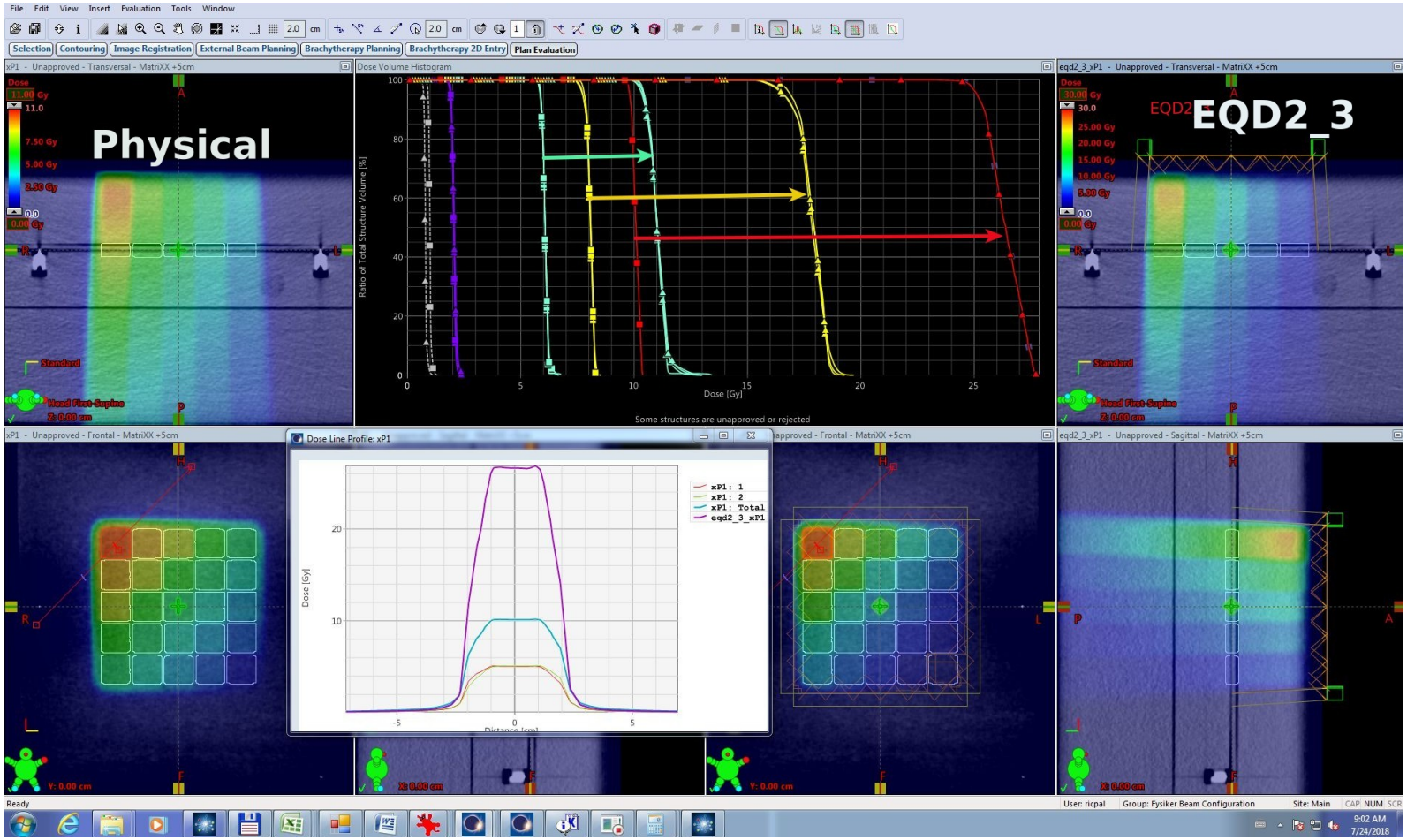
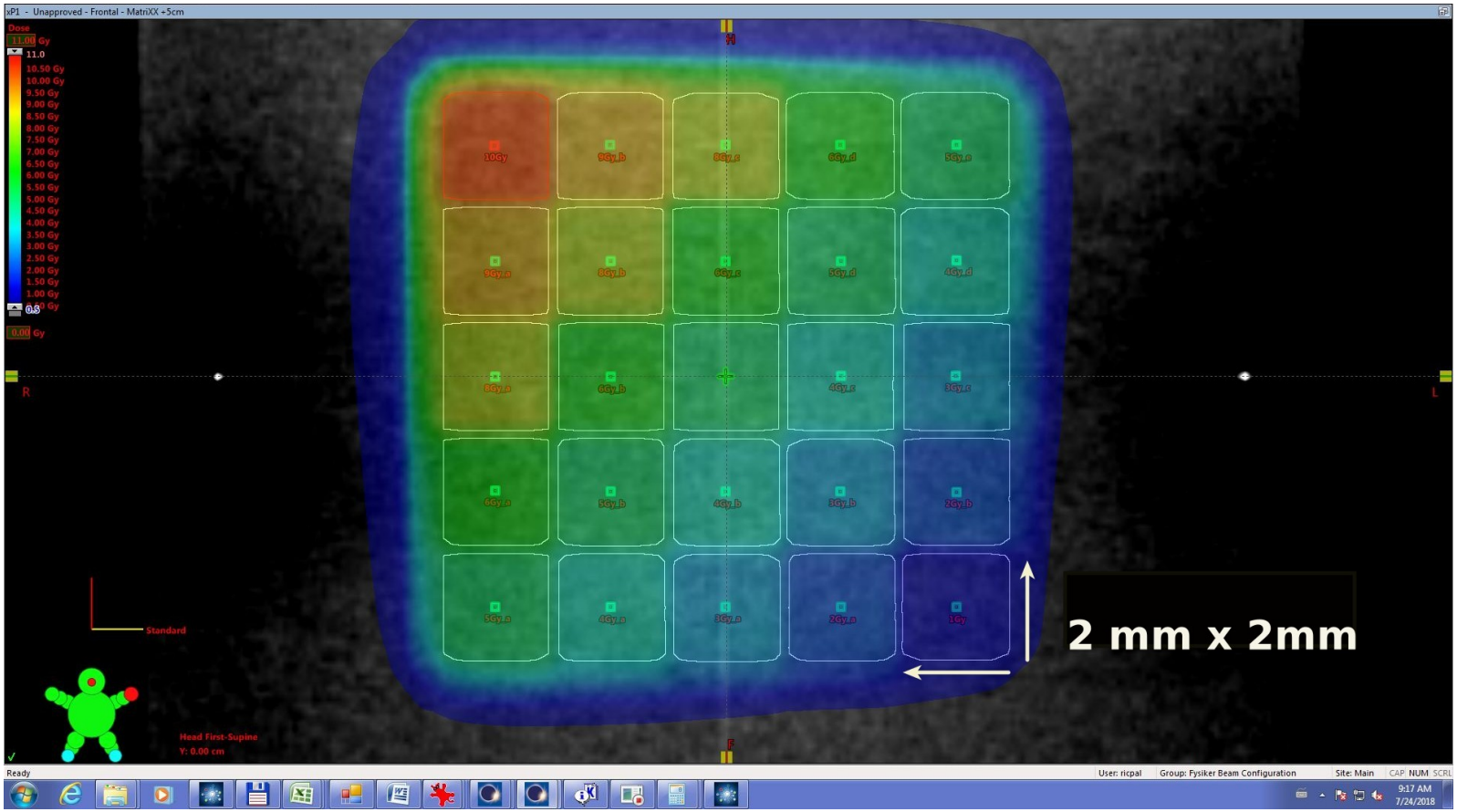


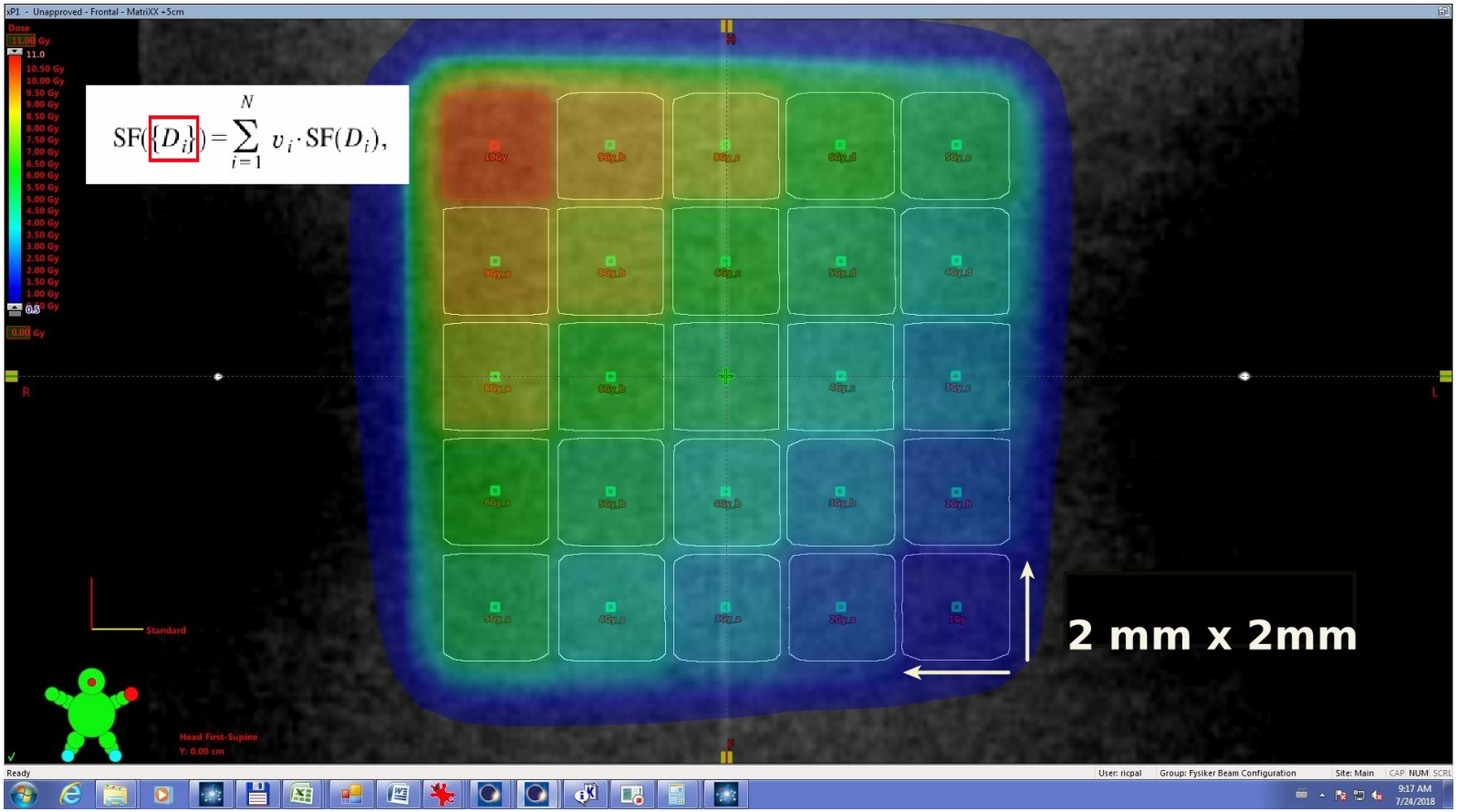
Metrics: Effects, Constraints

Let's make a *gedankenexperiment* now ... with voxels



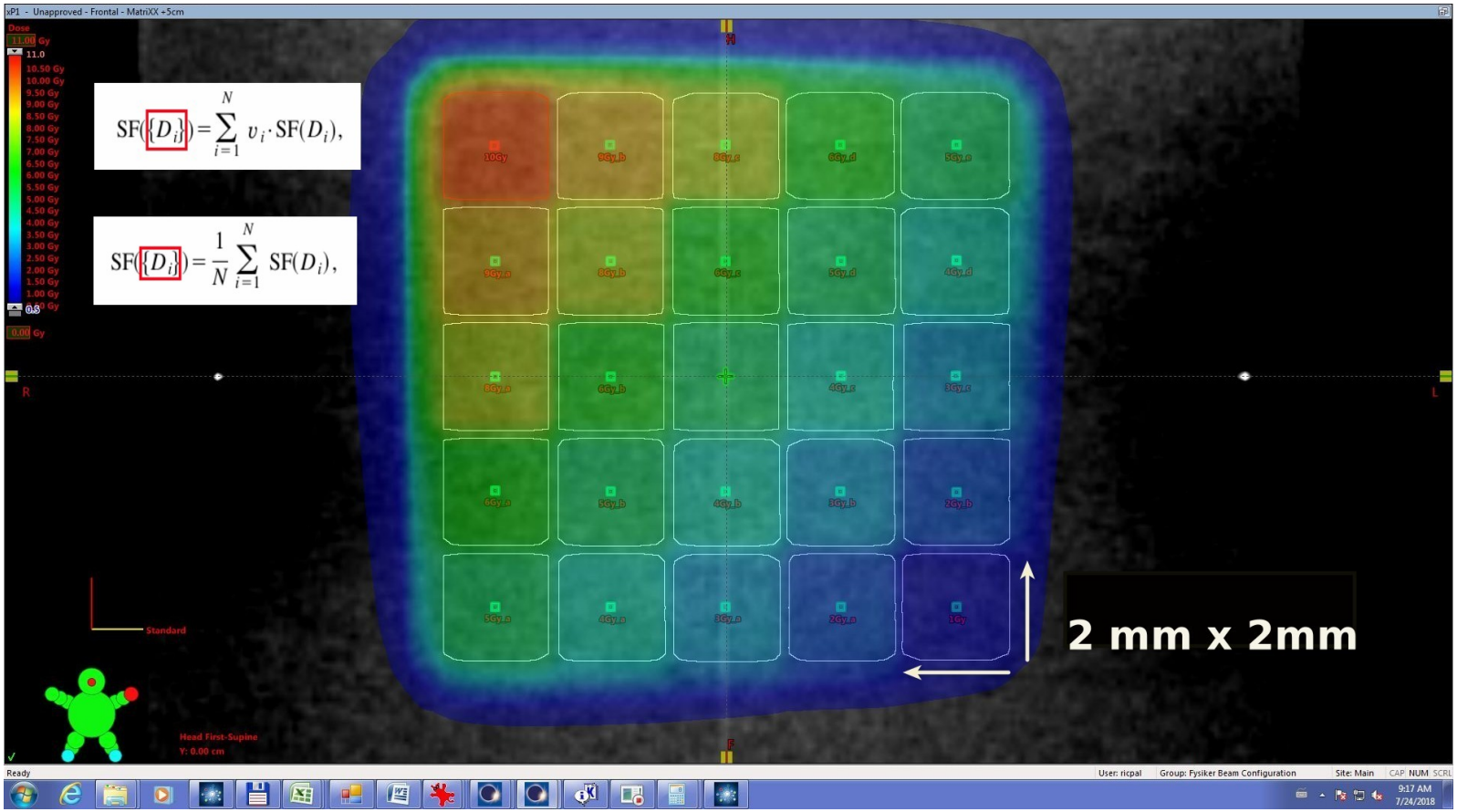
Metrics: Effects, Constraints

If voxels are considered Petri ... Niemierko 1996 proposed a metric (EUD concept)



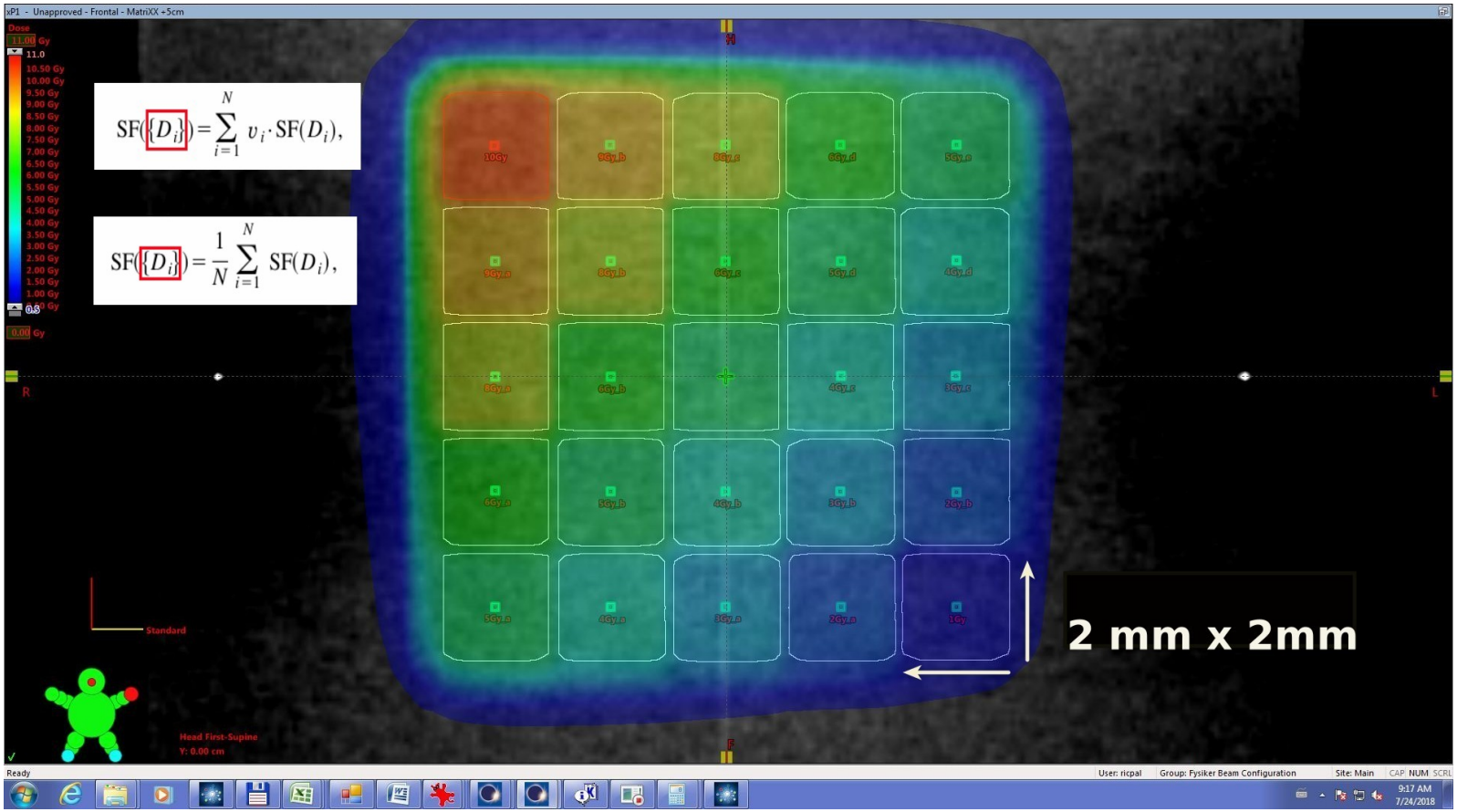
Metrics: Effects, Constraints

EUD (one-to-one $SF \leftrightarrow$ EUD $\leftrightarrow$ TCP). Use: complementary figure of merit for CTV_{min} or OAR_{max}



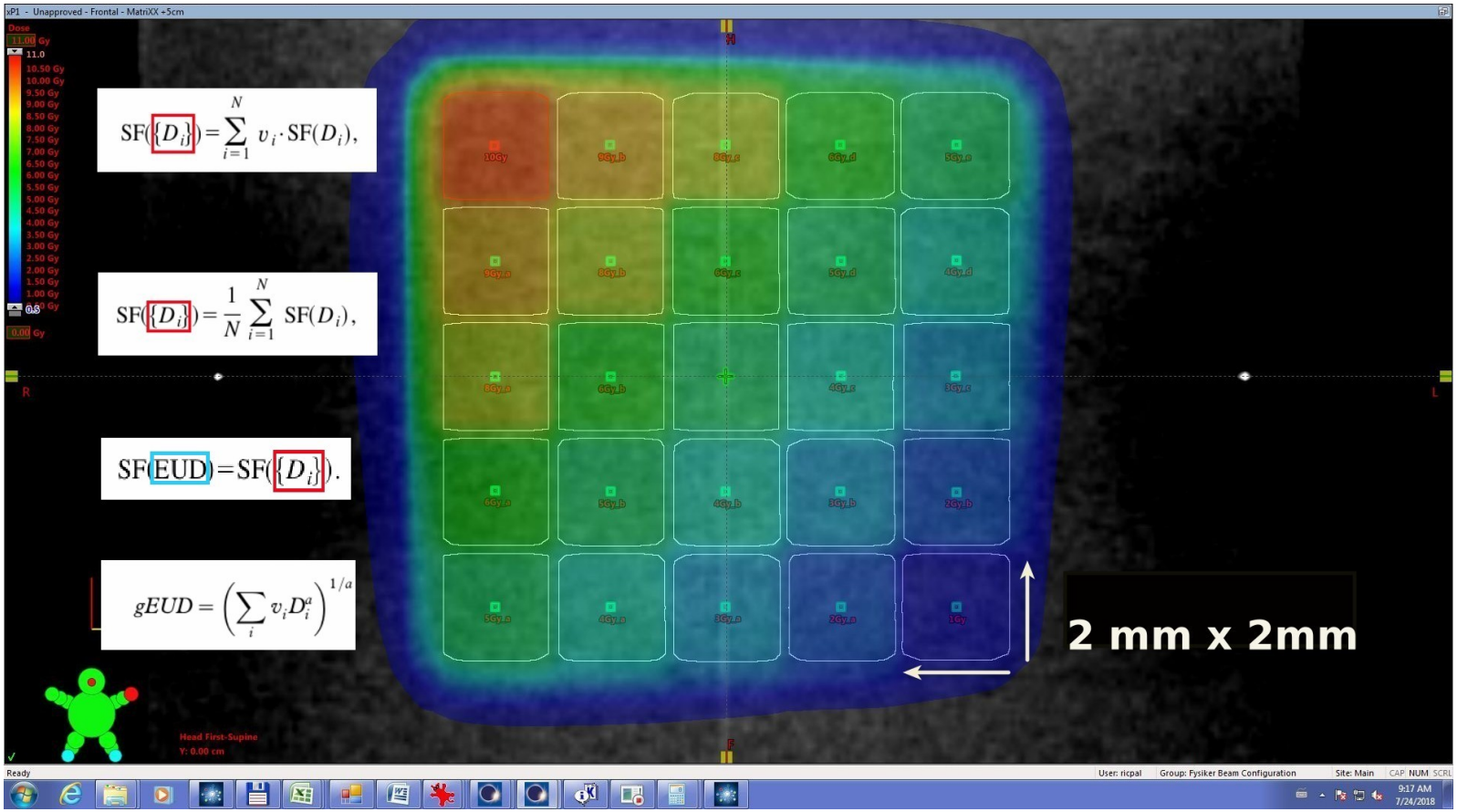
Metrics: Effects, Constraints

EUD (one-to-one $SF \leftrightarrow$ EUD $\leftrightarrow$ TCP). Use: a single-value that feeds TCP/NCTP formulas.



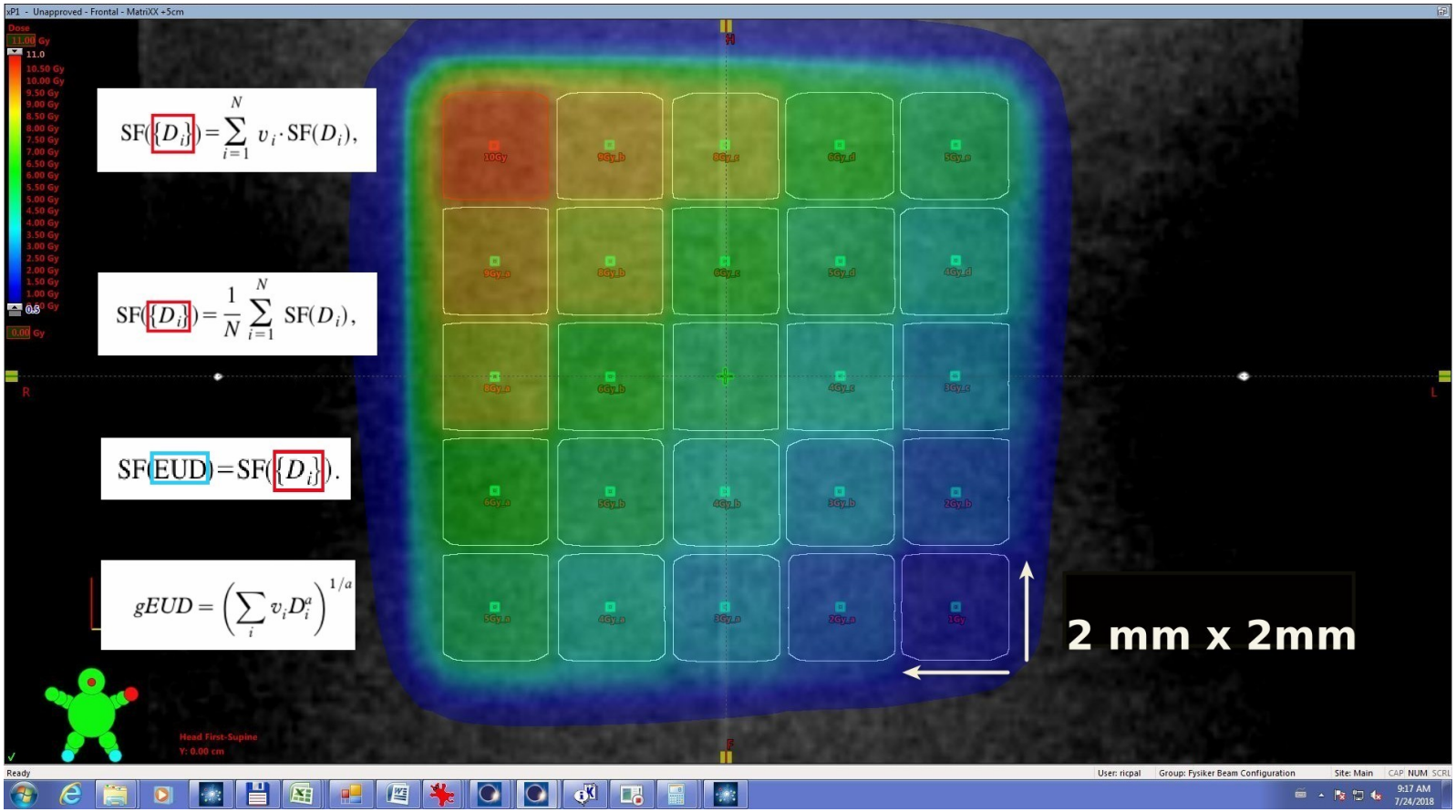
Metrics: Effects, Constraints

EUD (one-to-one *SF* $\leftrightarrow$ EUD $\leftrightarrow$ TCP). But: no 3D visualization, all parts of Target / OARs weight the same.



Metrics: Effects, Constraints

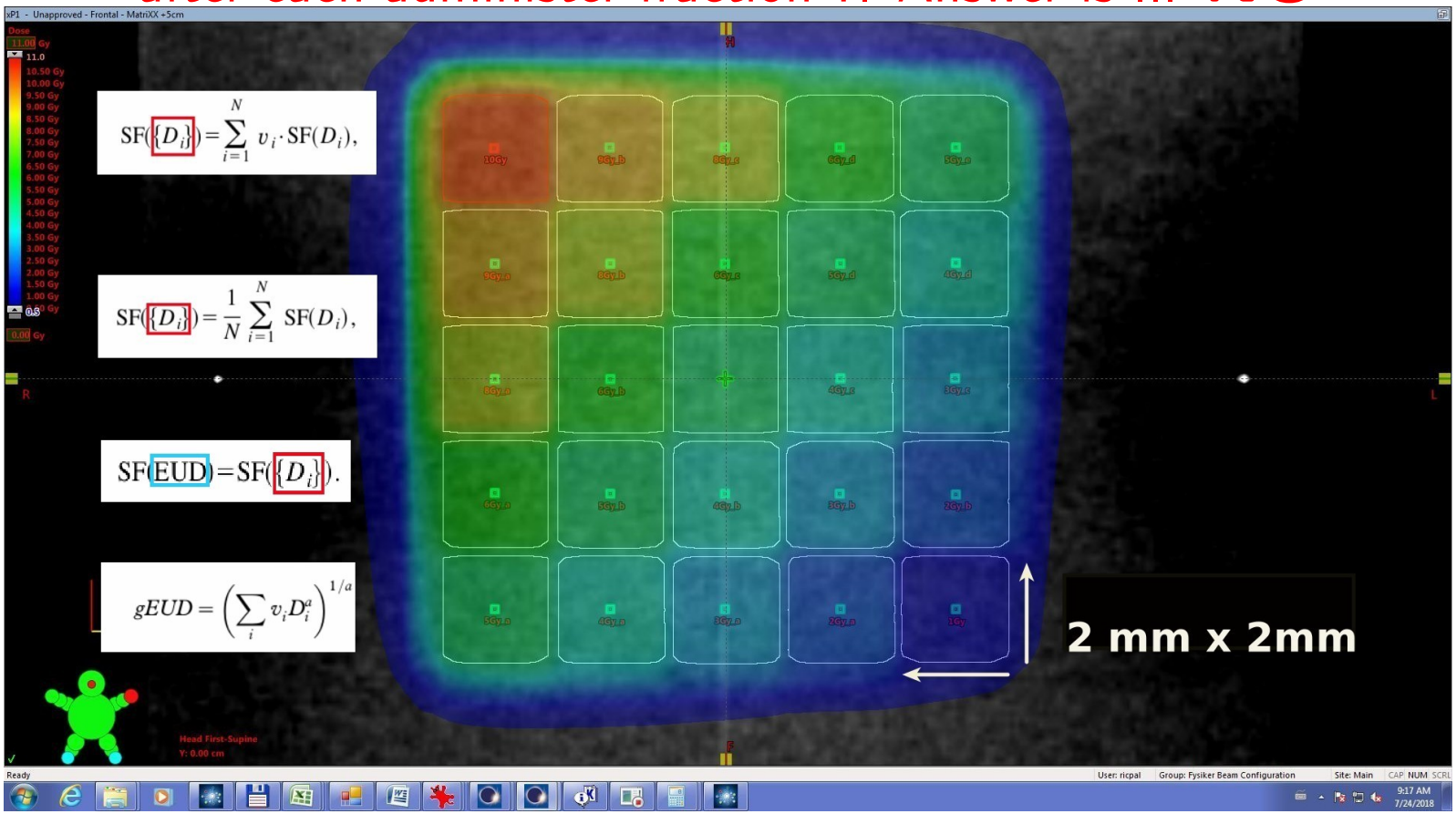
EUD (one-to-one $SF \leftrightarrow$ EUD $\leftrightarrow$ TCP). But: no 3D visualization $\Leftrightarrow$ many dose distrib. can have same EUD.



Question: can we determined experimentally SF at volume unit v_i after each administer fraction ?. Answer is ...

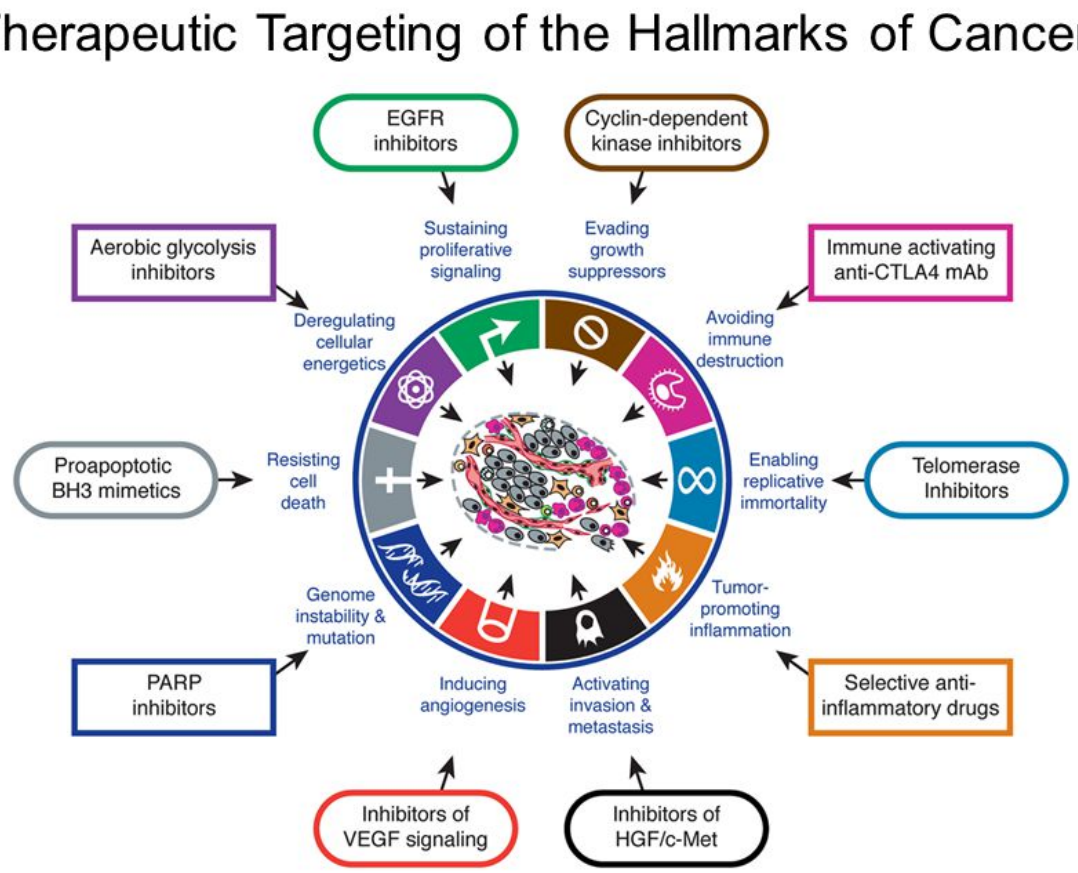
Metrics: Effects, Constraints

Question: can we determined experimentally *SF* at volume unit v_i after each administer fraction ?. Answer is ... **NO**



Metrics: Effects, Constraints

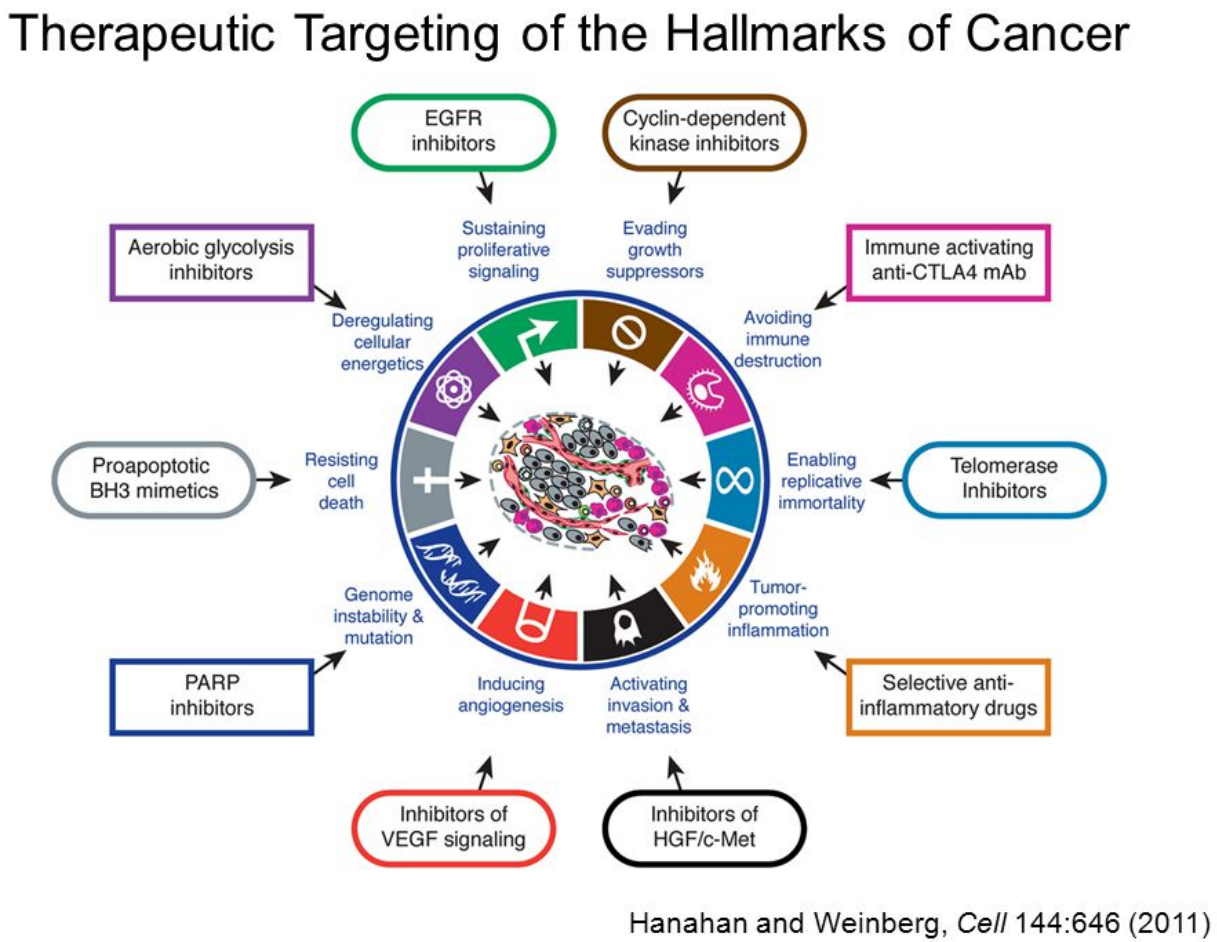
A clonogenic colony of cells in-vitro does not display all the "tricks" that cancer cells master ... $\Leftrightarrow SF_{pat}$?



Hanahan and Weinberg, *Cell* 144:646 (2011)

Metrics: Effects, Constraints

Same argument applies to healthy cells in-vitro, versus healthy cells conforming a tissue and in turn and organ



Metrics: Effects, Constraints

Question: can the concept of *SF* be used as a metric that bridges the intracellular effect of radiation (mechanistic models) to the extracellular macrospcopic effect of radiation at organ level (effects, end points) ?.

In fact, LQ based $EQDX_{\frac{\alpha}{\beta}}$ is used as a 3D-metric (in as much as EUD) if we see now α and $\frac{\alpha}{\beta}$ as fitting parameters (W. Dörr). Can rely on QUANTEC for this metrics but looking at specific end points and not only organ. Needs a revision (only 4 institutions involved) (W. Dörr)

Metrics: Effects, Constraints

Applying $EQDX_{\frac{\alpha}{\beta}}$ voxel by voxel ...

Each voxel (grid) $\Leftrightarrow$ different $\sharp$ fractions in X Gy/frac

Metrics: Effects, Constraints

Applying $EQDX_{\frac{\alpha}{\beta}}$ voxel by voxel ...

Used as a navigational tool only... Have to be aware of the kind of challenge we have

and take extra precautions ...Foreseable events

.

Metrics: Effects, Constraints

Applying $EQDX_{\frac{\alpha}{\beta}}$ voxel by voxel ...

Used as a navigational tool only... Have to be aware of the kind of challenge we have

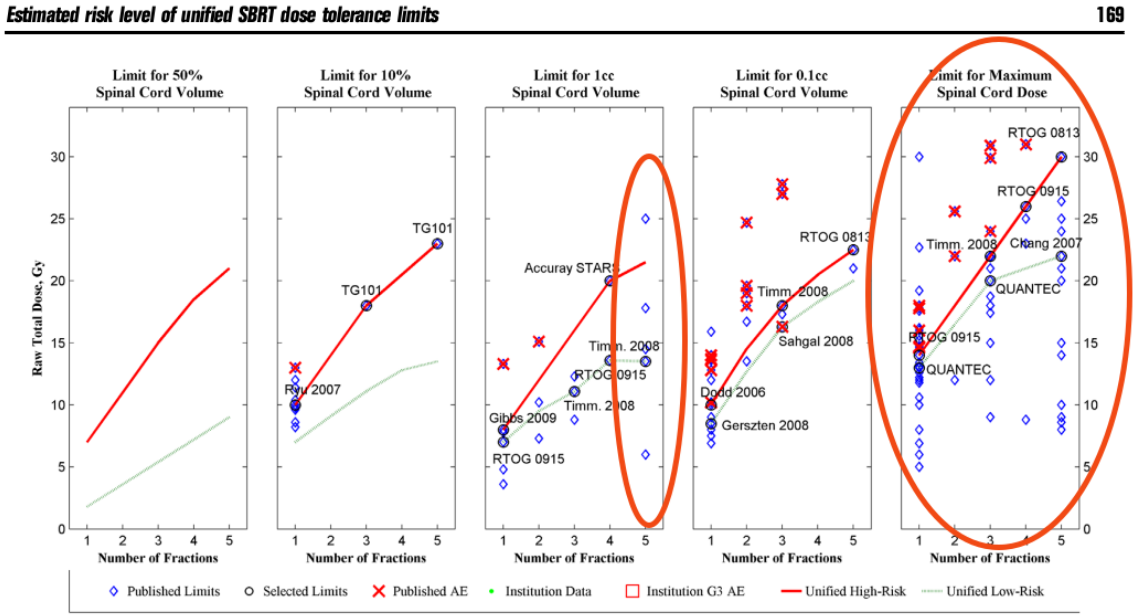
and take extra precautions ... unforeseable events

.

Metrics: Effects, Constraints

Applying $EQDX_{\frac{\alpha}{\beta}}$ voxel by voxel ...

Used as a navigational tool ... but where is the coast ? (e.g. Grim et al)

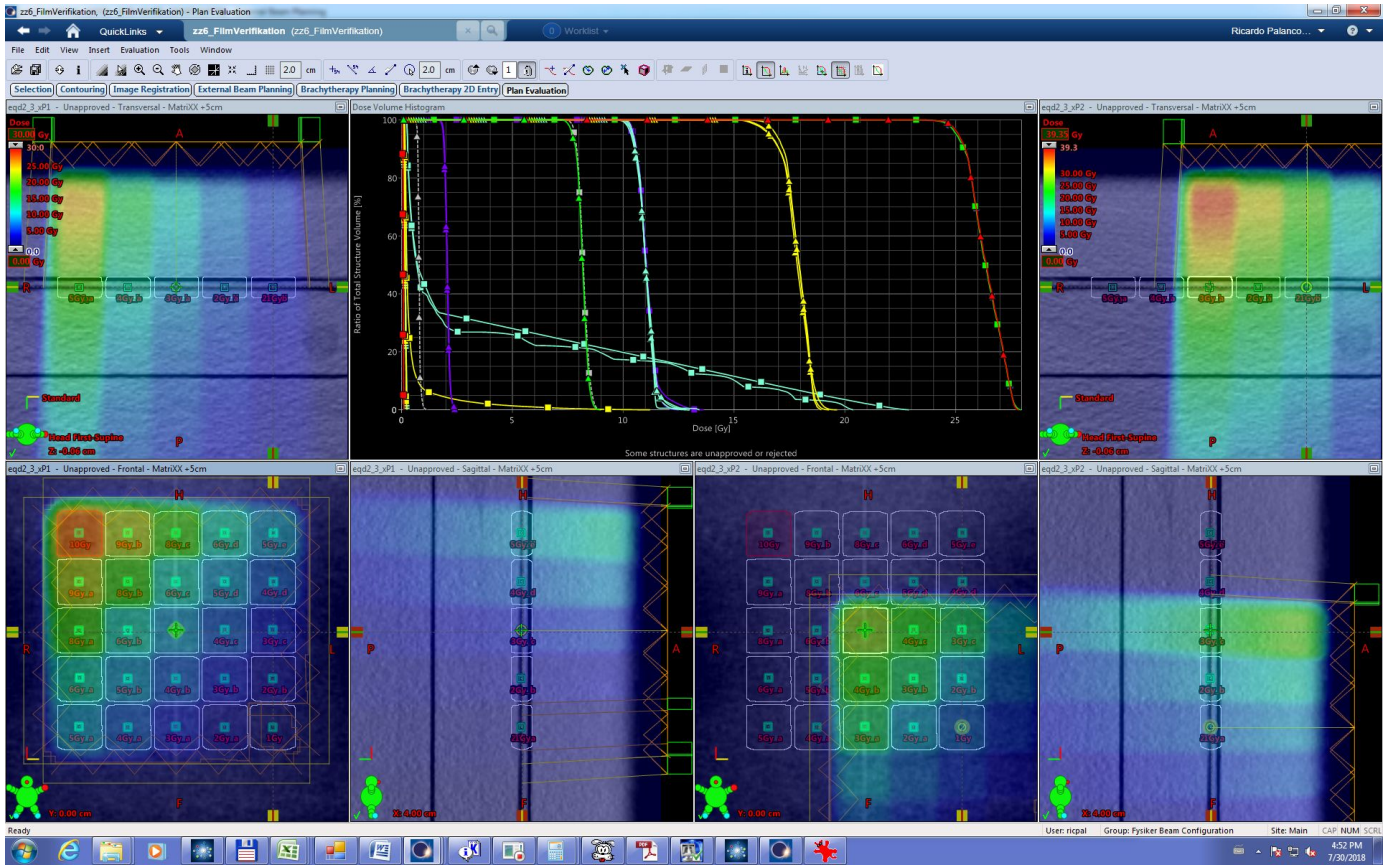


	Low Risk Limits					High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.1cc Limit (Gy)	Dmax Limit (Gy)	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.1cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*1.8*	*7.0*	**7.0, 0.1%**	**8.5, 0.1%**	**13.0, 0.9%**	*7.0*	**10.0**	**8.0, 0.2%**	**10.0, 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%**

Metrics: Effects, Constraints

Applying $EQDX_{\frac{\alpha}{\beta}}$ voxel by voxel ... RE-IRRADIATION

Used as a navigational tool only... Have to be aware what we are looking at



Metrics: Effects, Constraints

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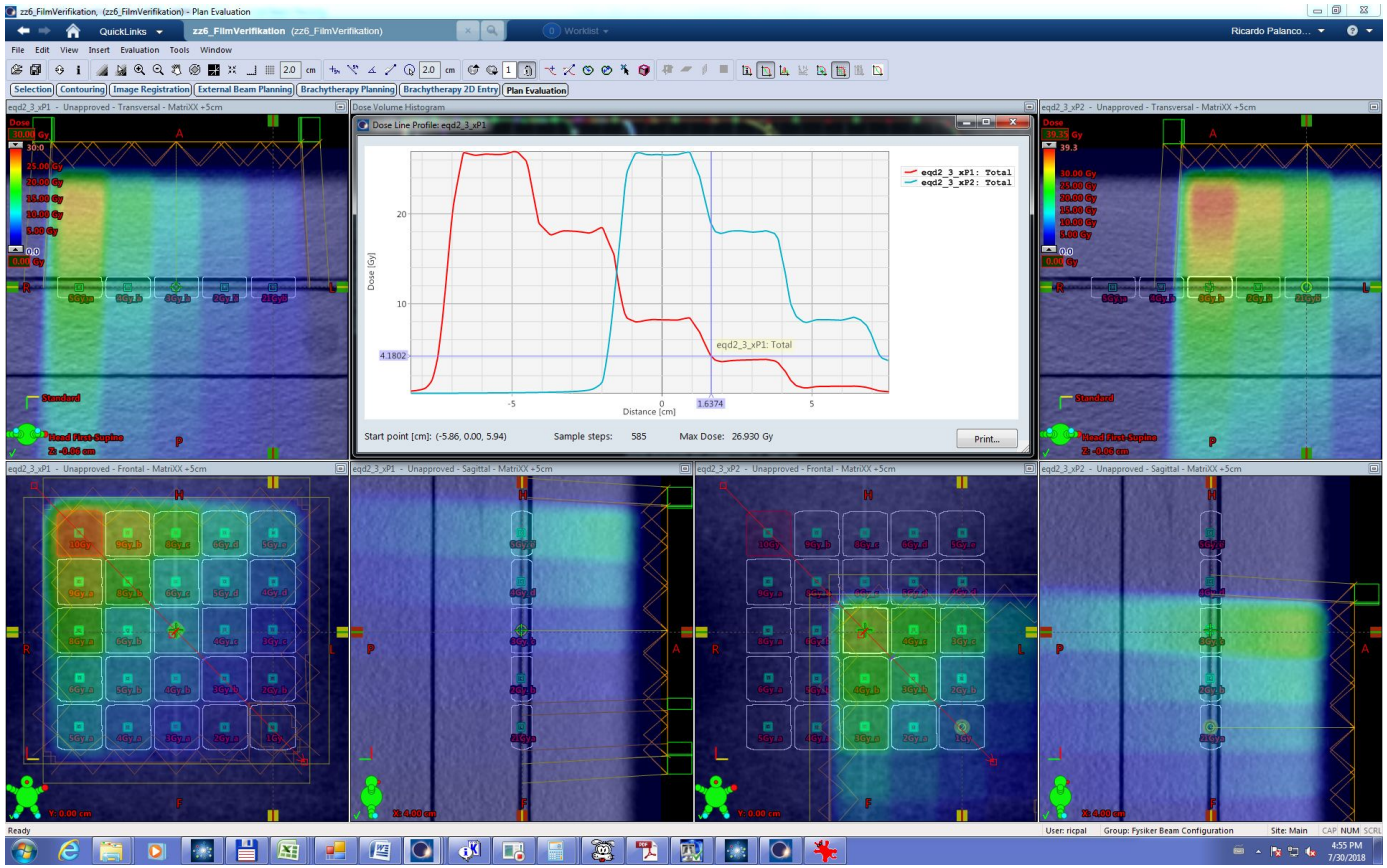
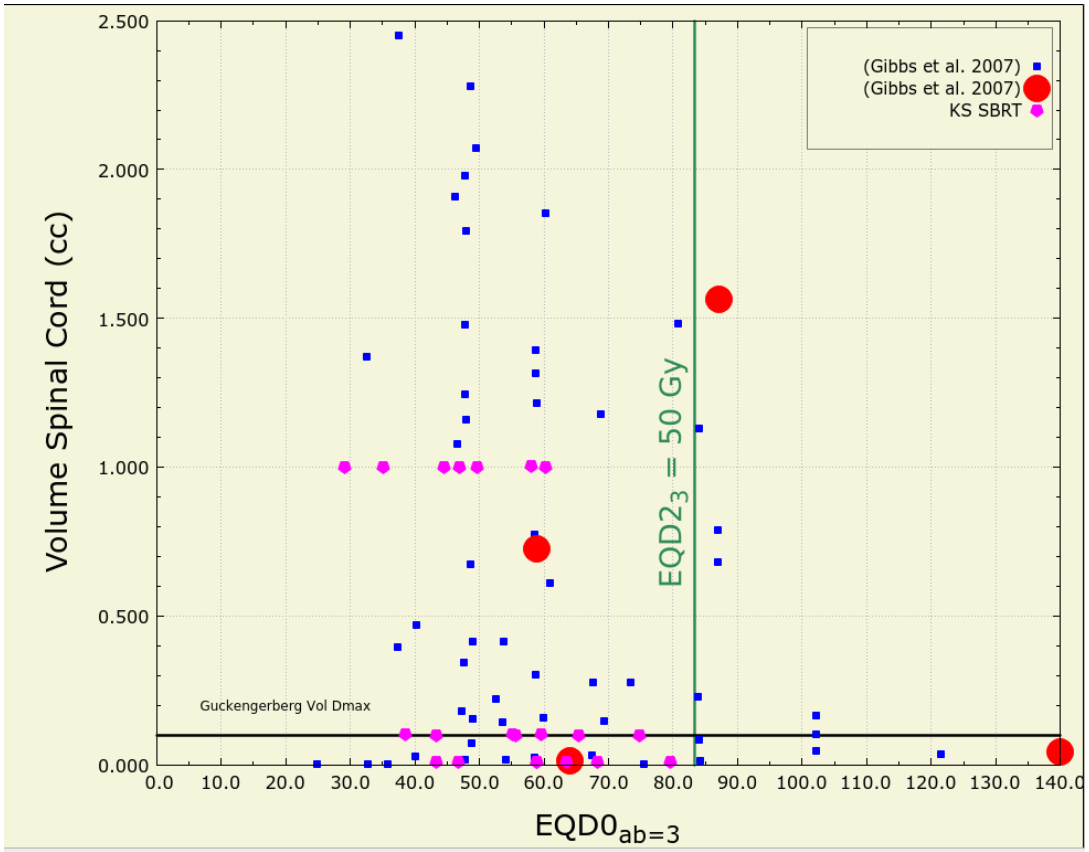


Metrics: Effects, Constraints

Applying $EQDX_{\frac{\alpha}{\beta}}$ to compare different schools of practice



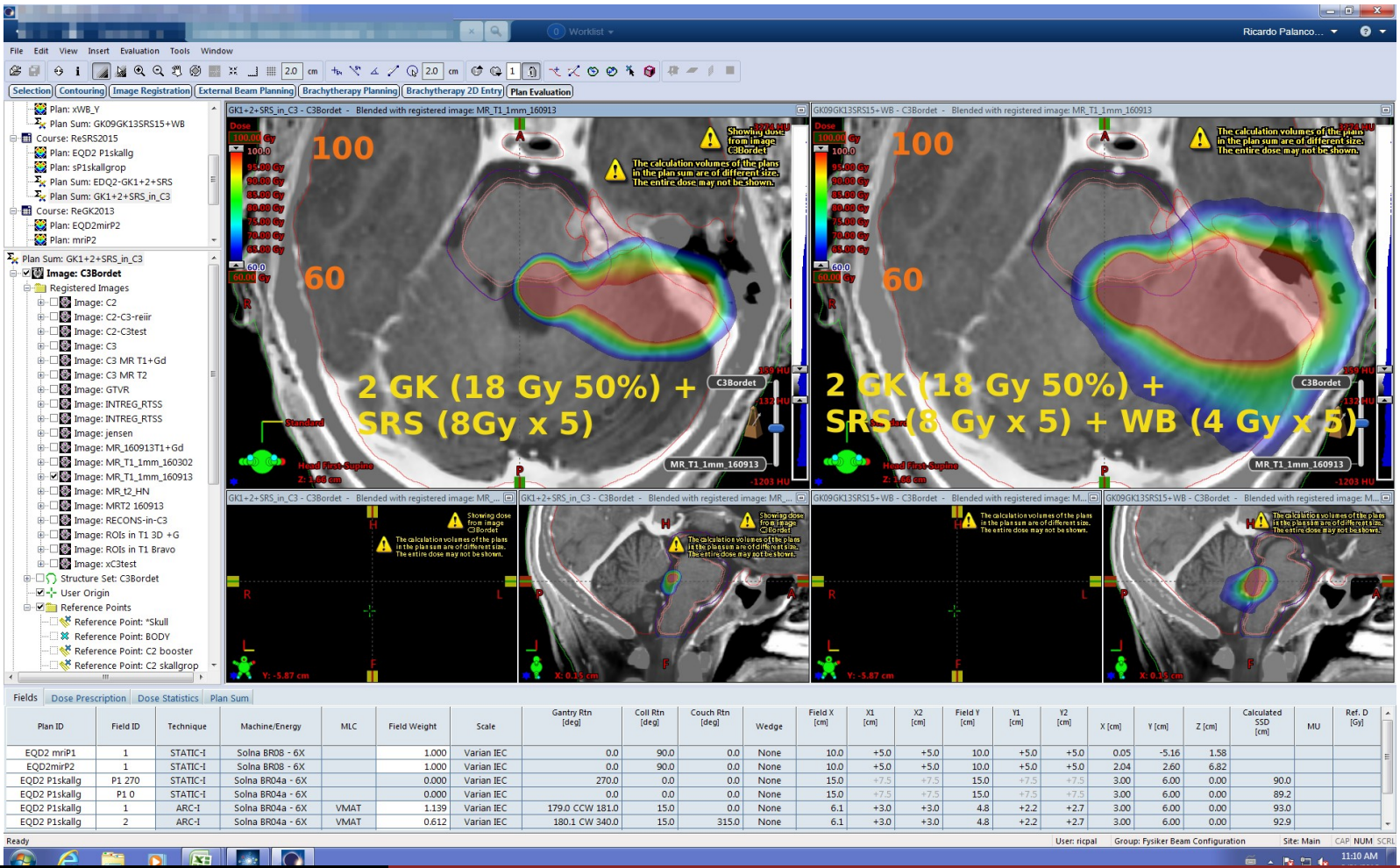
Metrics: Effects, Constraints

$EQDX_{\frac{\alpha}{\beta}}$ voxel by voxel ... RE-IRRADIATION

Best figures of merit for plan evaluation of a treatment ? Used as a navigational tool only... Have to be aware what we are looking at

Metrics: Effects, Constraints

$EQDX_{\frac{\alpha}{\beta}}$ voxel by voxel ... RE-IRRADIATION BED in GK not can be different from BED Linac



Metrics: Effects, Constraints

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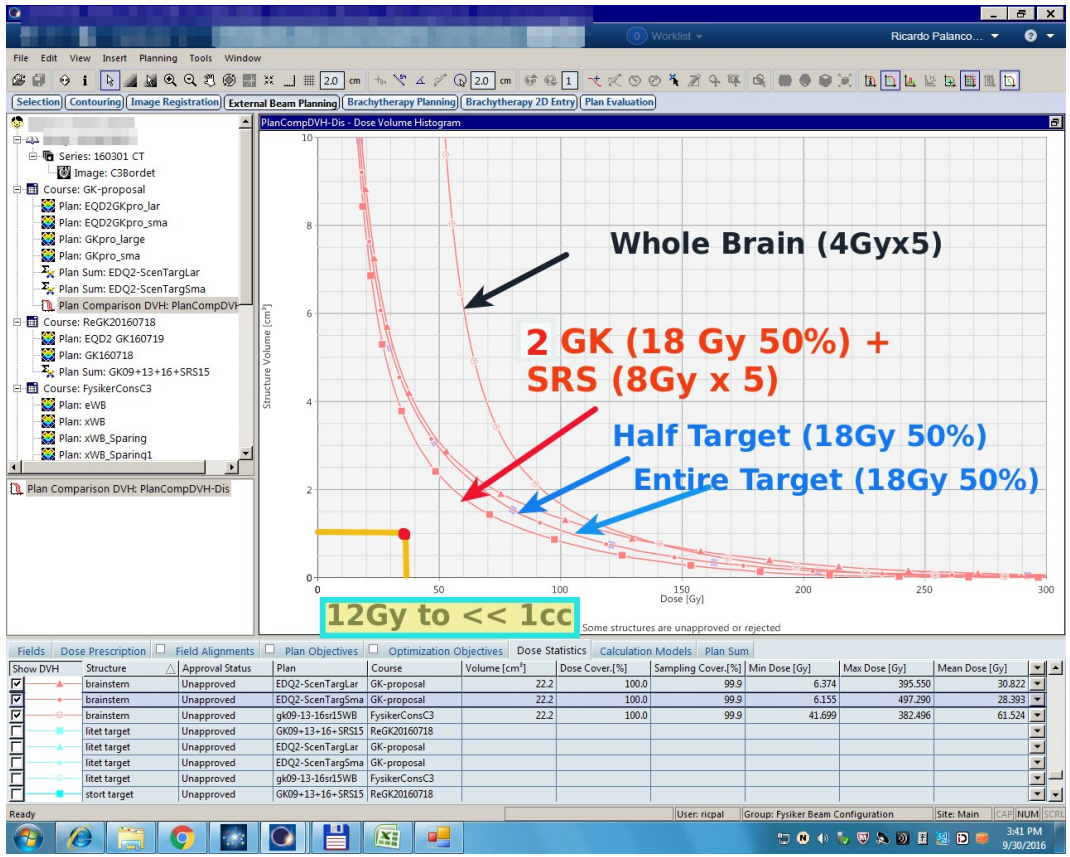

Metrics: Effects, Constraints

Recap so far ...

Is it LQ appropiate for *SBRT* ?

- It is a reasonably good
- Widely used
- Don't look upon the mechanistic view (at times ...)
- Use $EQDX_{\frac{\alpha}{\beta}}$ as metric (fitting par. α and β)
- Which figures of merit ?. *BED*, *EQD2*
- **No QUANTEC for RE-IRRAD**. Addition BED in 3D (with time corrections) only tool we have

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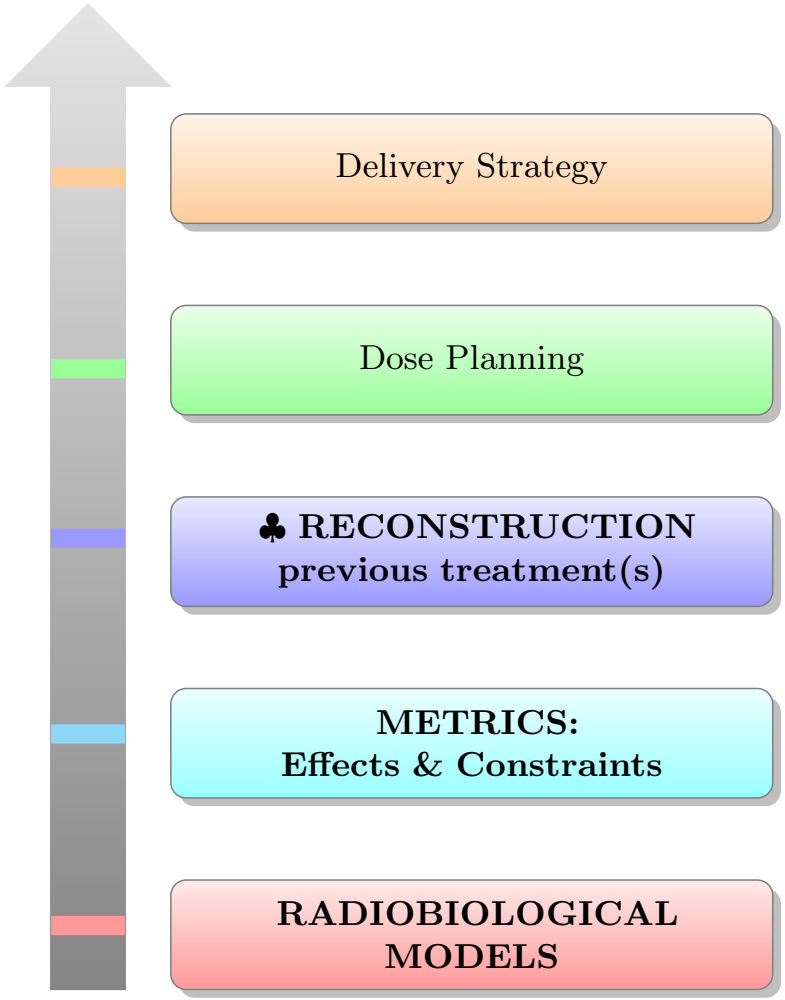

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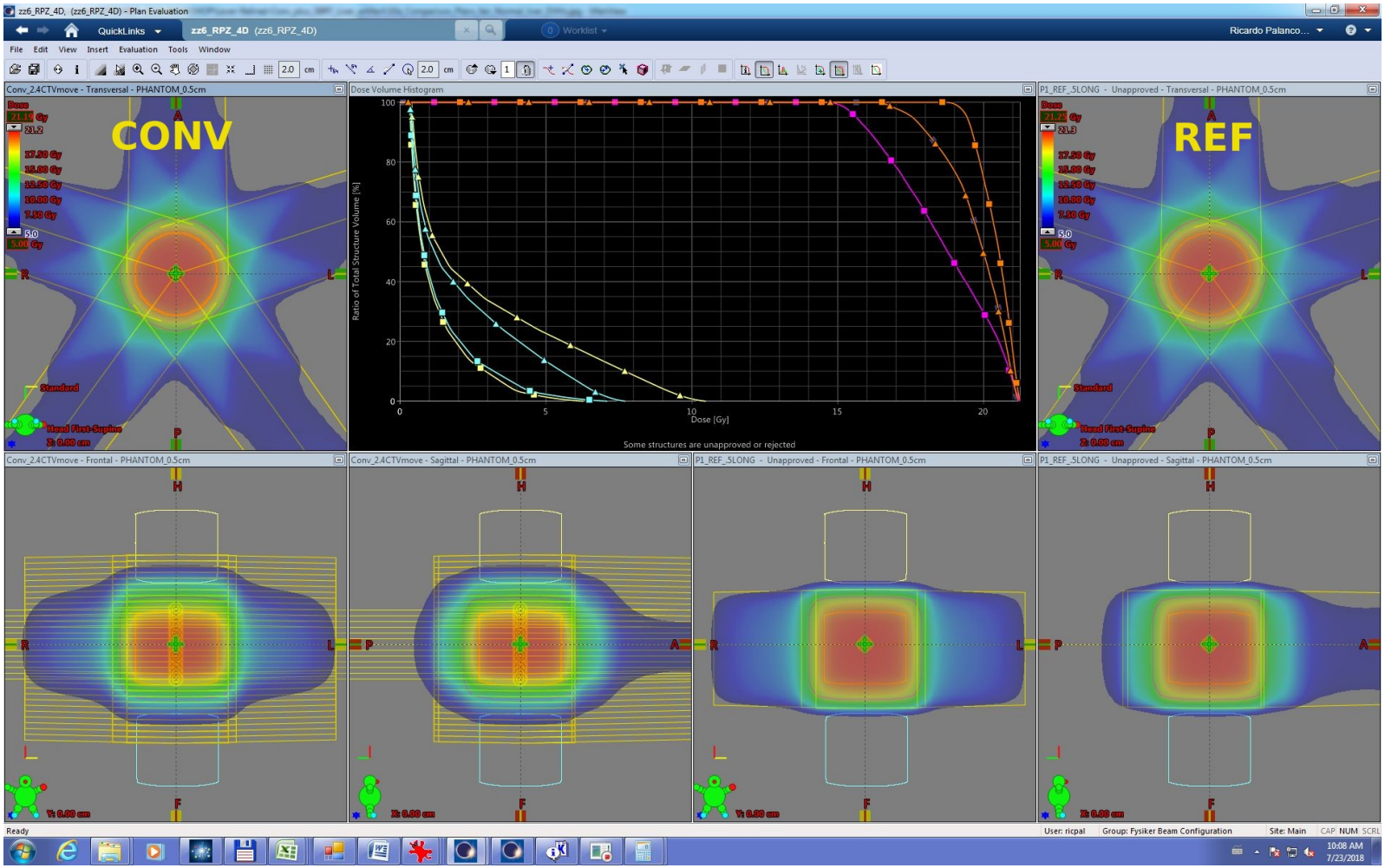
Reconstruction: planned vs potentially deliverable

Understanding SBRT prescription ...

planned vs potentially deliverable

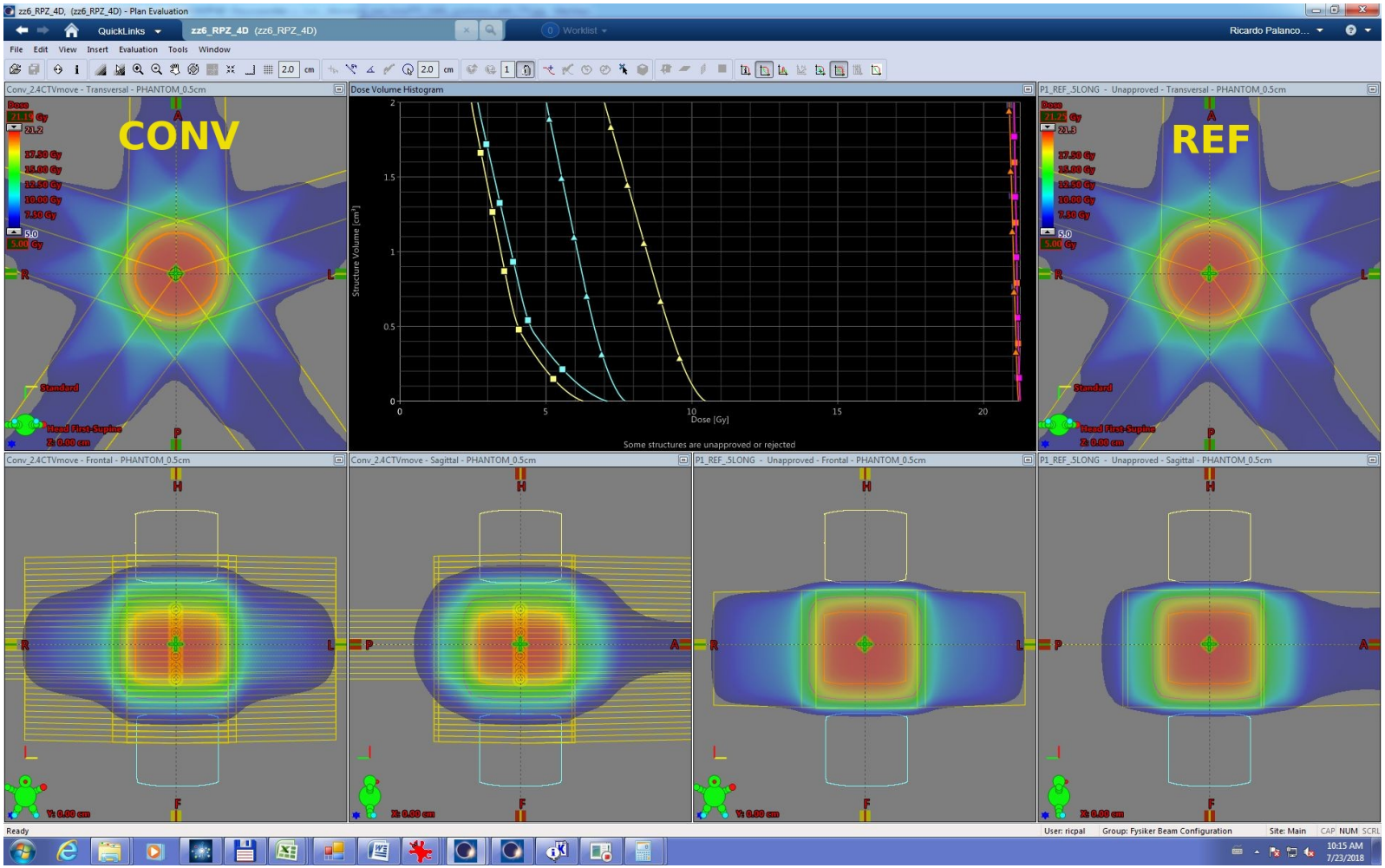
Reconstruction: planned vs potentially deliverable

Understanding SBRT prescription ...



Reconstruction: planned vs potentially deliverable

Understanding SBRT prescription ...



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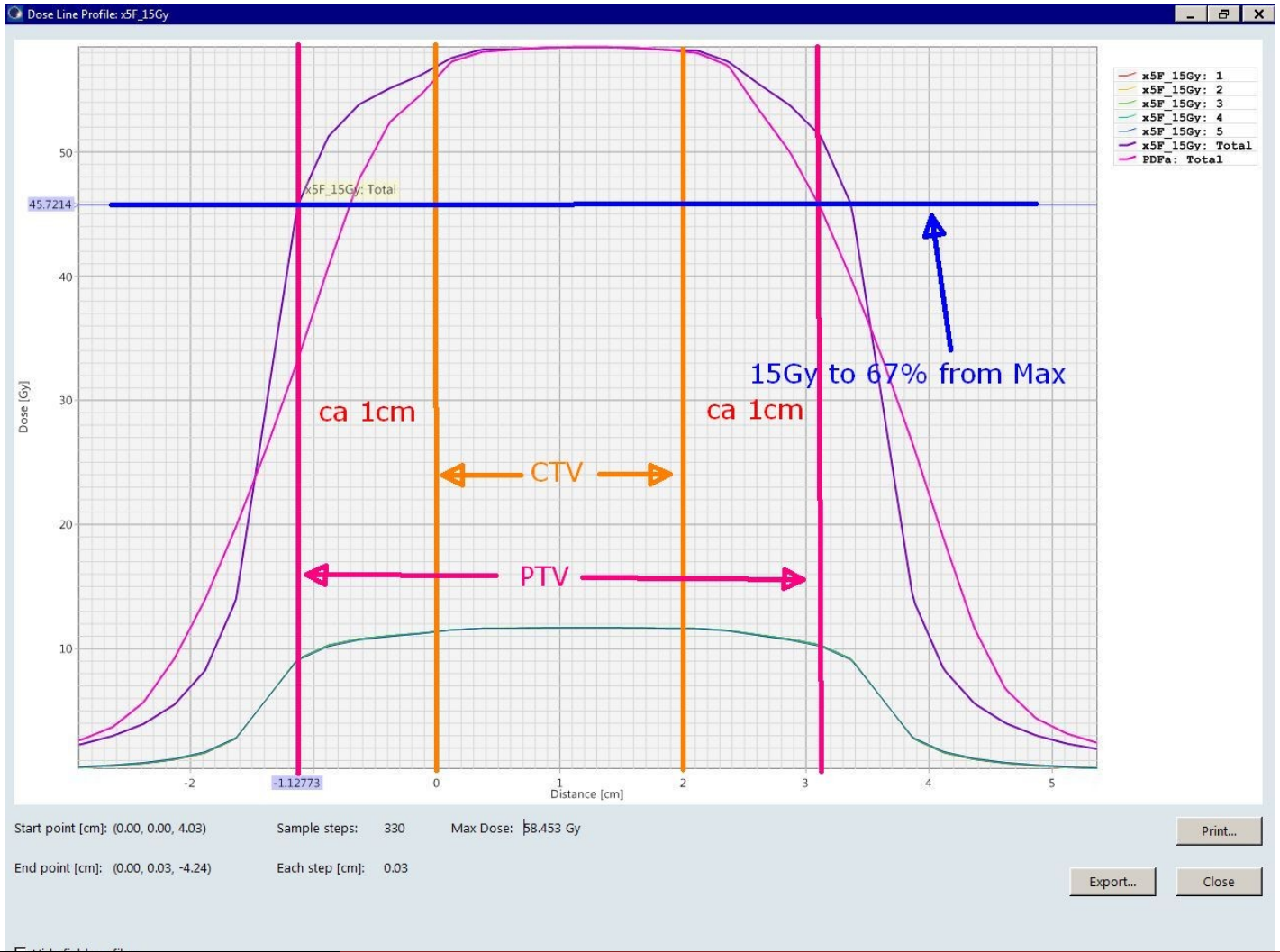

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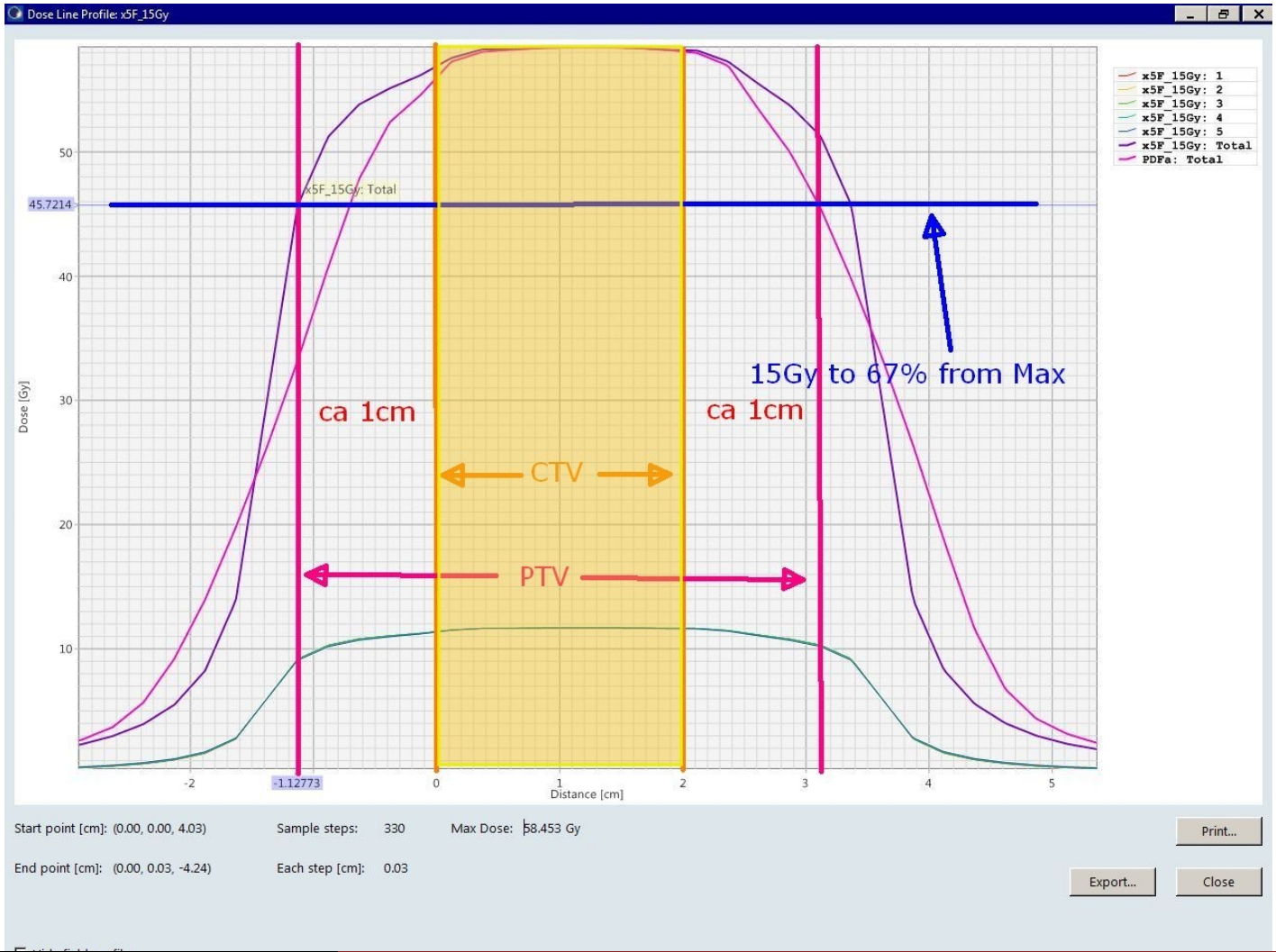

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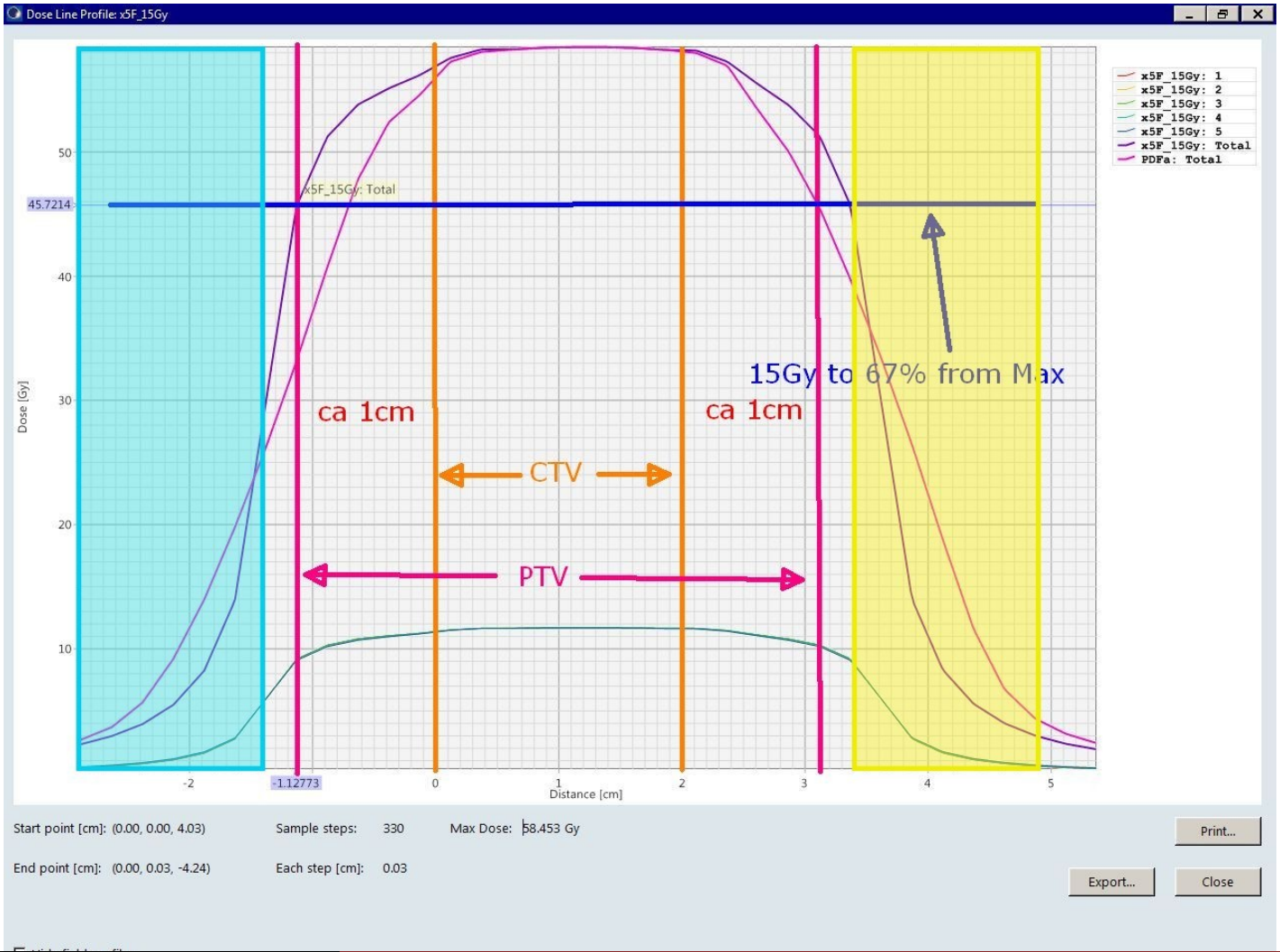
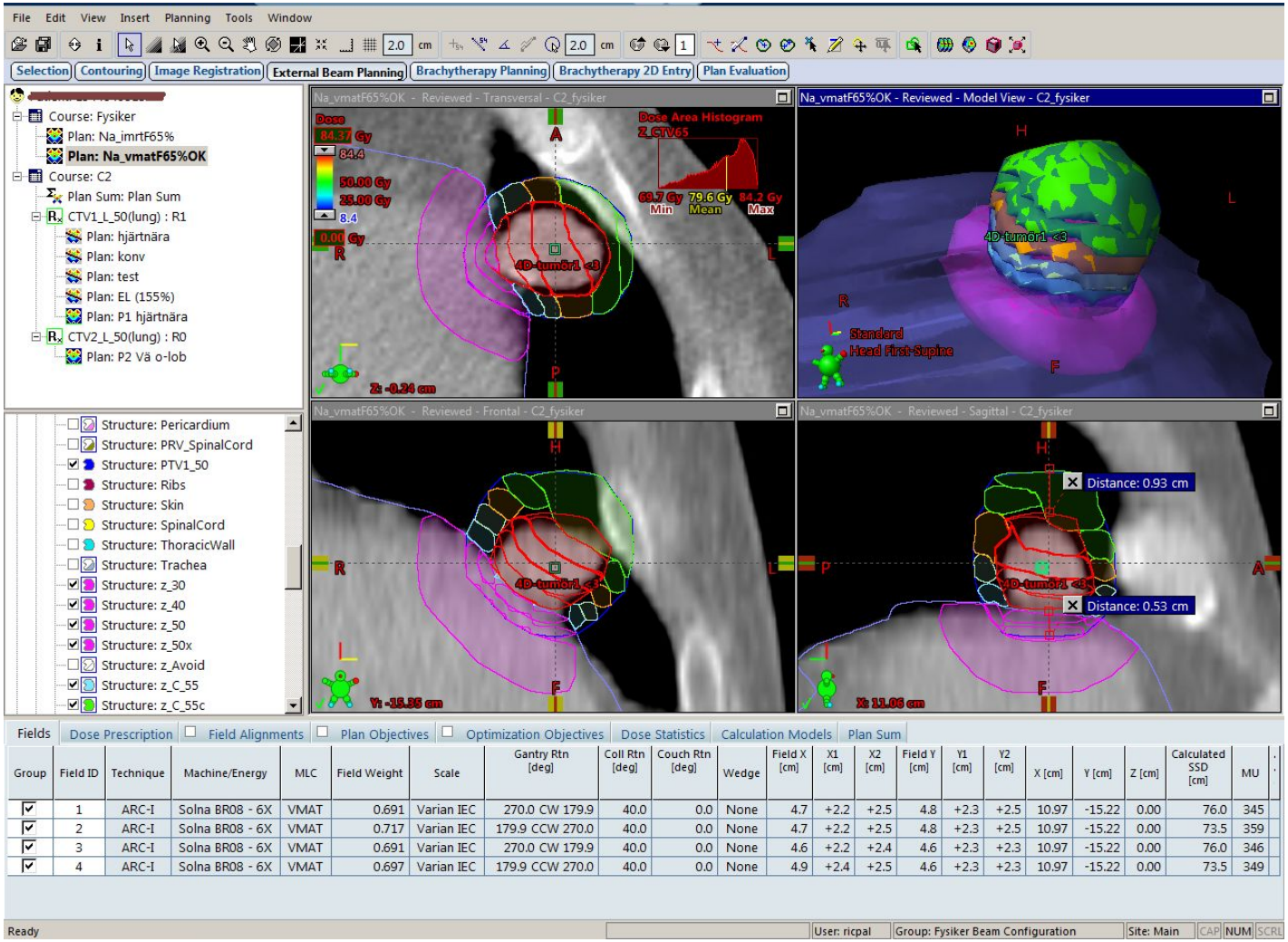


Reconstruction: planned vs potentially deliverable

What is the dose at OAR ?. Use dose-metrics $\rightsquigarrow$ effects



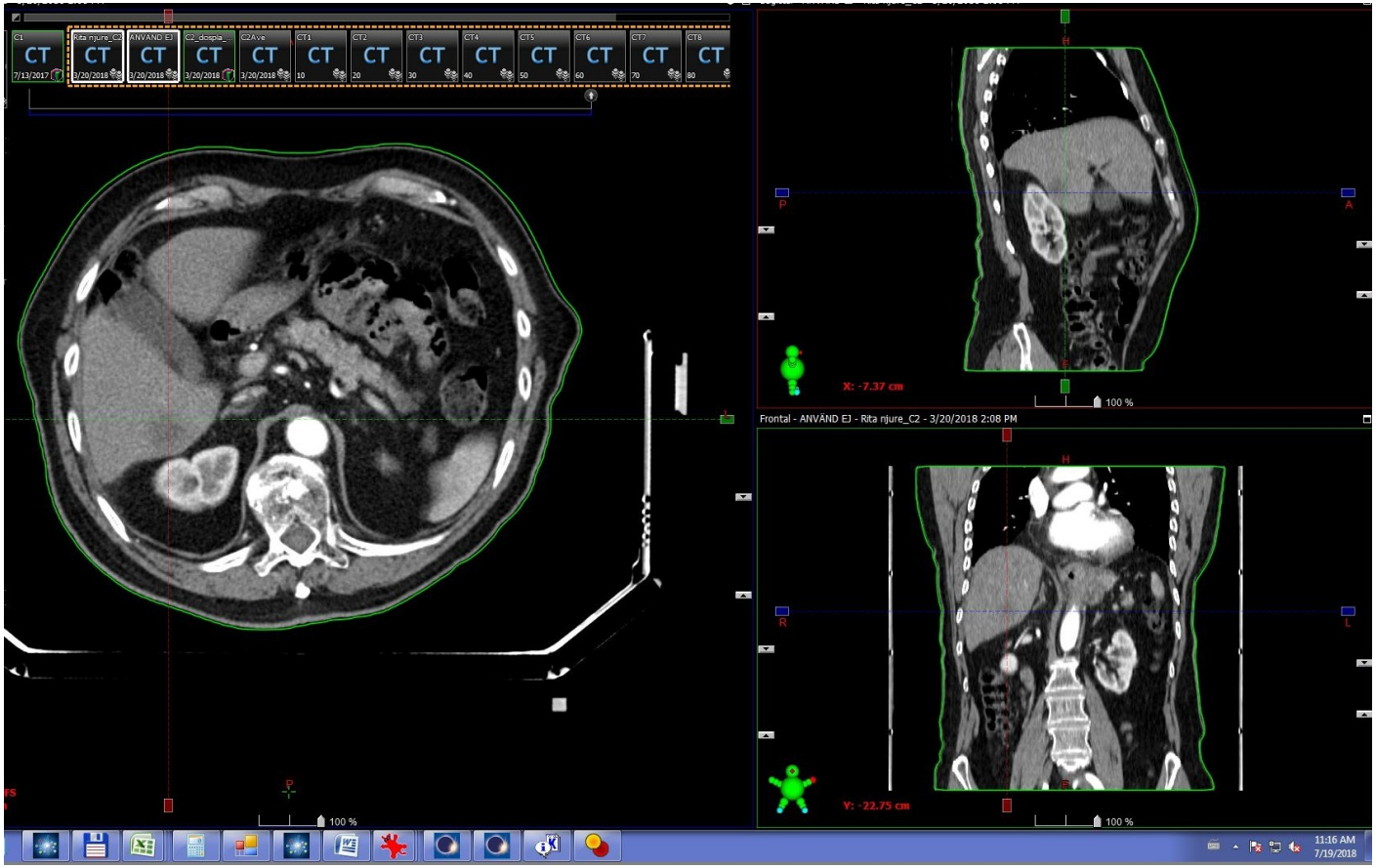
Reconstruction: planned vs treated (Liver-Artifacts)

What does the target/OAR look like ...

planned vs potentially doing something else

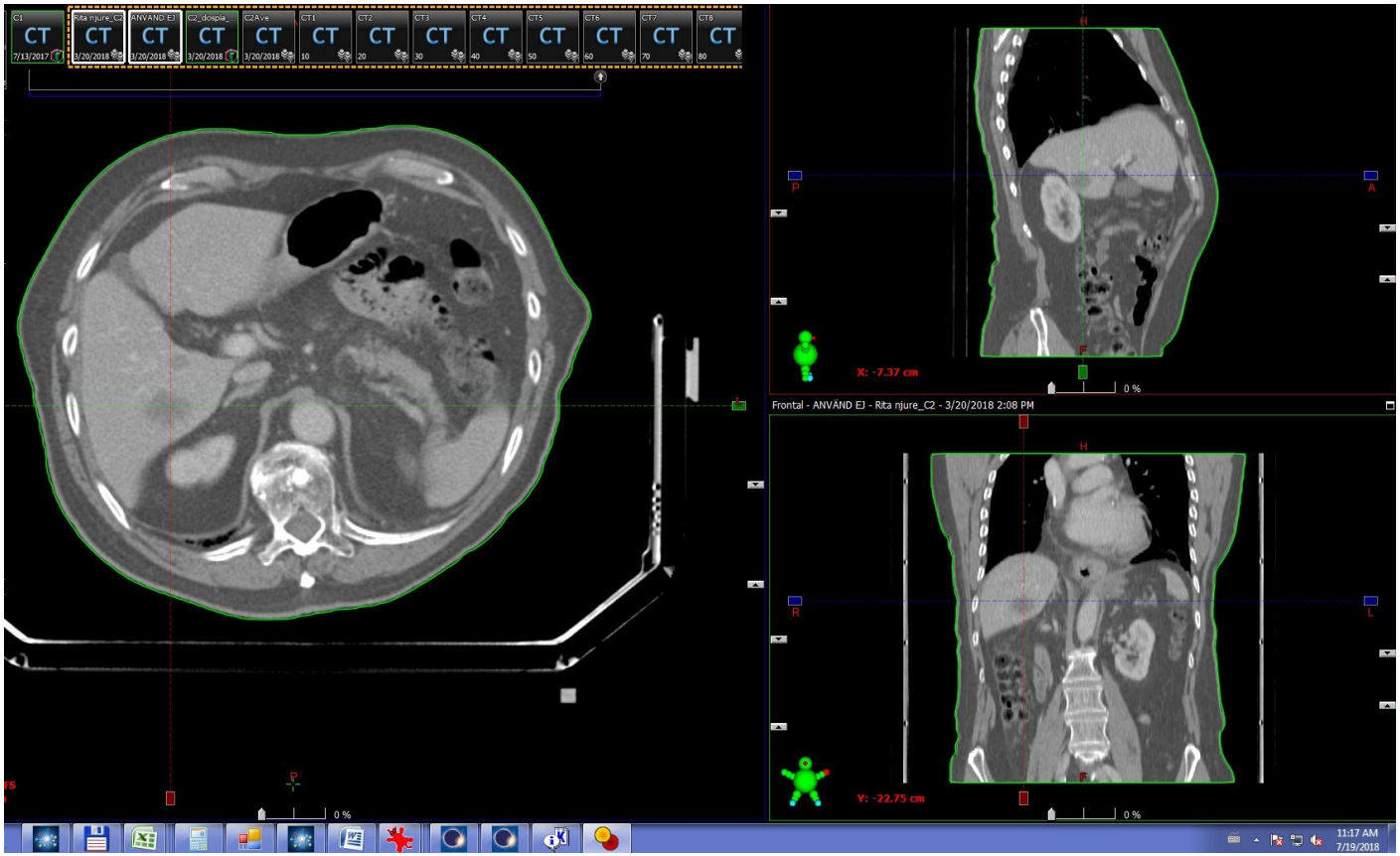
Reconstruction: planned vs treated (Liver-Artifacts)

Liver Contrast (Aorta phase 15 s) ...



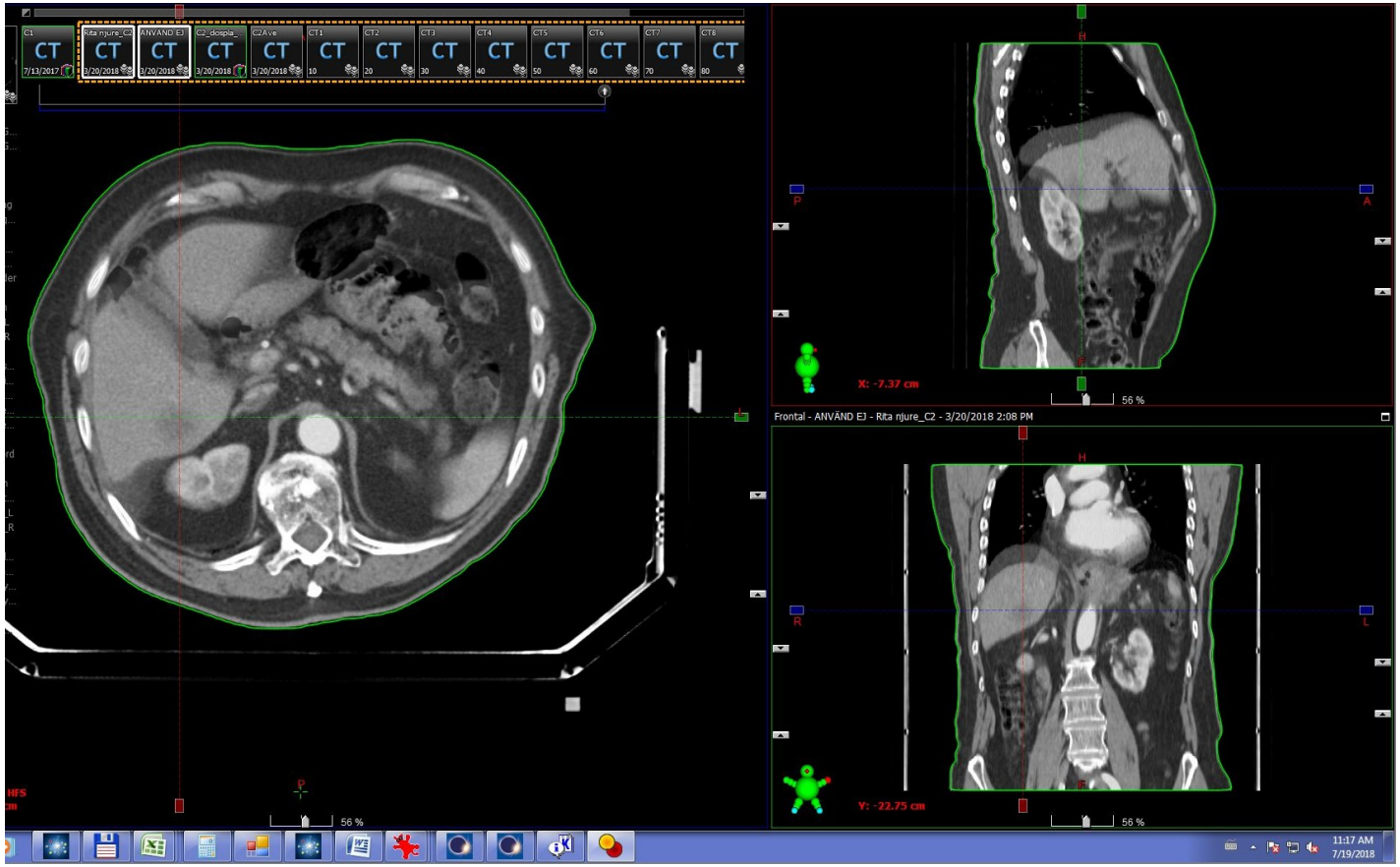
Reconstruction: planned vs treated (Liver-Artifacts)

Liver Contrast (Porta phase 30 s) ...



Reconstruction: planned vs treated (Liver-Artifacts)

Which ? (extra observations, Average CT) ...



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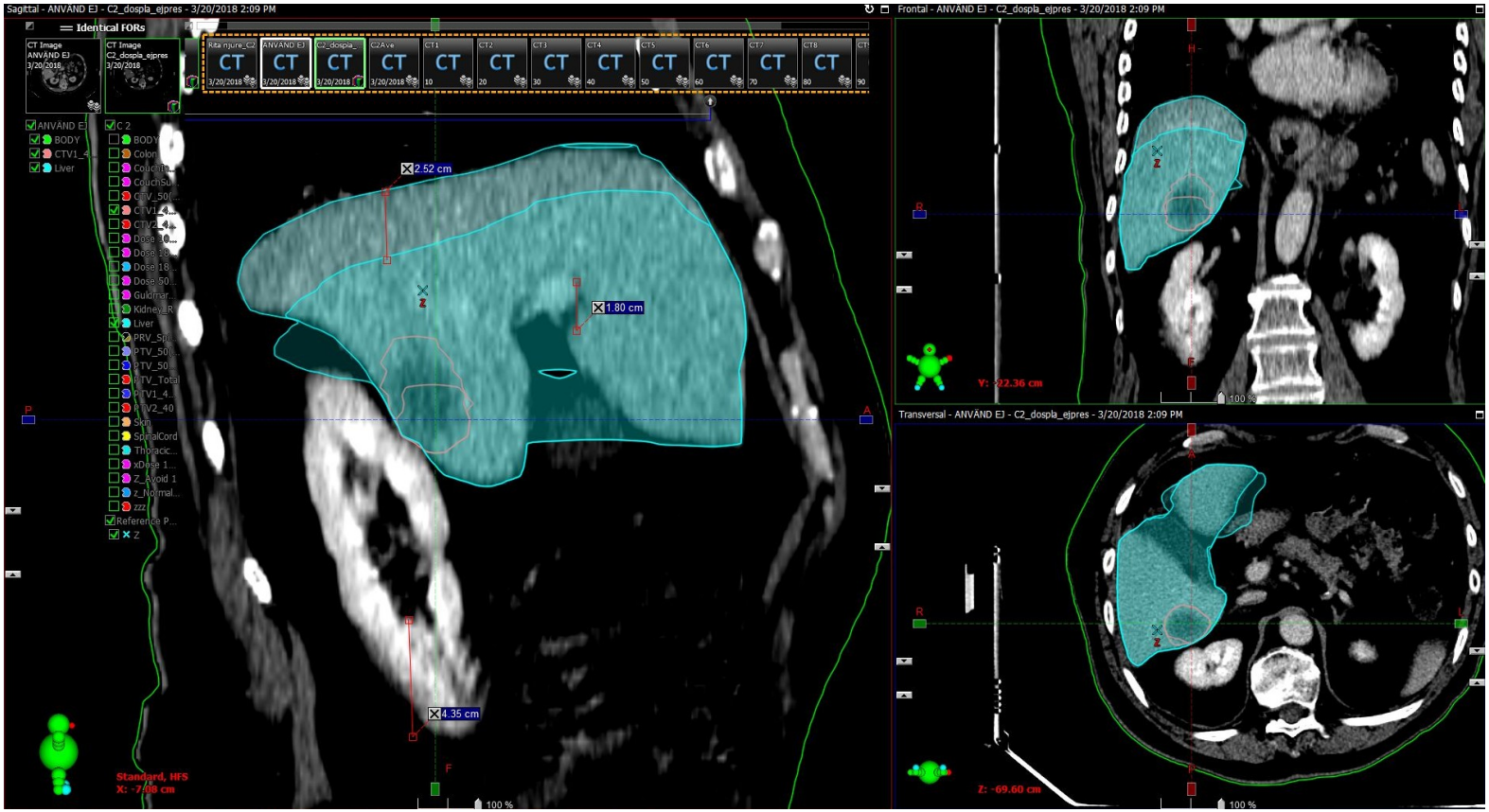

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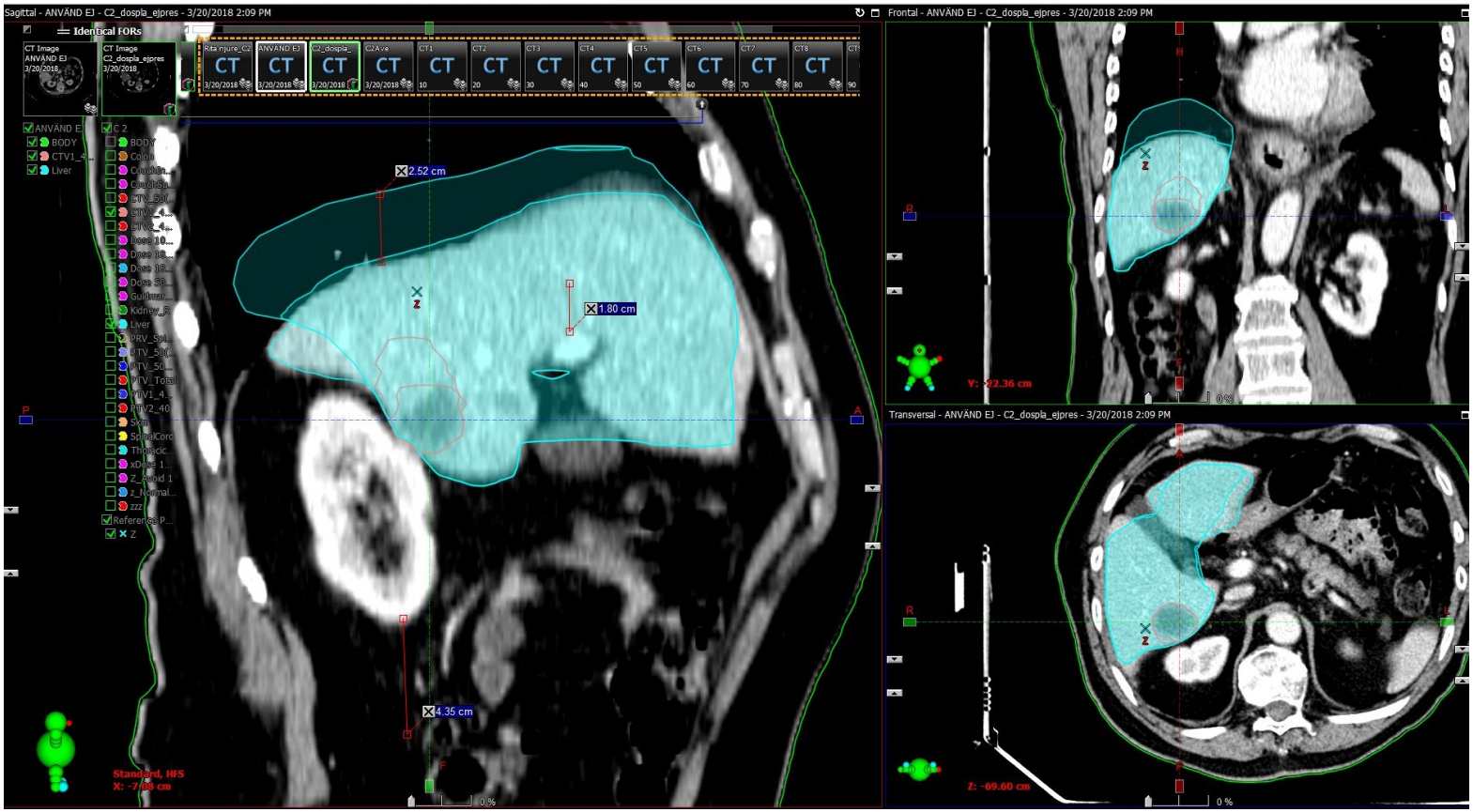


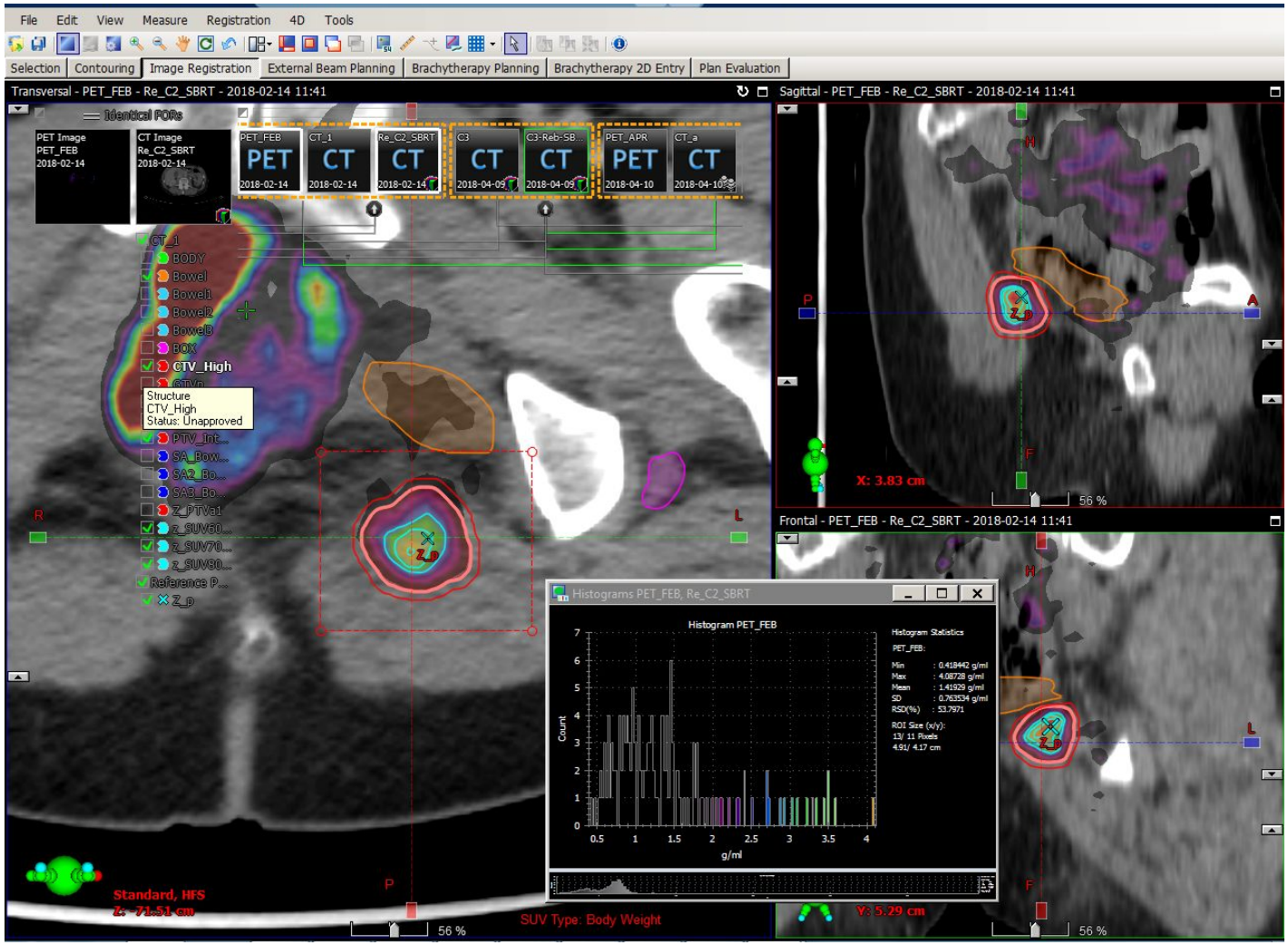
Re-irradiation: conventional + SBRT

Case: pre-op recti 5Gy x 5

Recurrence: 10Gy x 5 at 70%

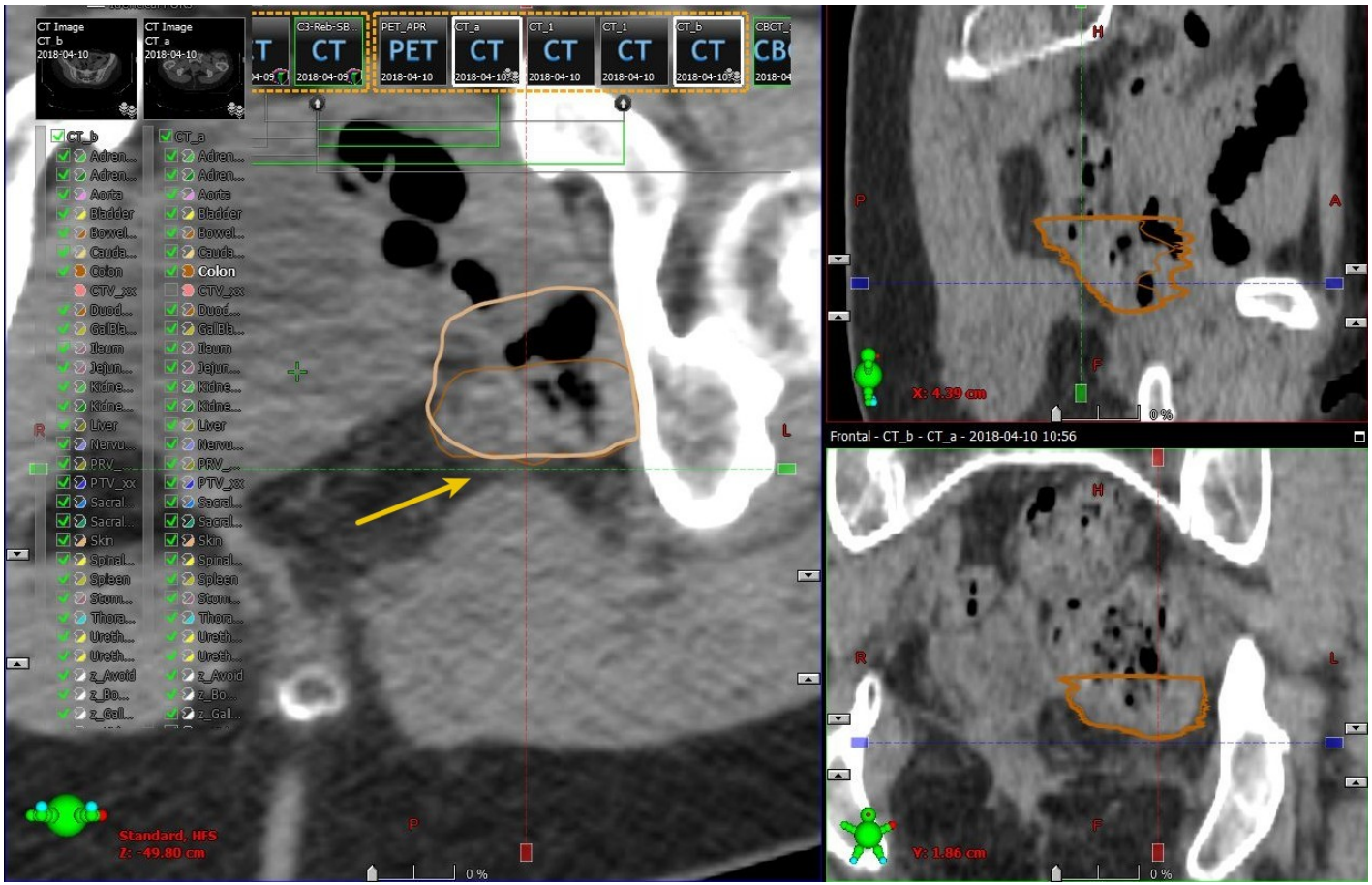
Re-irradiation: conventional + SBRT

Study plan ...



Re-irradiation: conventional + SBRT

Margins: Intrafraction motion (CT-CT 10 min at PET/CT unit)



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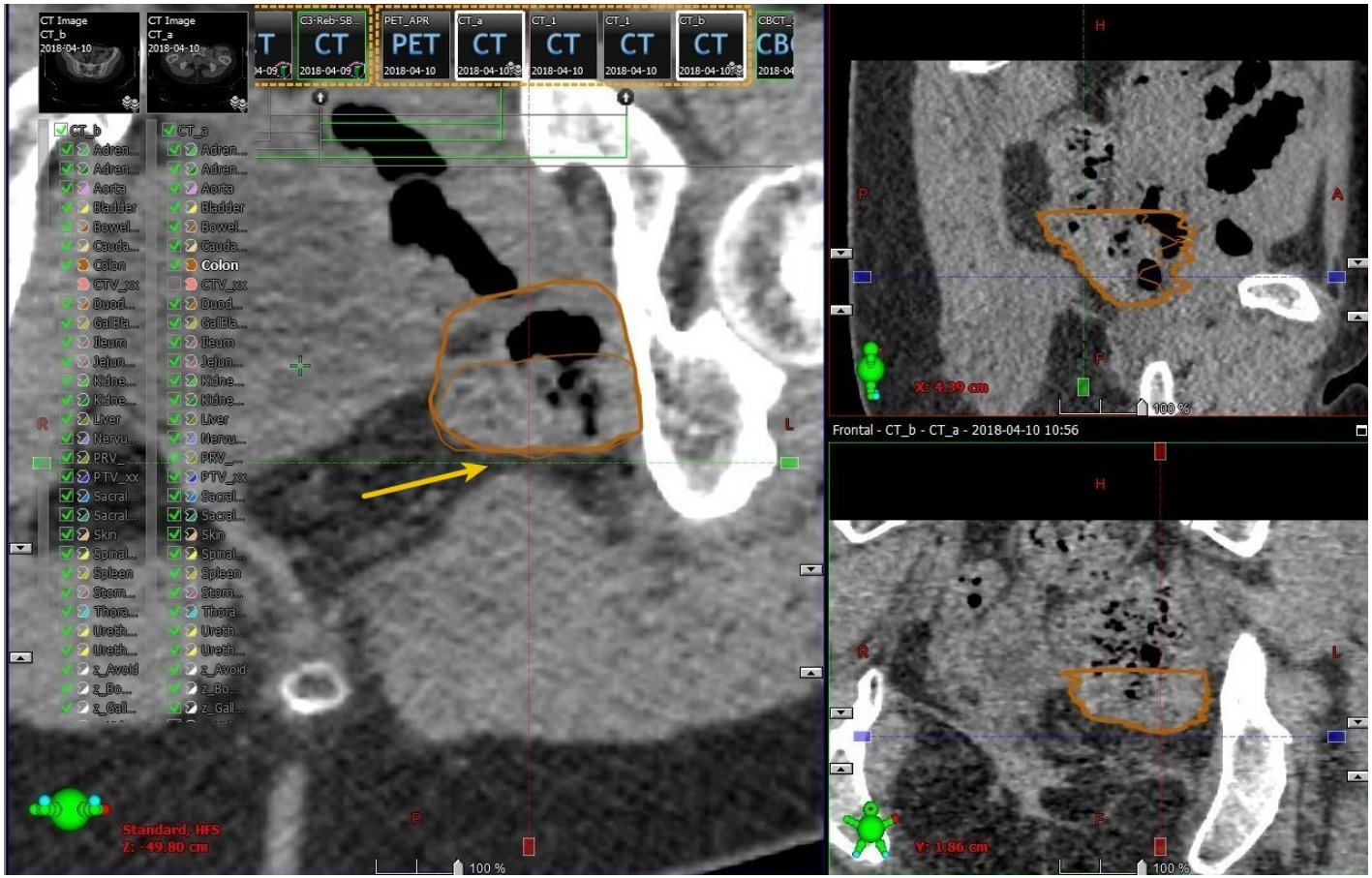
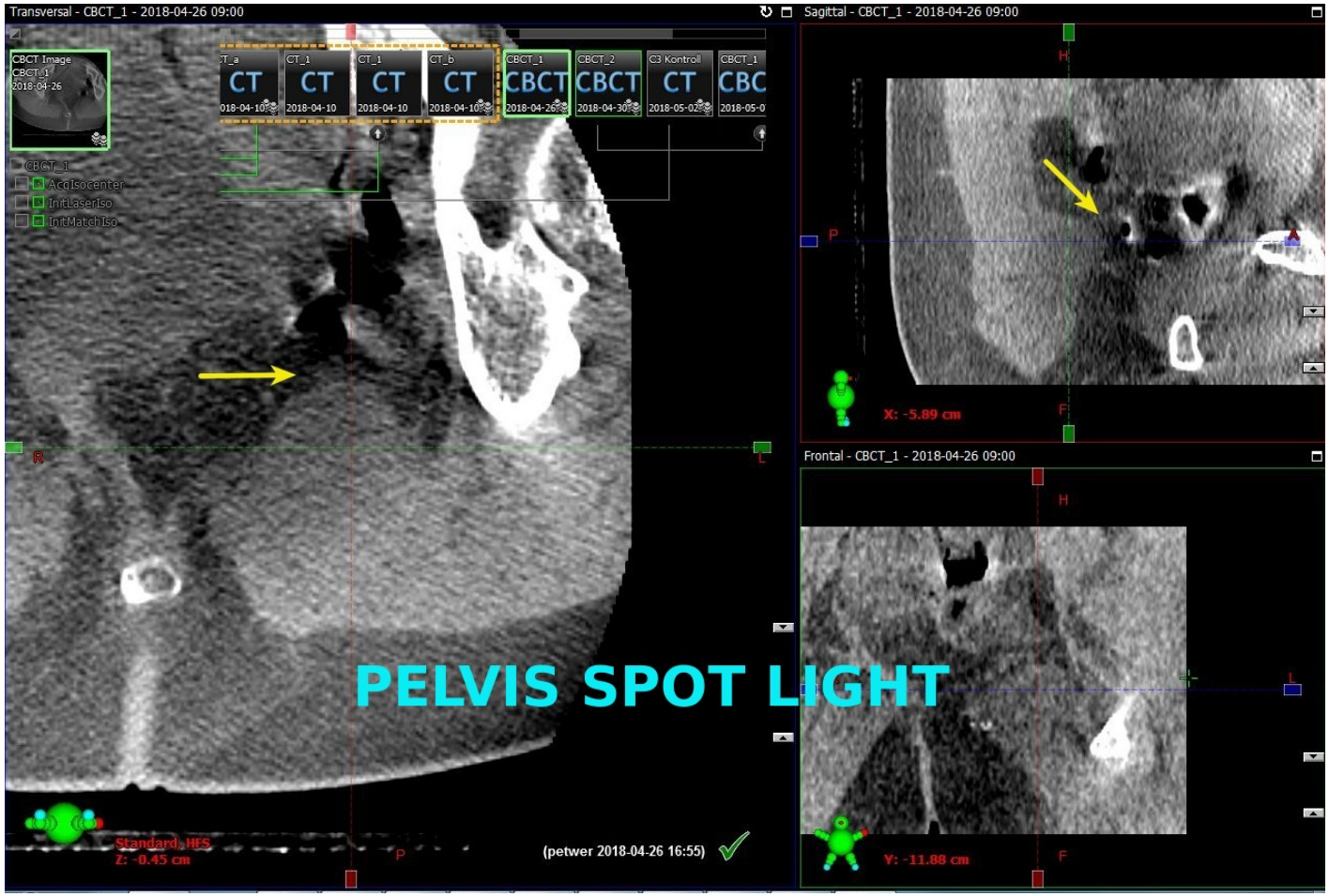


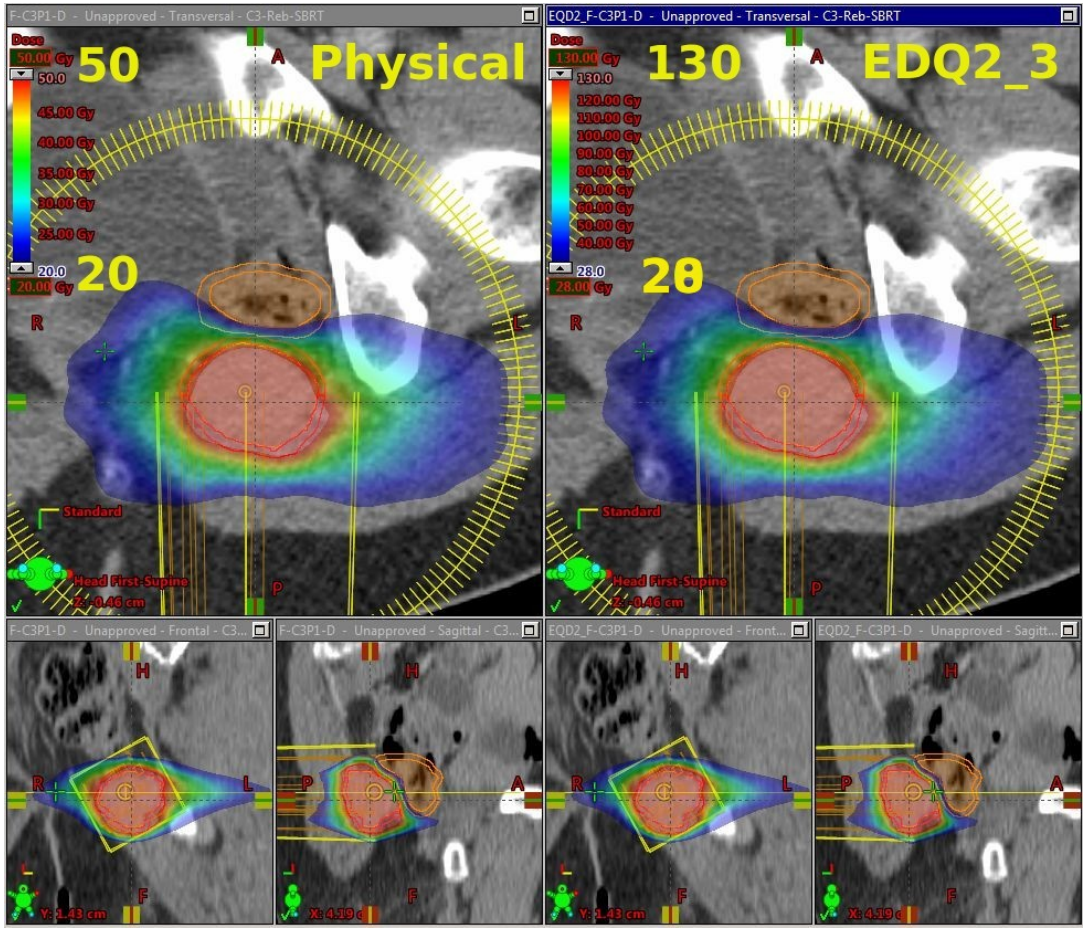
Re-irradiation: conventional + SBRT

Margins: Pre-plan CBCT (expect seeing vs. actually seeing)



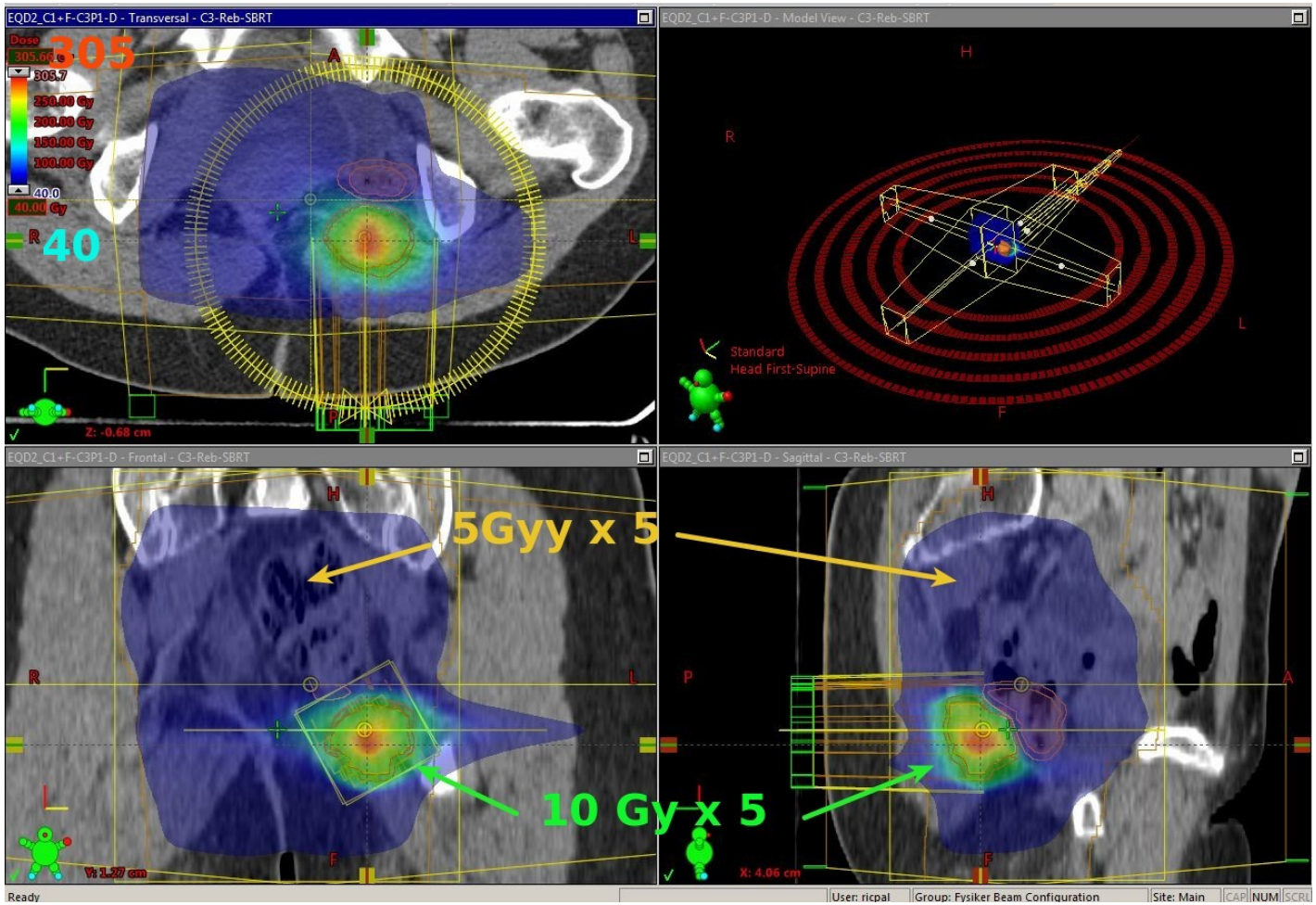
Re-irradiation: conventional + SBRT

Plan Evaluation: 3D-dose distrib ($EQD2_3$)



Re-irradiation: conventional + SBRT

Plan Evaluation: Sum 3D-dose distrib ($EQD2_3$)



Re-irradiation: conventional + SBRT

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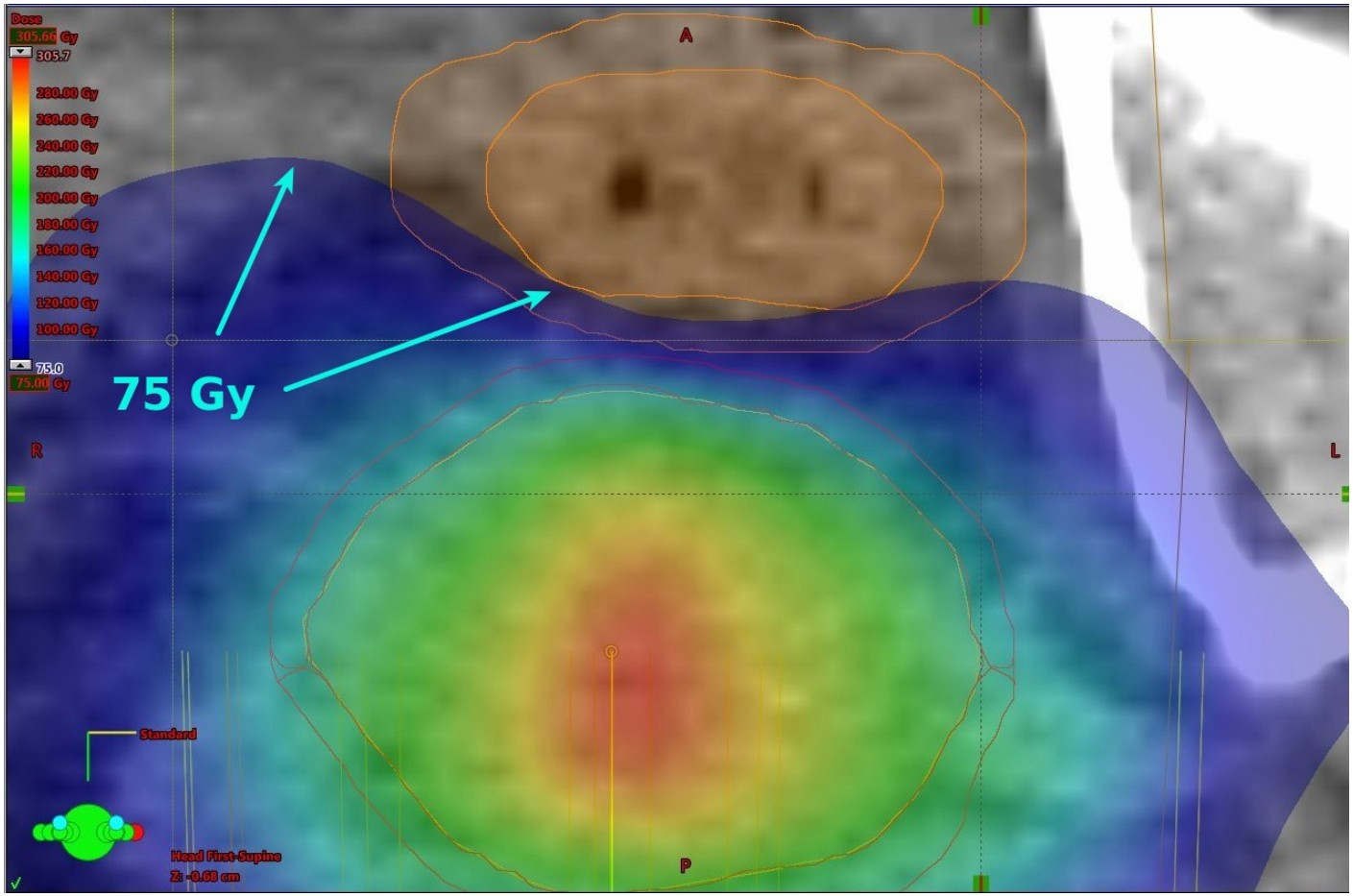

Re-irradiation: conventional + SBRT

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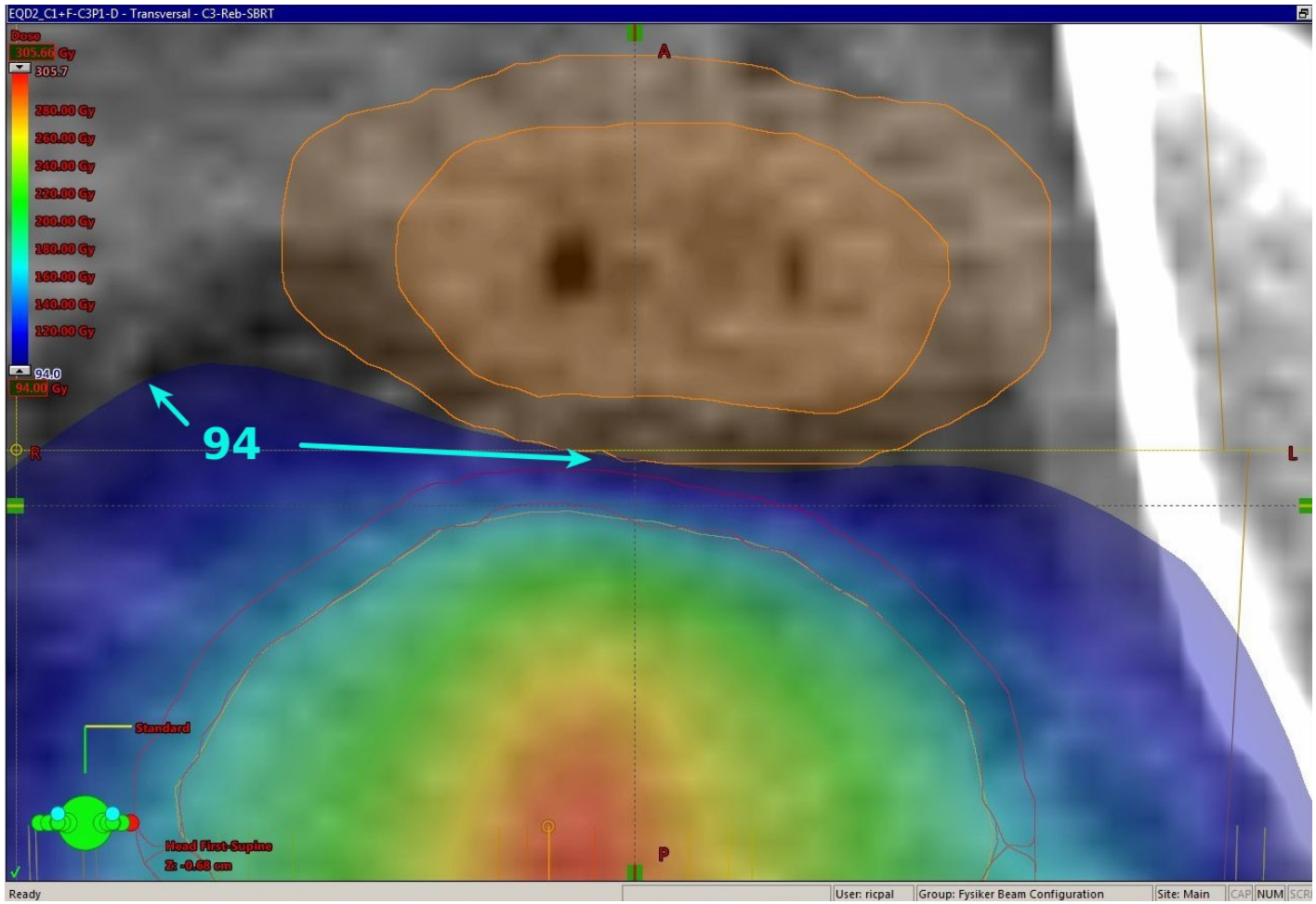
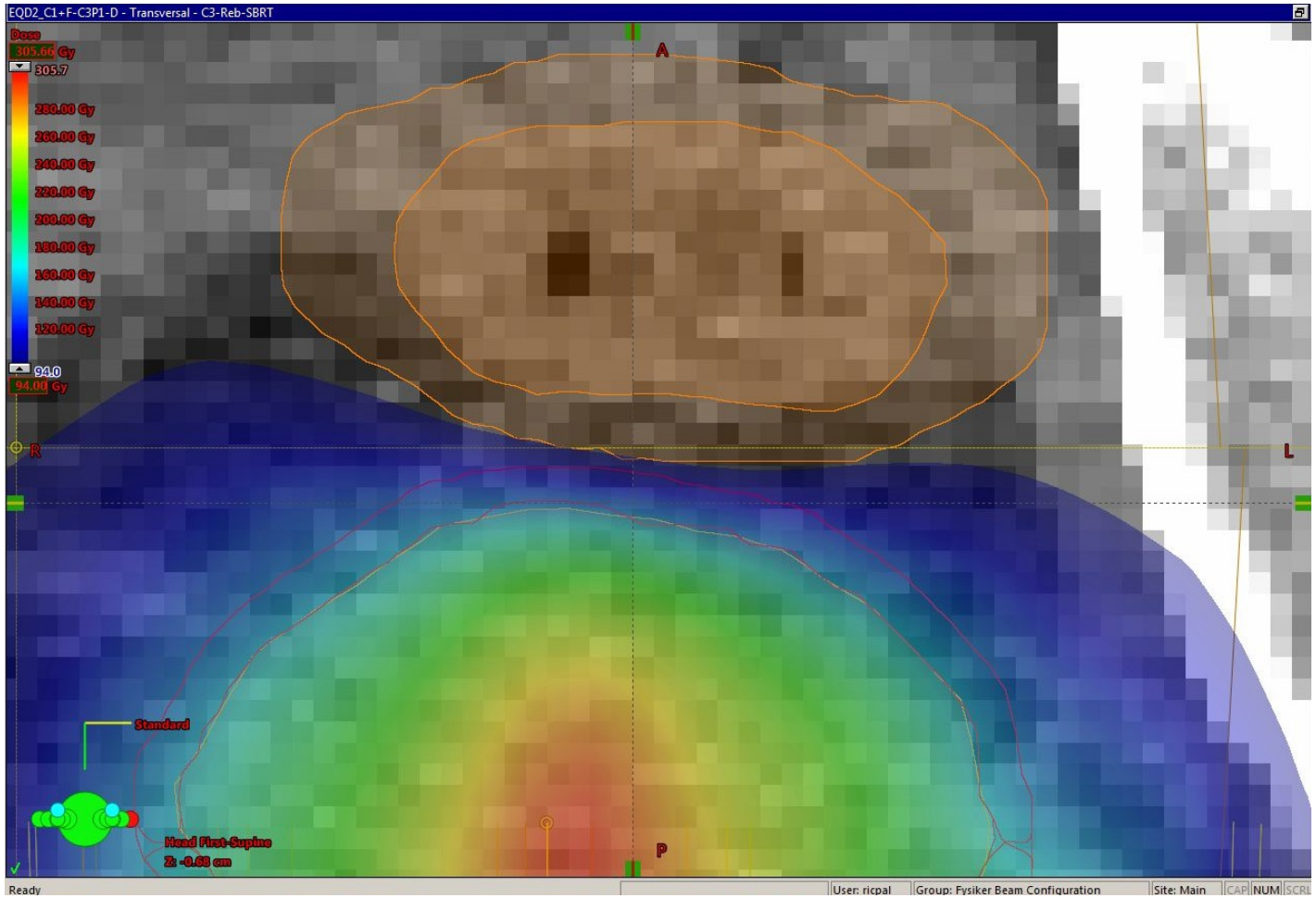


Re-irradiation: conventional + SBRT

Remember the gedankexperiment? ? ($EQD2_3$ as a metric)



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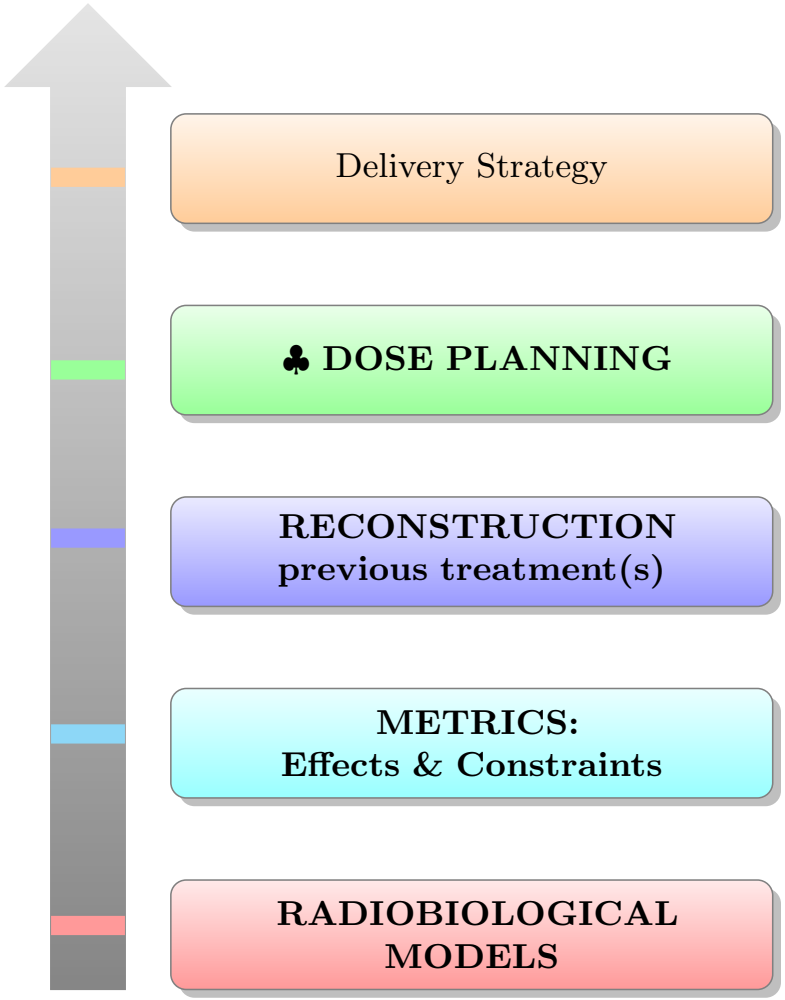

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Optimization: the cost function

QUESTION....actually...."THE QUESTION"

Is there a really good plan (near optimal) for these:

- particular set of delineated structures ?
- particular set of constraints ?

Optimization: the cost function

QUESTION....actually...."THE QUESTION"

Is there a really good plan (near optimal) for these:

- particular set of delineated structures ?
- particular set of constraints ?

Part of the answer lies in cost function and its minimization

Optimization: the cost function

Definition of cost function

$$F_i^A = \frac{w_A}{M_A} \sum_{k=1}^{M_A} c(k) \left[D_p^A(k) - D_i^A(k) \right]^2$$

(E.g.: Spirou 1997,Bortfeld 2003,..., ICRU 83)

i = ith iteration

k = kth voxel

M_A = number of voxels in structure A

w_A = priority (penalty) for structure A

D_p^A = Objective (Dose) for structure A

$c(a(k))$ = a switch (0,1)

Optimization: the cost function

Definition of cost function

$$F_i^A = \frac{w_A}{M_A} \sum_{k=1}^{M_A} c(a(k)) \left[D_p^A(k) - D_i^A(k) \right]^2$$

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For OARs:

$$c(a(k)) = \begin{cases} 1, & \text{if } a(k) \equiv \left[D_p^A(k) - D_i^A(k) \right] < 0. \\ 0, & \text{otherwise.} \end{cases}$$

- ... even a voxel can make this not converge (HARD CONSTRAINT = CANNOT BE VIOLATED)

Optimization: the cost function

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- ... even a voxel can make this not converge (HARD CONSTRAINT = CANNOT BE VIOLATED)
- ... HARD CONSTRAINTS (not user steered in Eclipse) apply to Machine ar.: inst.gantry speed, mlc speed, mlc over travel, fluence rate, ...

Optimization: the cost function

Definition of cost function

$$F_i^A = \sum_{k=1}^{M_A} c(a(k)) \left[D_p^A(k) - D_i^A(k) \right]^2$$

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w_A no use

Optimization: the cost function

Definition of cost function

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w_A no use

HARD CONSTRAINT

Optimization: the cost function

Definition of cost function

$$F_i^A = w_A \sum_{k=1}^{M_A} c(a(k)) \left[\frac{1}{\sqrt{M_A}} D_p^A(k) - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

(E.g.: Spirou 1997,Bortfeld 2003,..., ICRU 83)

For OARs:

$$c(a(k)) = \begin{cases} 1, & \text{if } a(k) \equiv \frac{1}{\sqrt{M_A}} \left[D_p^A(k) - D_i^A(k) \right] < \epsilon. \\ 0, & \text{otherwise.} \end{cases}$$

- ... Now CONSTRAINT (SOFT) CAN BE VIOLATED with fixed tolerance ϵ

Optimization: the cost function

Definition of cost function

$$F_i^A = w_A \sum_{k=1}^{M_A} c(a(k)) \left[\frac{1}{\sqrt{M_A}} D_p^A(k) - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

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Optimization: the cost function

Definition of cost function

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- ... Now CONSTRAINT (SOFT) CAN BE VIOLATED with fixed tolerance ϵ
- ... If $M_A \longrightarrow \infty$ then CONSTRAINT easily fullfilled
- ... If $M_A \longrightarrow 0$ then CONSTRAINT approaches to a HARD CONSTRAINT

Optimization: the cost function

- Cost function Str A

$$\circlearrowleft \dots \circlearrowleft \; F_i^A = w_A \cdot \sum_{k=1}^{M_A} c(k) \cdot \left[\frac{1}{\sqrt{M_A}} D_p^A(k) - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

Optimization: the cost function

- Cost function Str A

$$\circlearrowleft \ldots \circlearrowleft \; F_i^A = w_A \cdot \sum_{k=1}^{M_A} c(k) \cdot \left[\frac{1}{\sqrt{M_A}} D_p^A(k) - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

- Step function (switch)

Optimization: the cost function

- Cost function Str A

$$\circlearrowleft \ldots \circlearrowleft \; F_i^A = w_A \cdot \sum_{k=1}^{M_A} c(k) \cdot \left[\frac{1}{\sqrt{M_A}} D_p^A(k) - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

- Step function (switch)
- Prescribed (or Limit) dose

Optimization: the cost function

- Cost function Str A

$$\circlearrowleft \ldots \circlearrowleft \; F_i^A = w_A \cdot \sum_{k=1}^{M_A} c(k) \cdot \left[\frac{1}{\sqrt{M_A}} D_p^A(k) - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

- Step function (switch)
- Prescribed (or Limit) dose
- Priority (penalty)

Optimization: the cost function

$$\overset{\curvearrowright}{\bigcirc}\overset{\curvearrowright}{\bigcirc}\ldots\overset{\curvearrowright}{\bigcirc} F_i^A = \quad w_A \quad \cdot \sum_{k=1}^{M_A} c(k) \cdot \left[\frac{1}{\sqrt{M_A}} D_p^A(k) \; - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

Optimization: the cost function

$$\circlearrowleft\circlearrowleft \ldots \circlearrowleft F_i^A = w_A \cdot \sum_{k=1}^{M_A} c(k) \cdot \left[\frac{1}{\sqrt{M_A}} D_p^A(k) - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

Optimization: the cost function

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Optimization: the cost function

... Don't forget that tolerance $\epsilon \propto M_A$ (Structure size)

$$\circlearrowleft\circlearrowleft \ldots \circlearrowleft F_i^A = \quad w_A \quad \cdot \sum_{k=1}^{M_A} c(k) \cdot \left[\frac{1}{\sqrt{M_A}} D_p^A(k) \; - \frac{1}{\sqrt{M_A}} D_i^A(k) \right]^2$$

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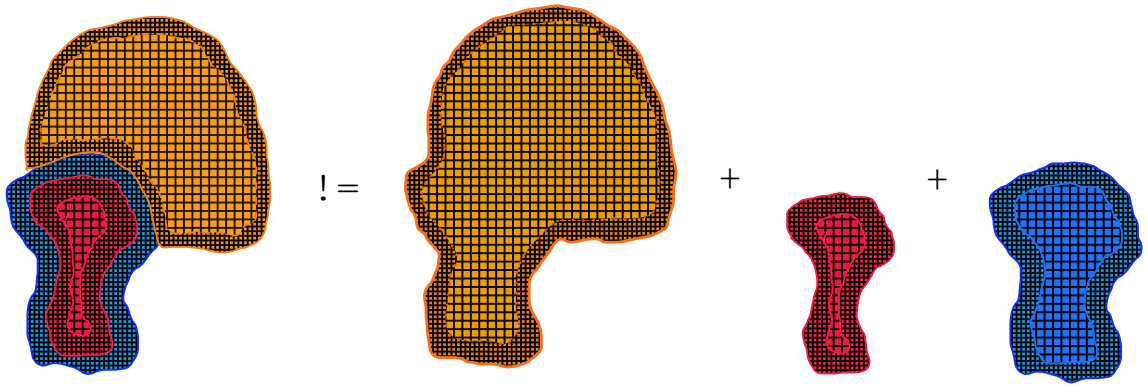
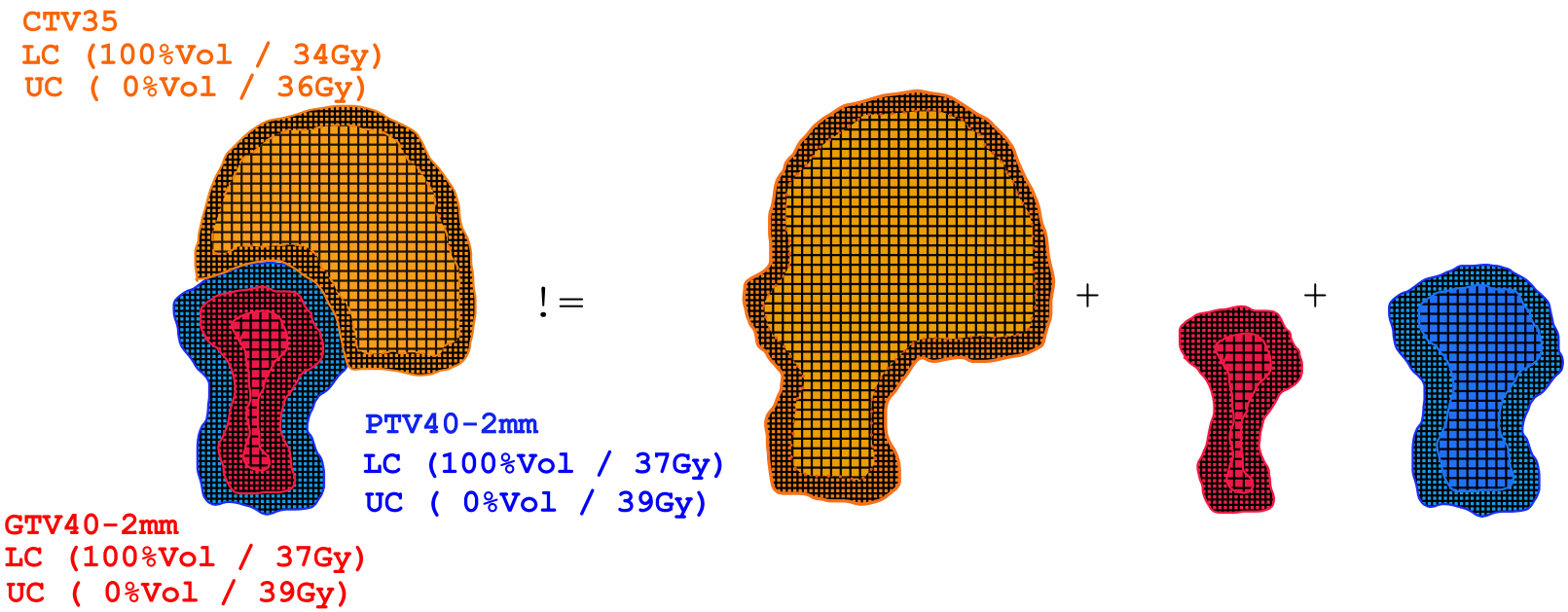
Optimization: cost function and structures

Some voxels undergo action of 3 or more Objetive Func (OF) acting (ambiguity/contradiction)



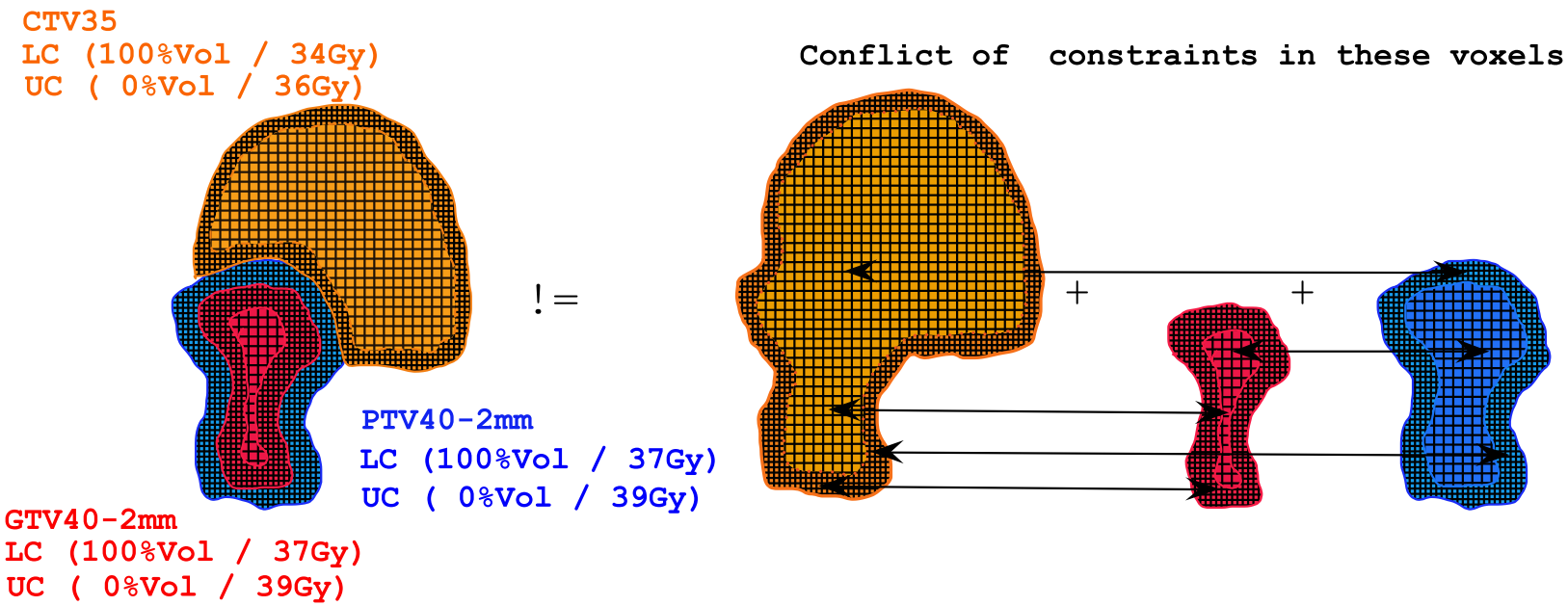
Optimization: cost function and structures

Simple example: consider this 3 structures



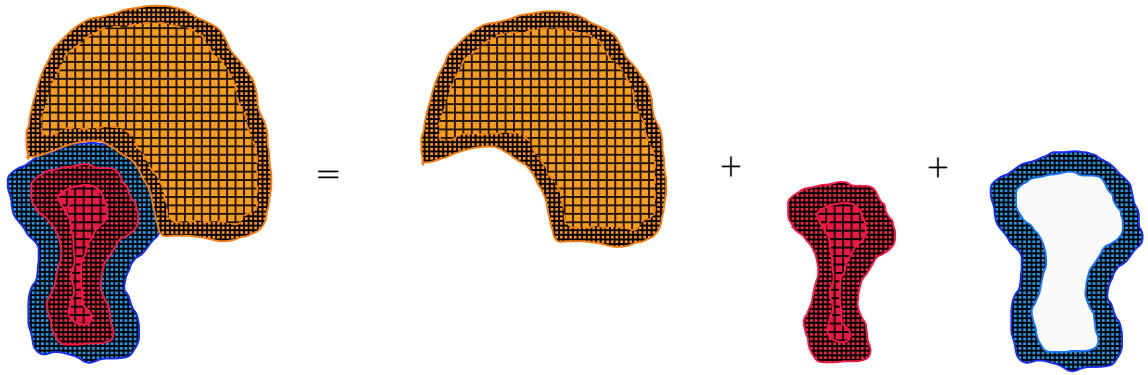
Optimization: cost function and structures

Simple example: consider this 3 structures



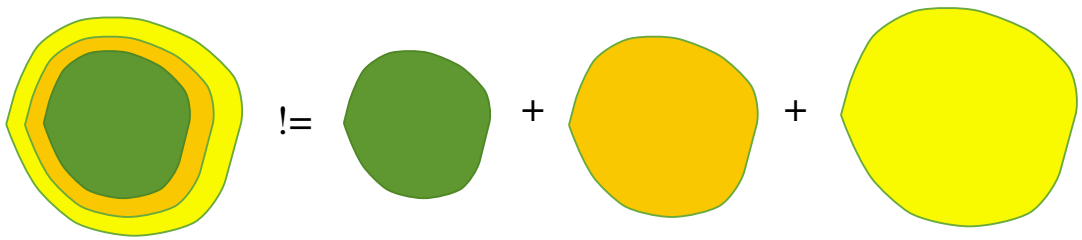
Optimization: cost function and structures

If structures are disjoint then each voxel belongs only structures with common goals (same OF) (no ambiguity/no contradiction)



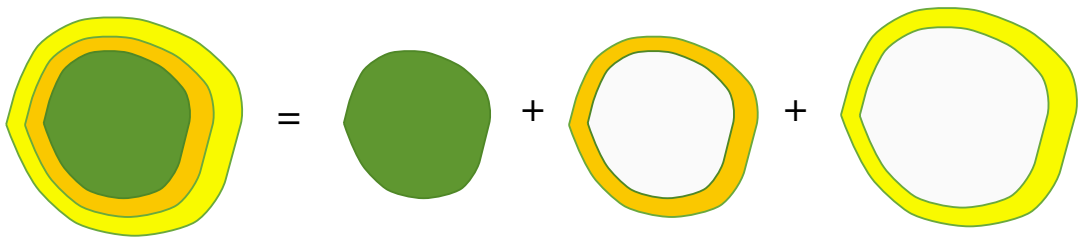
Optimization: cost function and structures

Another example. OF for this PRVs (orange and yellow) is ambiguos as for Upper constraints ...



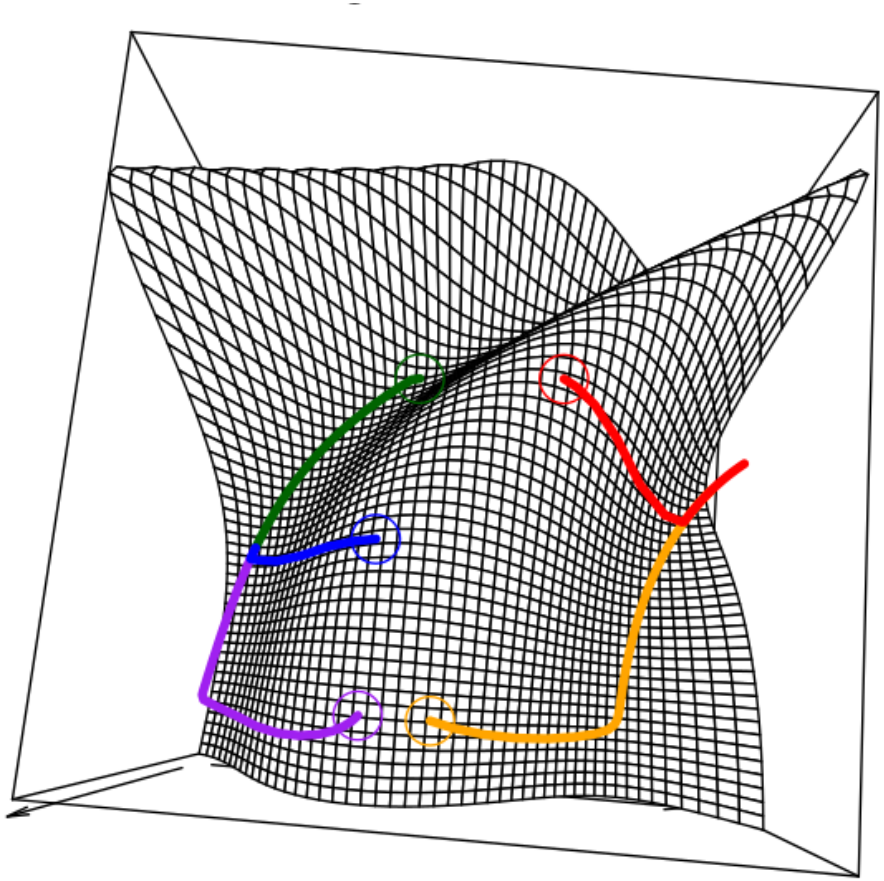
Optimization: cost function and structures

...The OF for PRVs (orange and yellow) is now no ambiguous as for Upper constraints ...



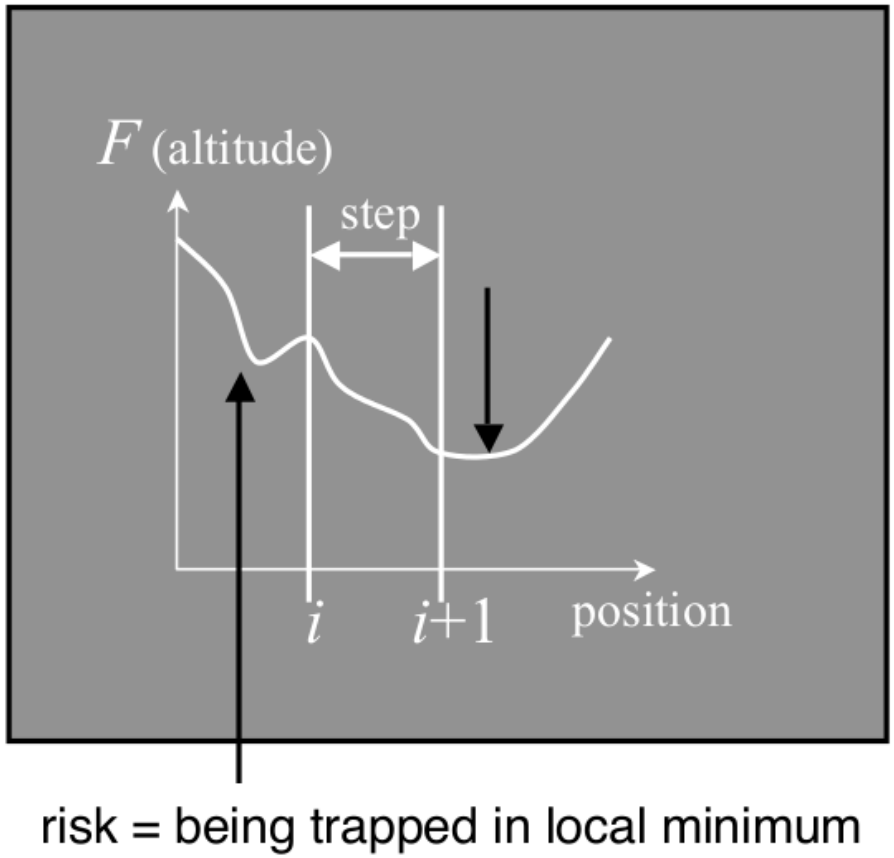
Optimization: cost function and structures

Cost Function is shaped by the structures and constraints



Optimization: cost function and structures

Minimizing the Cost Function (walker analogy)



Optimization: cost function and structures

Convergence to different minima with different algorithms ...

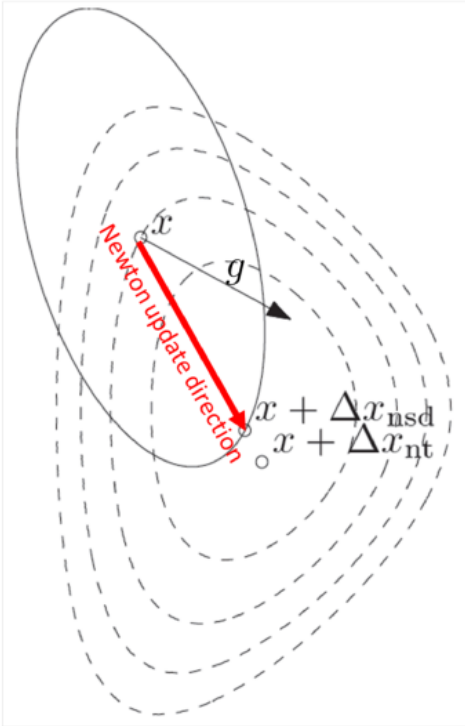


Figure 11.2: Direction of step for gradient descent and Newton's method.

Optimization: cost function and structures

Convergence to different minima with different algorithms ...

TRUE BUT

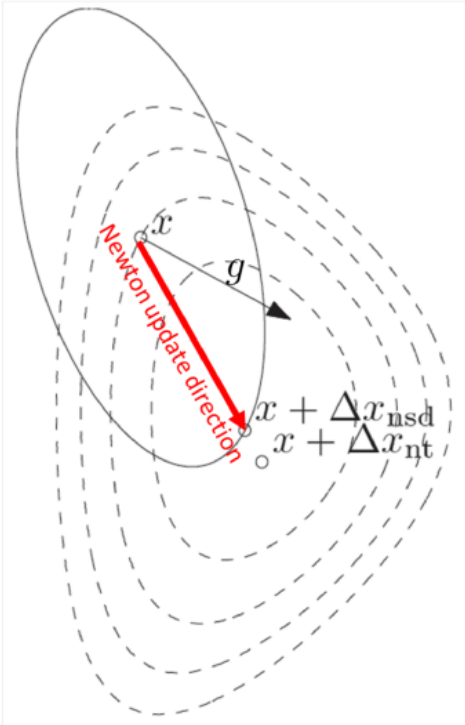


Figure 11.2: Direction of step for gradient descent and Newton's method.

Optimization: cost function and structures

Convergence to different minima with different algorithms ...

HAS NOT BIG IMPACT once the no. fields and directions is set

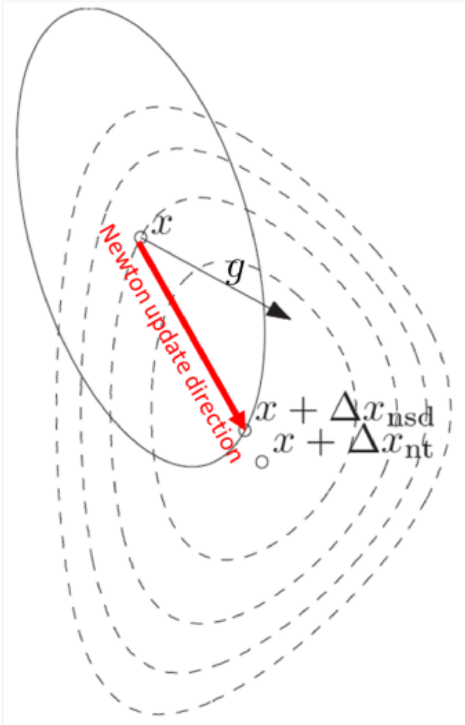
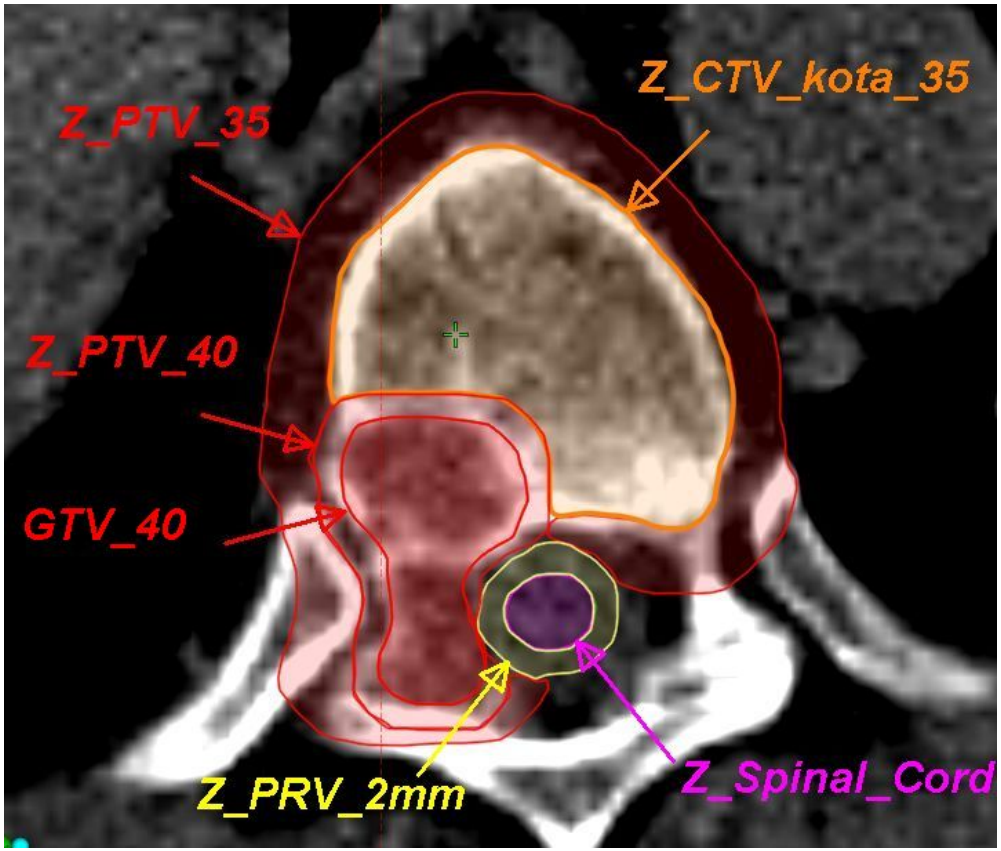


Figure 11.2: Direction of step for gradient descent and Newton's method.

Optimization: cost function and structures

Just state clearly and succintly what you want ...

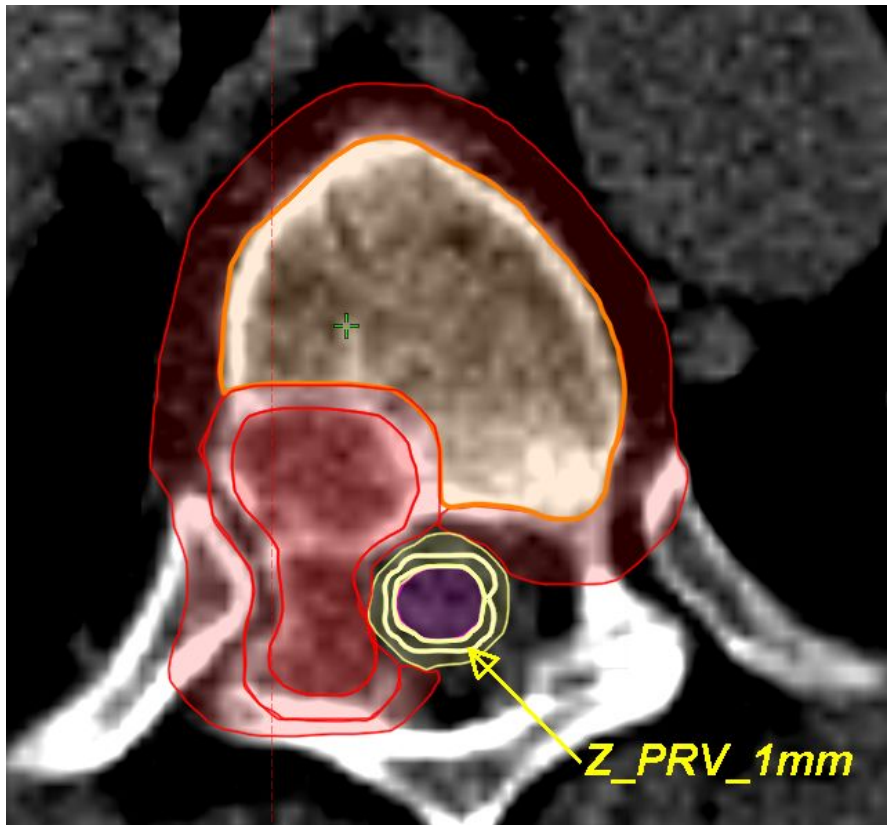
SUCH AS THIS ...



Optimization: cost function and structures

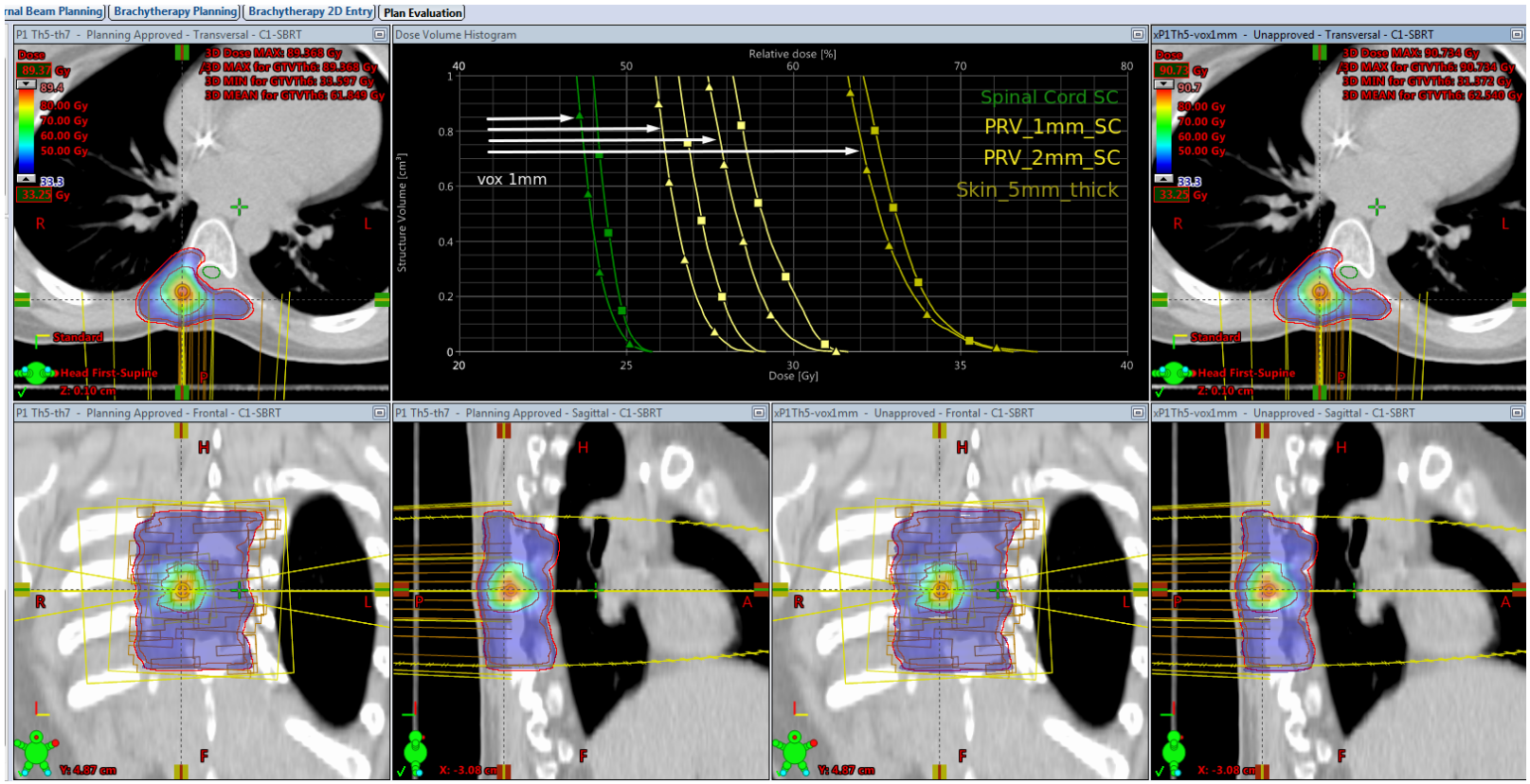
Just state clearly and succintly what you want ...

AND LIKE THIS ... We care about the final dose distribution and the fullfilled constraints



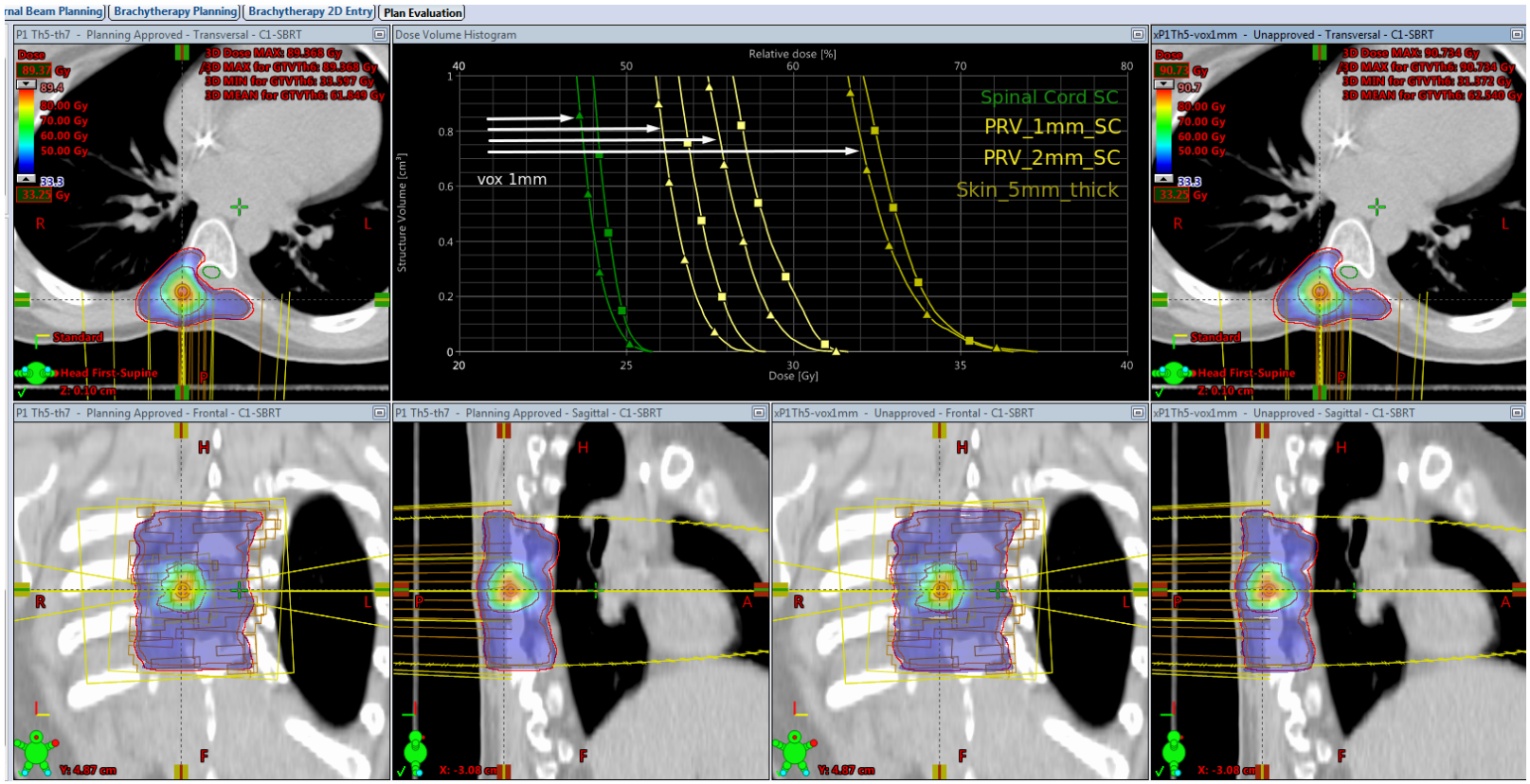
Constraints and Plan Evaluation

For plan evaluation: recalculate plan with 1 mm voxel size



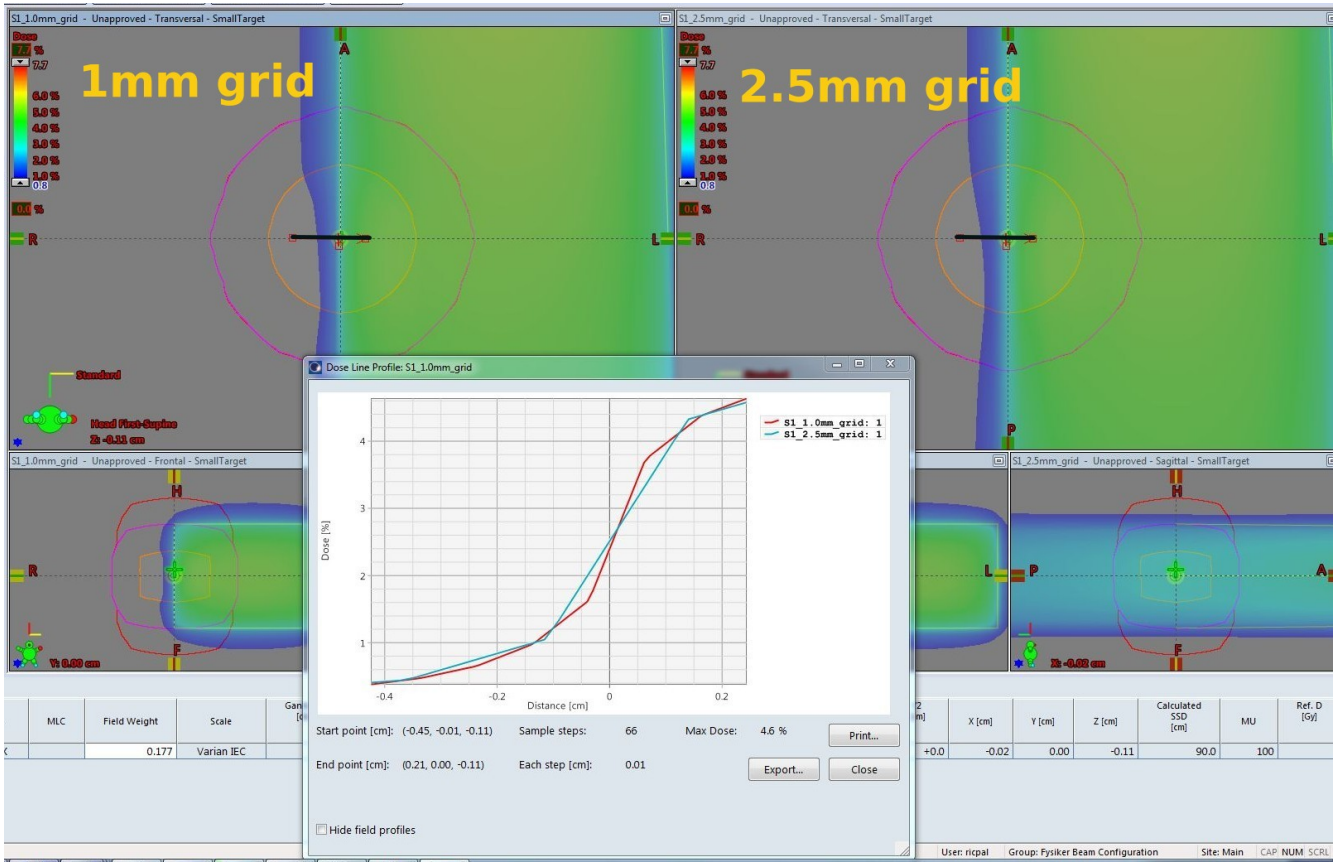
Constraints and Plan Evaluation

Large voxel sizes smear out (volume effect) dose gradient zones



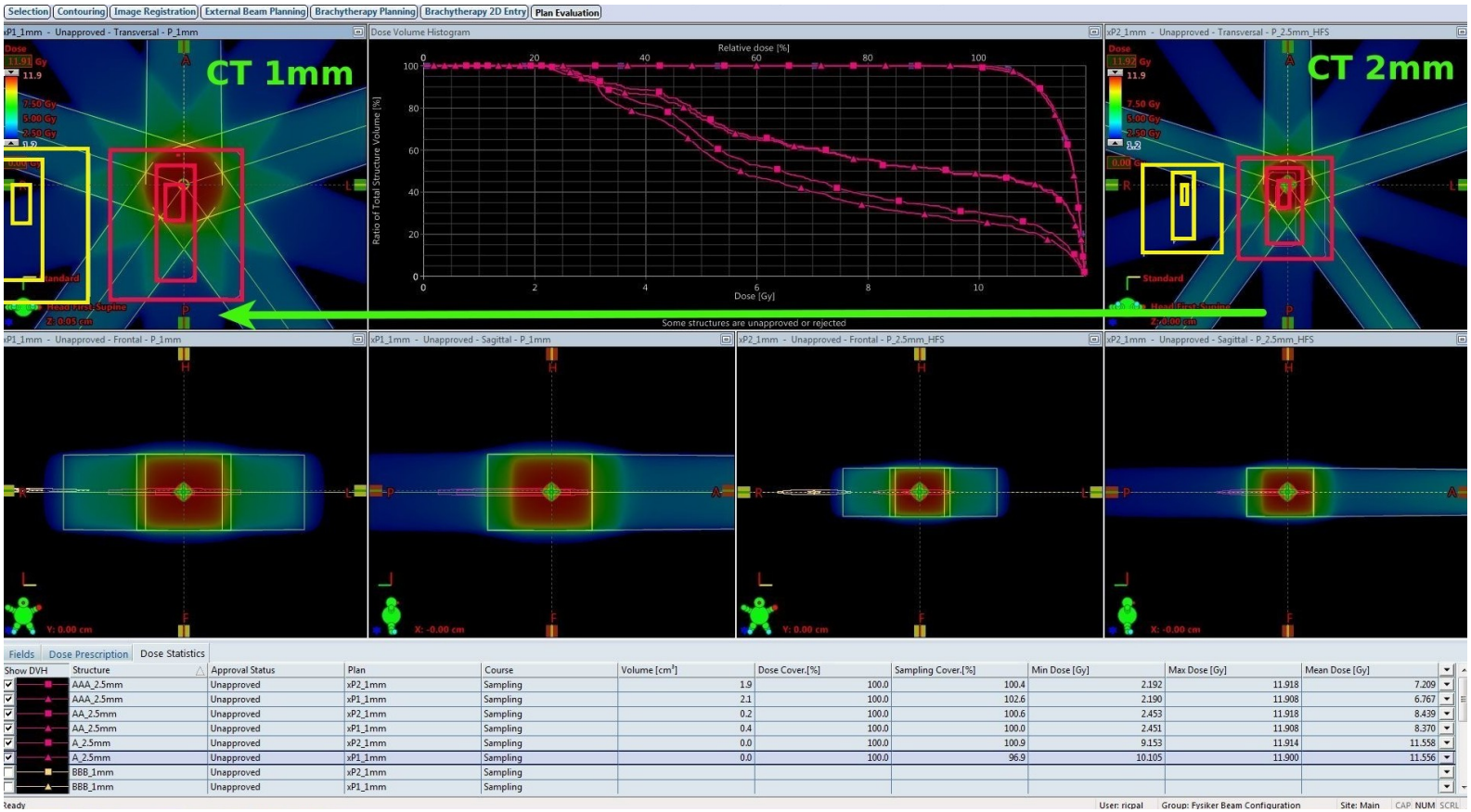
Constraints and Plan Evaluation

Volume effect and calc. grid. AAPM TG-101 ($\leq$ 2 mm)



Constraints and Plan Evaluation

Beware slice thickness!. Transfer of thin structures between 3D images



Constraints and Plan Evaluation

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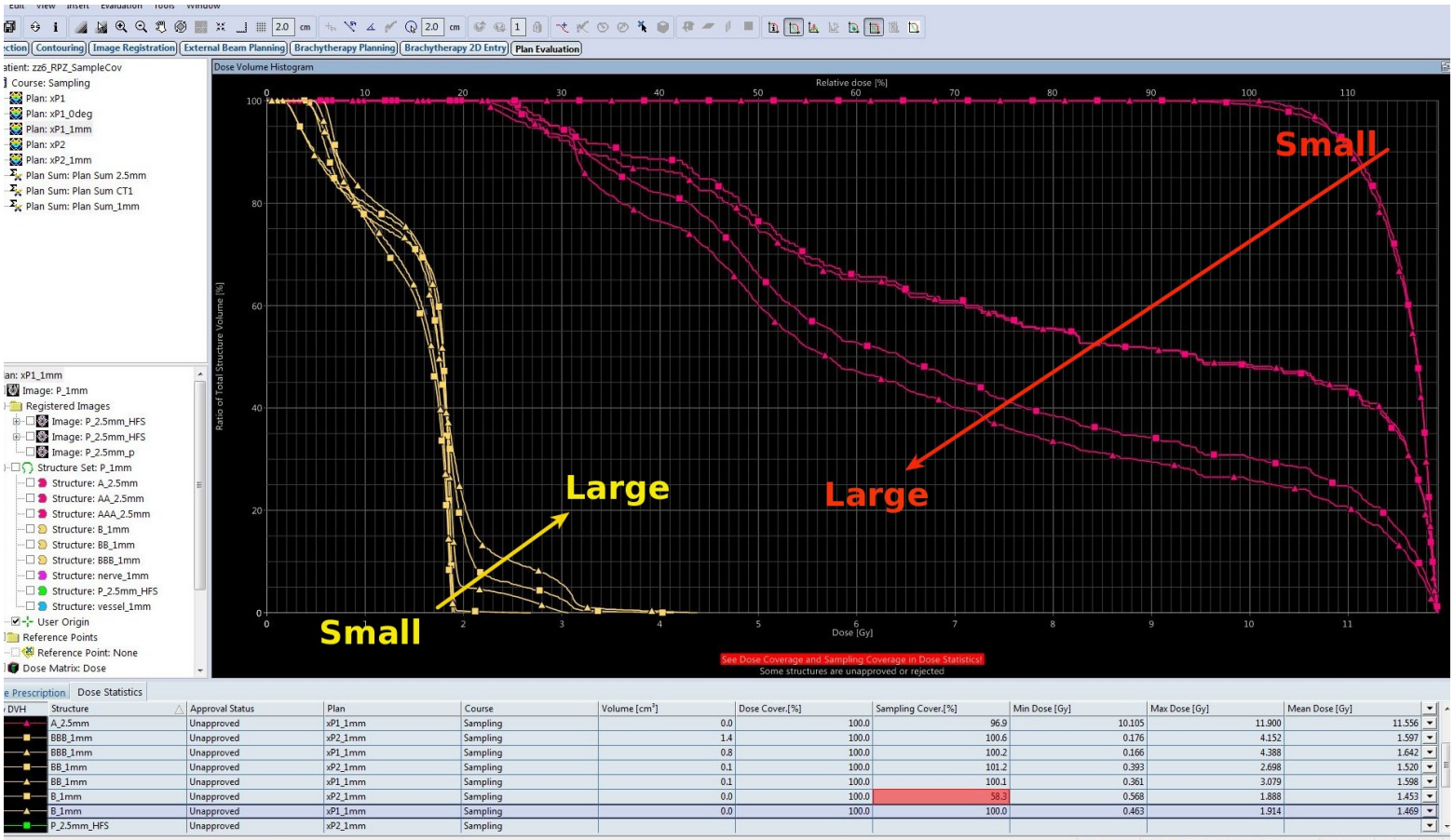

Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
A_2.5mm	Unapproved	xP1_1mm	Sampling	0.0	100.0	96.9	10.105	11.900	11.556
BBB_1mm	Unapproved	xP2_1mm	Sampling	1.4	100.0	100.6	0.176	4.152	1.597
BBB_1mm	Unapproved	xP1_1mm	Sampling	0.8	100.0	100.2	0.166	4.388	1.642
BB_1mm	Unapproved	xP2_1mm	Sampling	0.1	100.0	101.2	0.393	2.698	1.520
BB_1mm	Unapproved	xP1_1mm	Sampling	0.1	100.0	100.1	0.361	3.079	1.598
B_1mm	Unapproved	xP2_1mm	Sampling	0.0	100.0	58.3	0.568	1.888	1.453
B_1mm	Unapproved	xP1_1mm	Sampling	0.0	100.0	100.0	0.463	1.914	1.469
P_2.5mm_HFS	Unapproved	xP2_1mm	Sampling						

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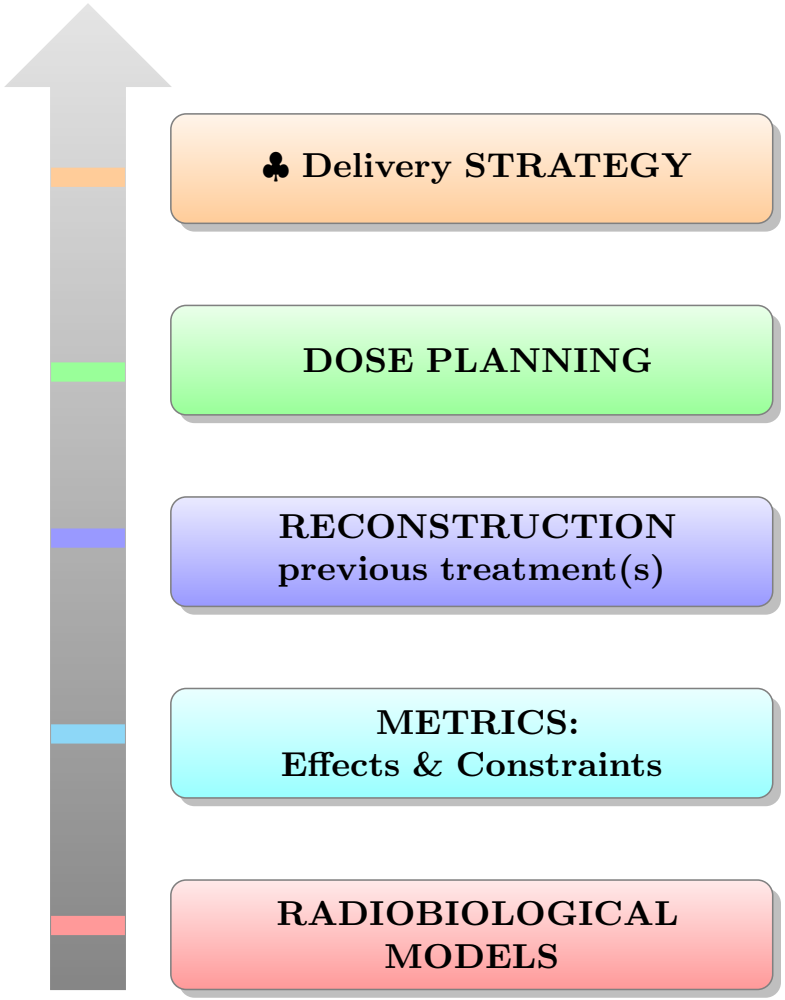

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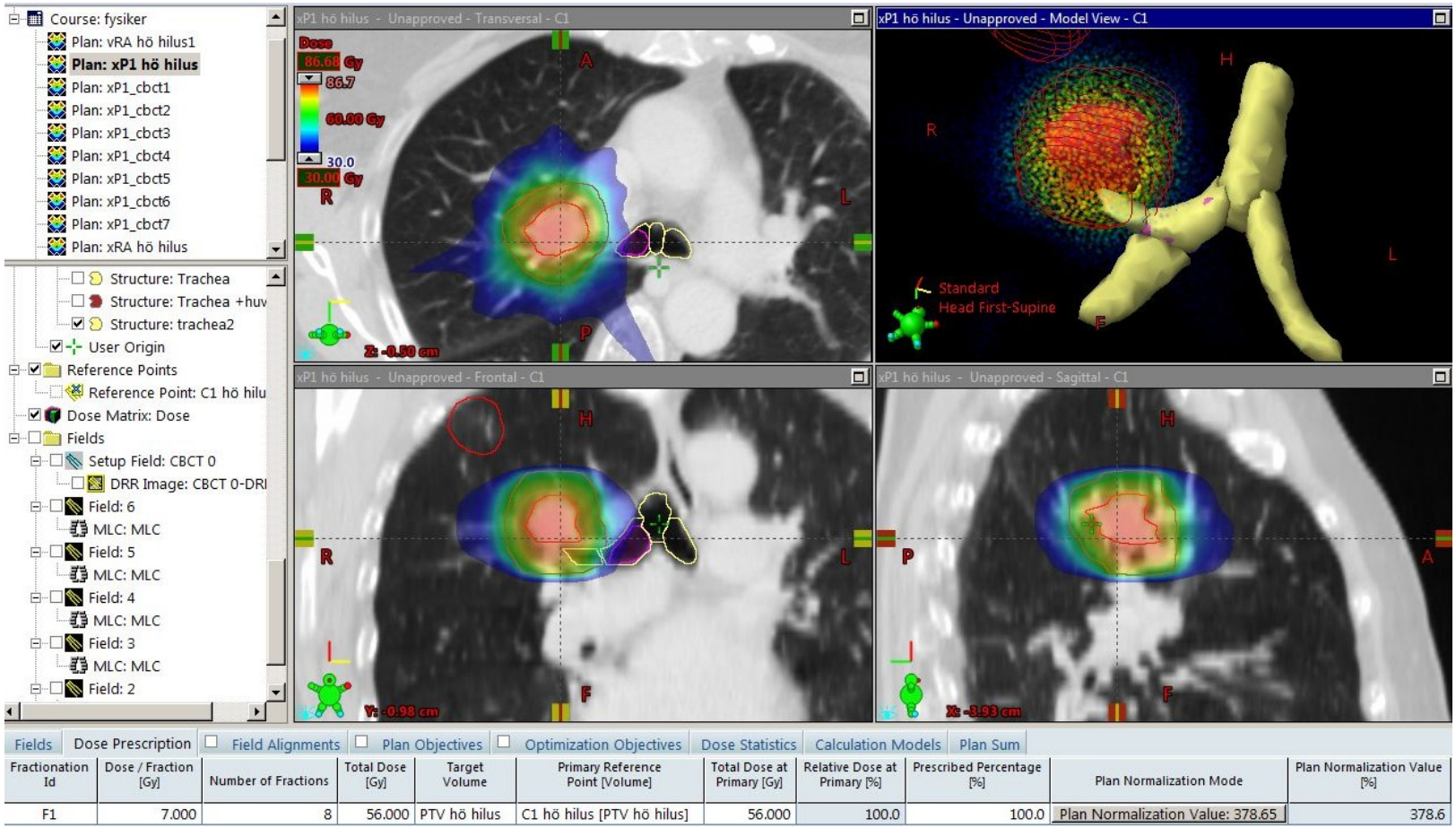
Delivery Strategy

Strategy as a team

- **Specialized team** for SBRT (clinical ronds)
- Team must be well aware of the **treatment's goal**
- On-line match **team must know the strategy** to achieve that goal
- Team must have an **understanding** on the **performance of fix** systems
- Team must have an good **understanding** on the **performance of imaging** systems
- **Reconstruction** of fractions that differ from planned and matched

Delivery Strategy

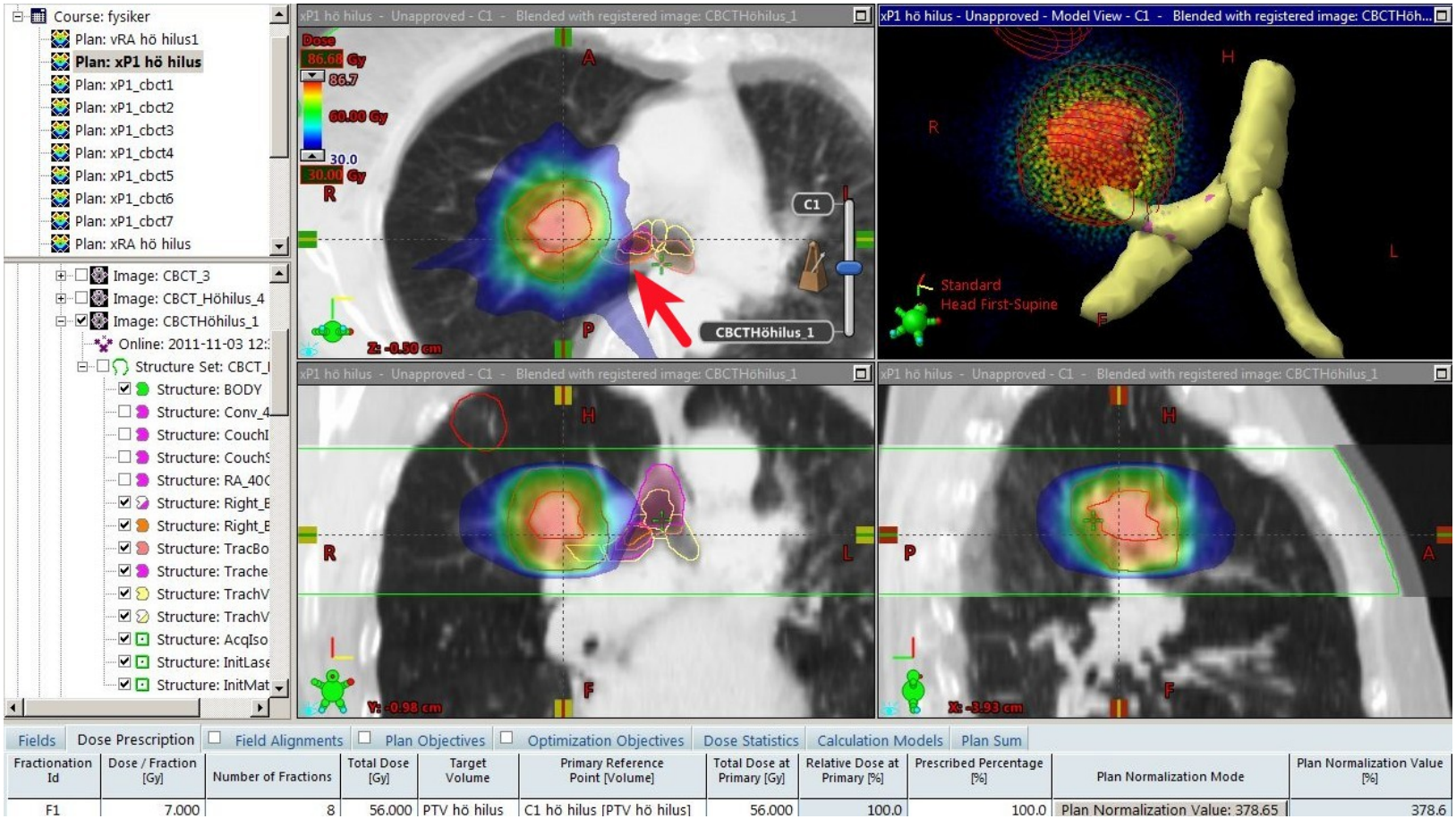
Case 1: Rotations and matching tumor (at what cost) ?



Fractionation Id	Dose / Fraction [Gy]	Number of Fractions	Total Dose [Gy]	Target Volume	Primary Reference Point [Volume]	Total Dose at Primary [Gy]	Relative Dose at Primary [%]	Prescribed Percentage [%]	Plan Normalization Mode	Plan Normalization Value [%]
F1	7.000	8	56.000	PTV hö hilus	C1 hö hilus [PTV hö hilus]	56.000	100.0	100.0	Plan Normalization Value: 378.65	378.6

Delivery Strategy

Case 1: Rotations and matching tumor (at what cost) ?



Delivery Strategy

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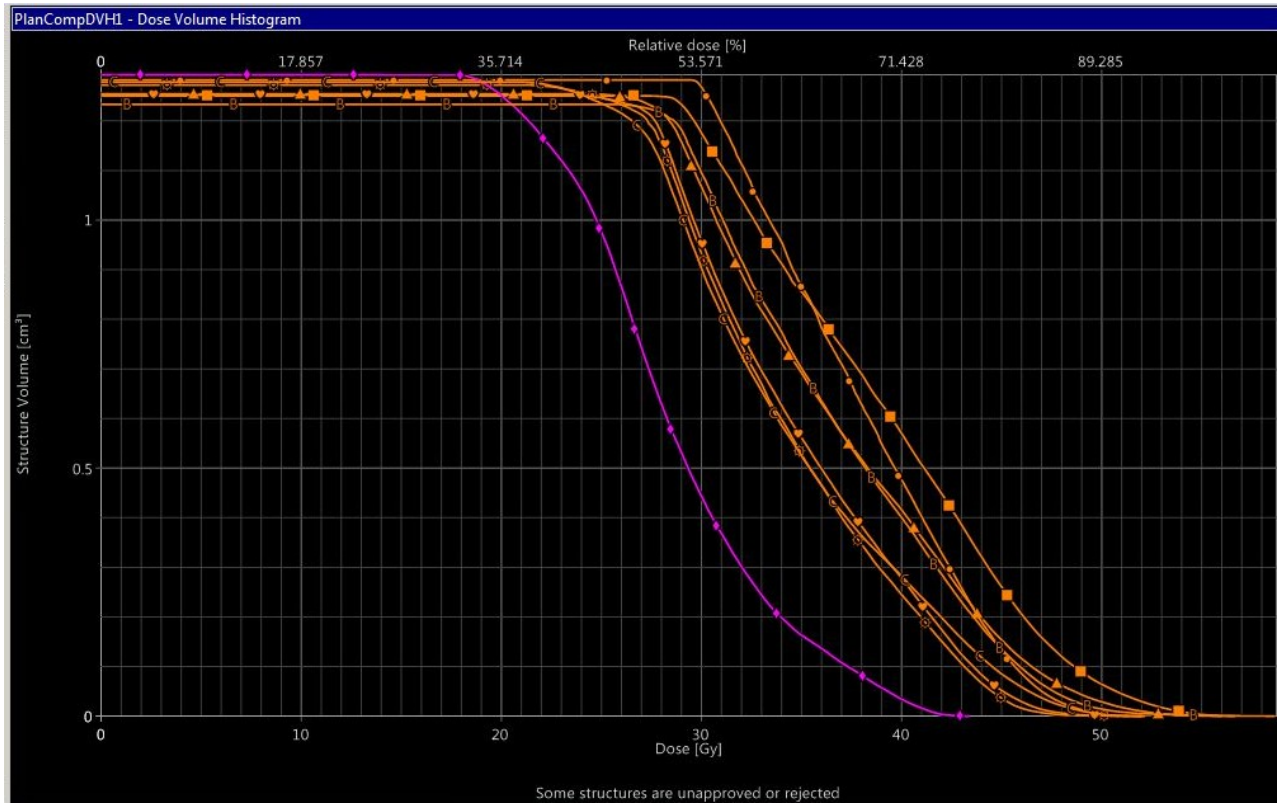

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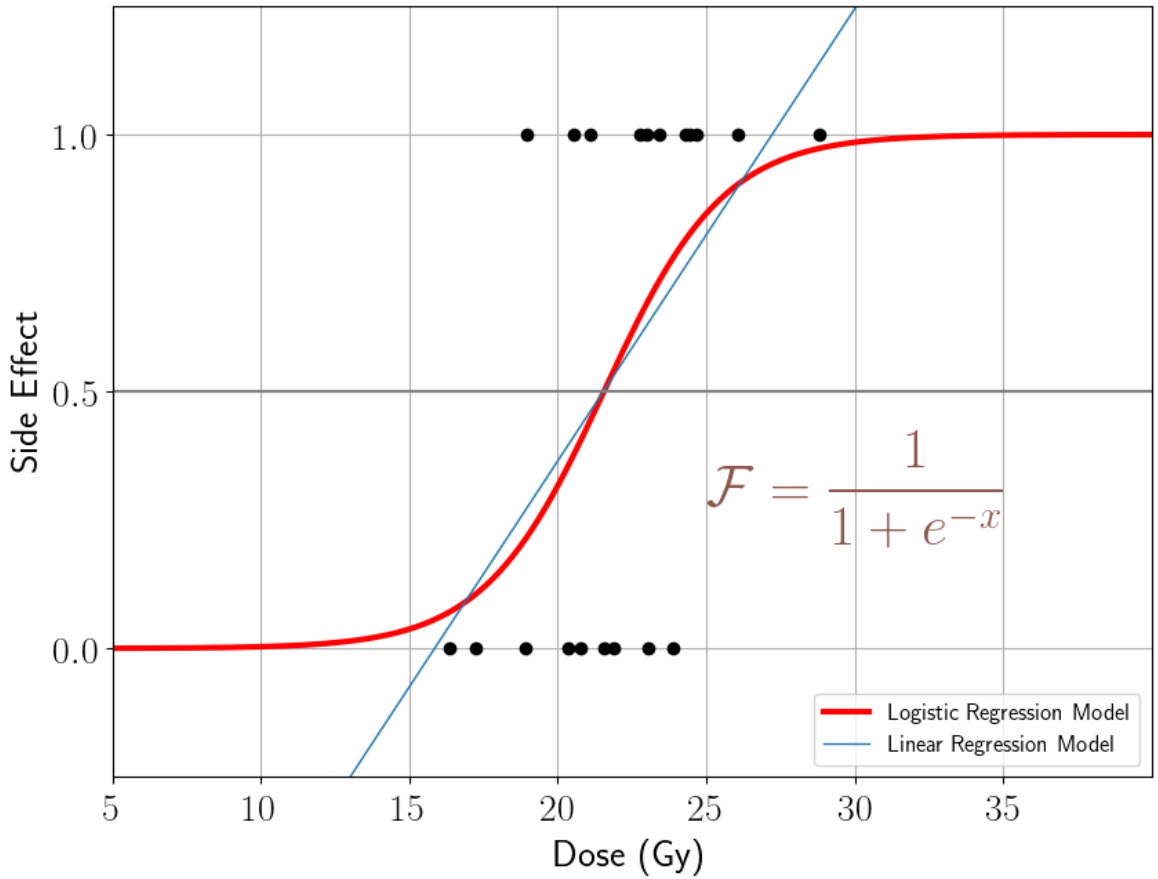

Delivery Strategy

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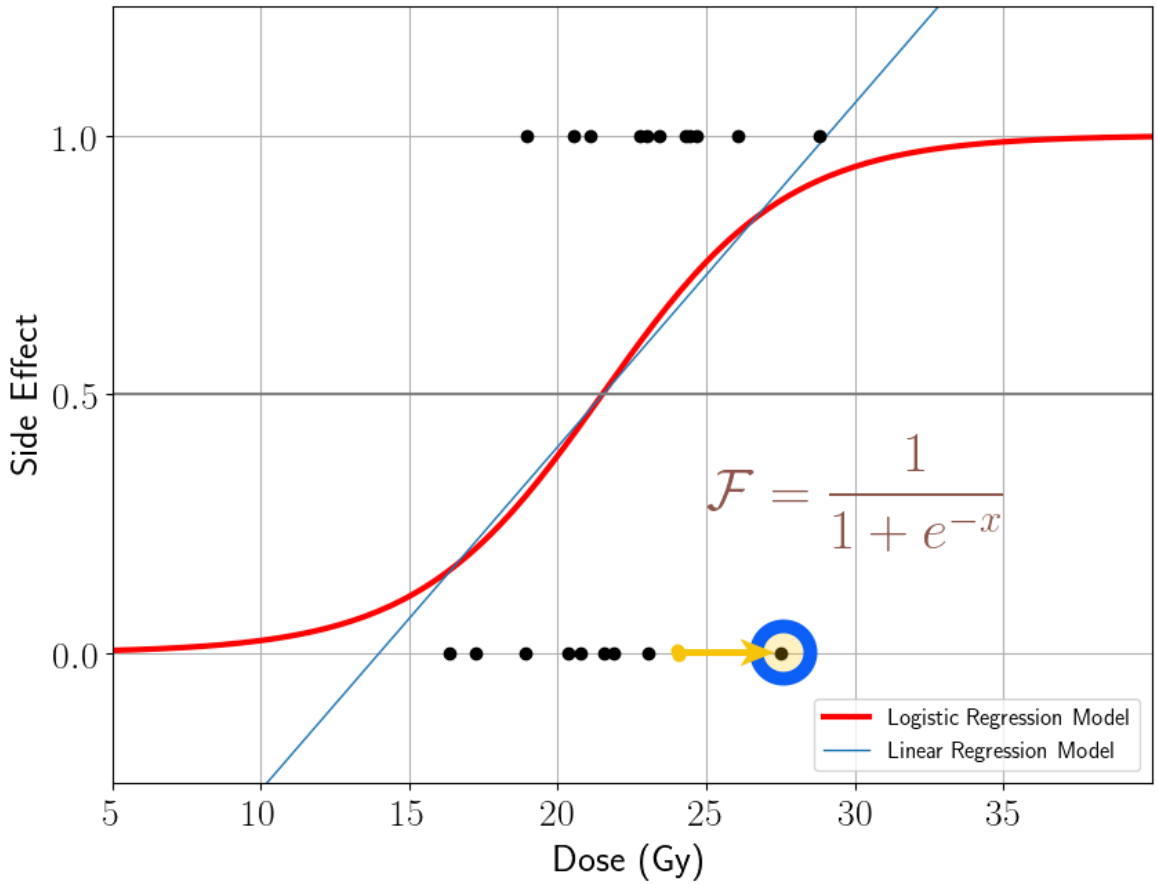
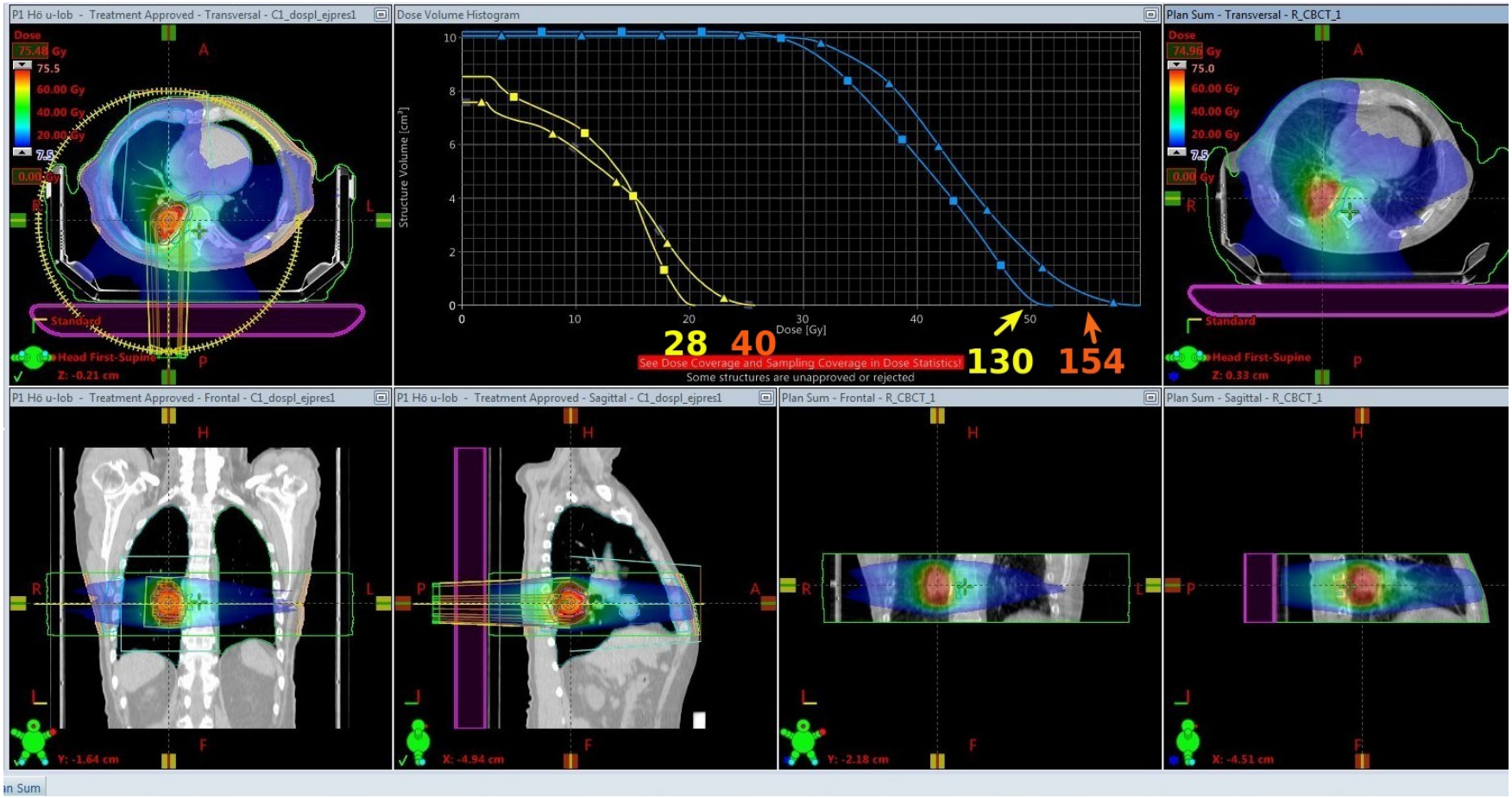


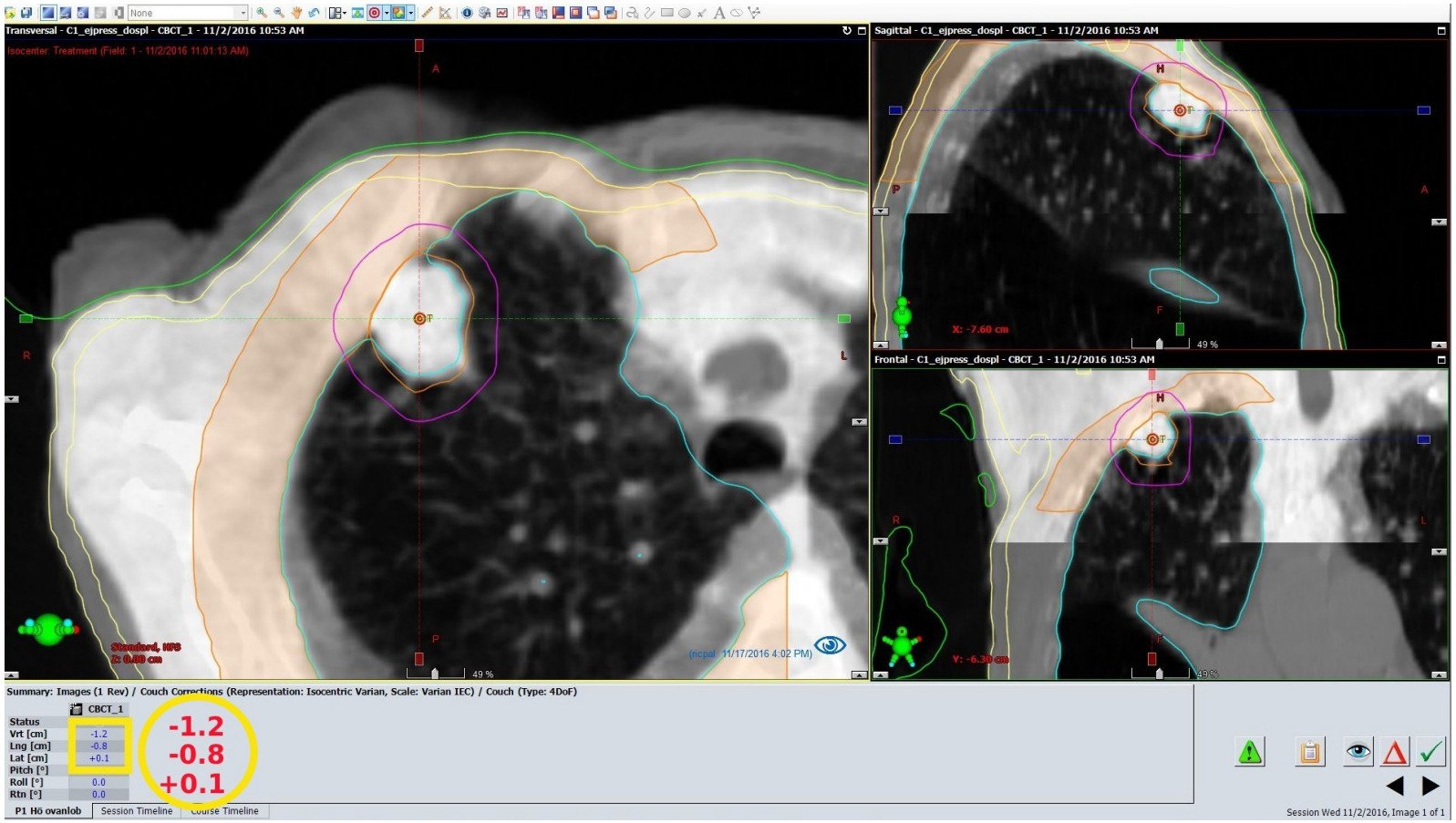
Delivery Strategy

Case 2: Rotations and matching tumor (at what cost) ?



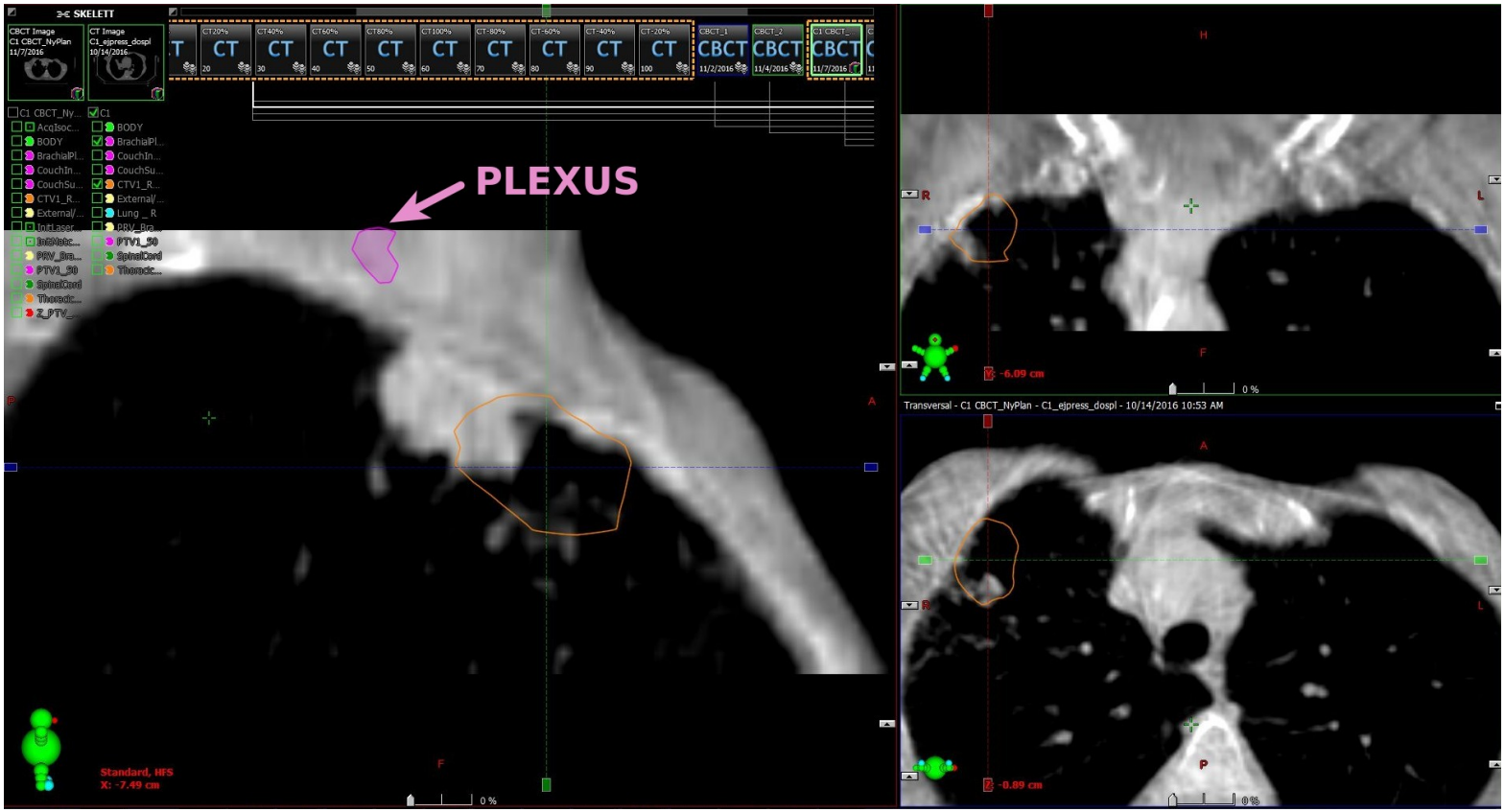
Delivery Strategy

Case 3: Based-line shifts and tumor match (at what cost) ?



Delivery Strategy

Case 3: Based-line shifts and tumor match (at what cost) ?



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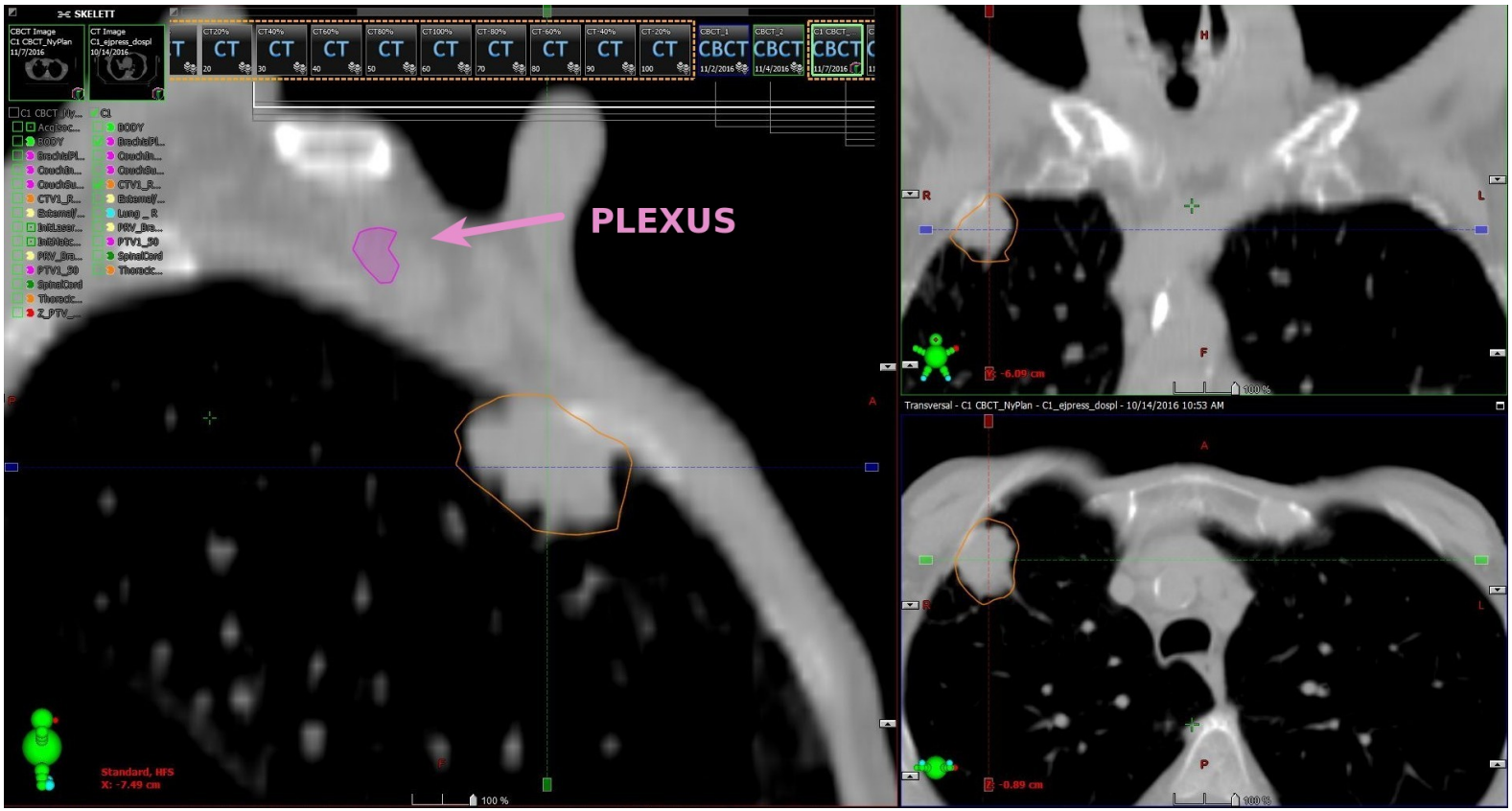

Delivery Strategy

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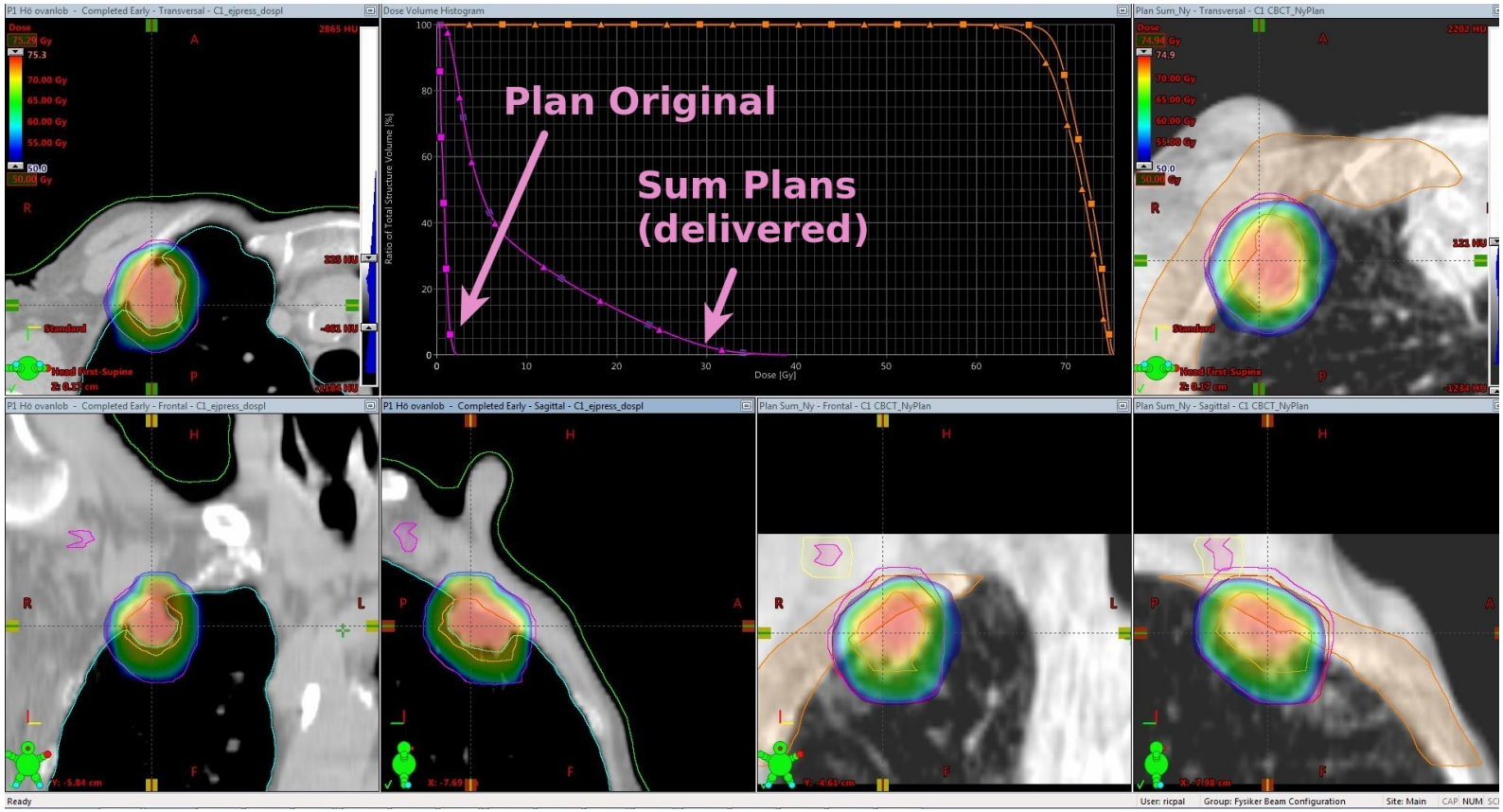
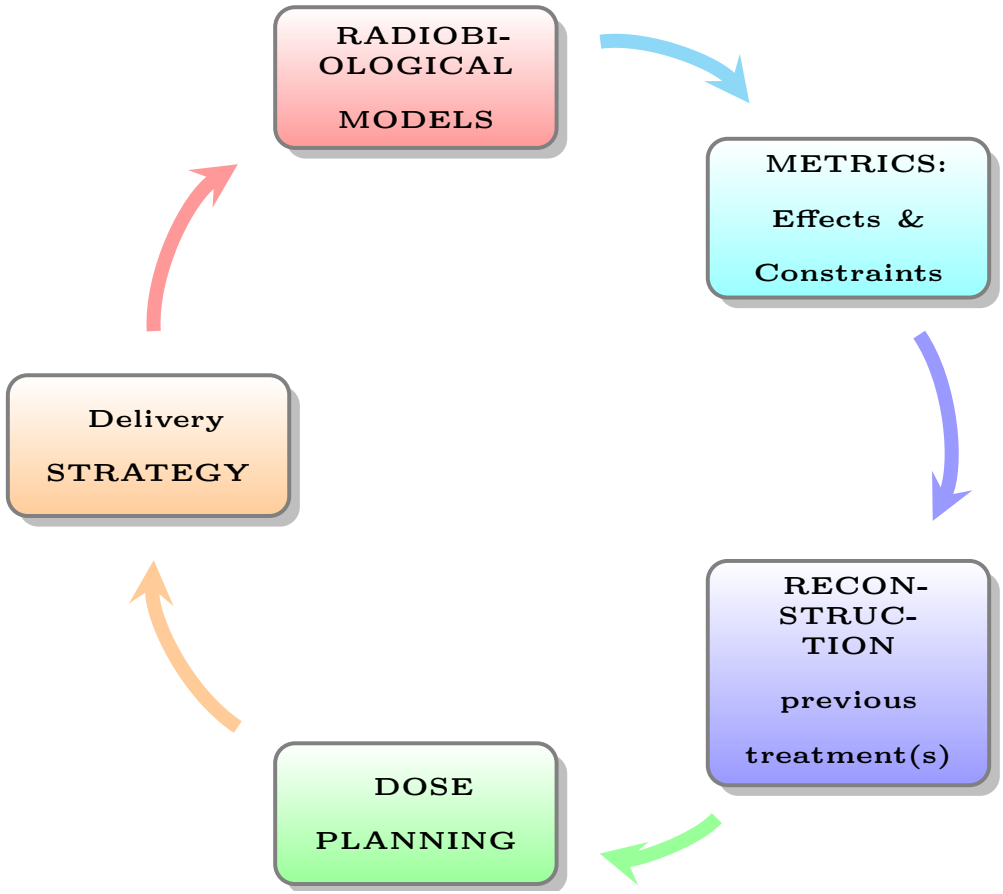


Final remarks



THANK YOU