Workshop: Practical Application of Radiobiology - Physics

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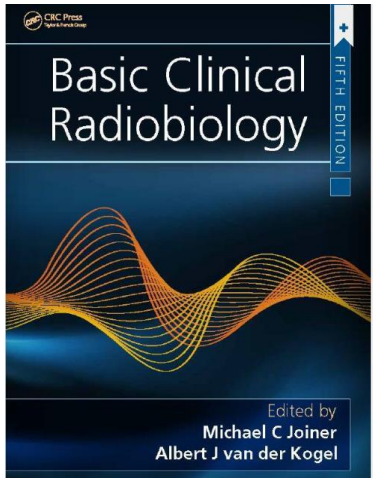
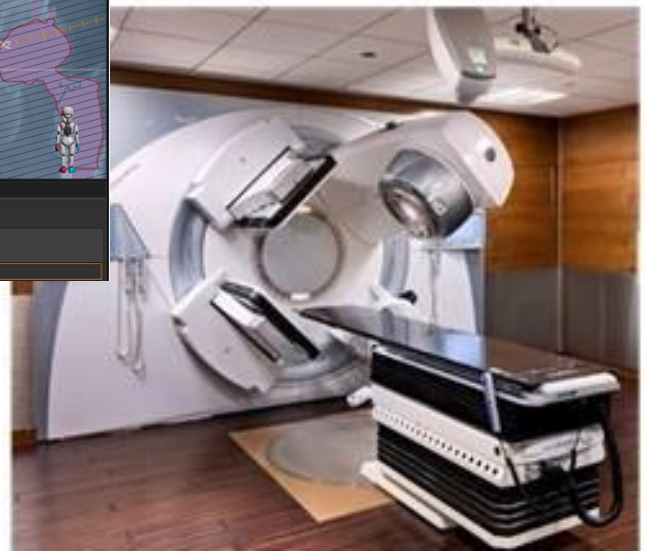
Learning Objectives: Part I



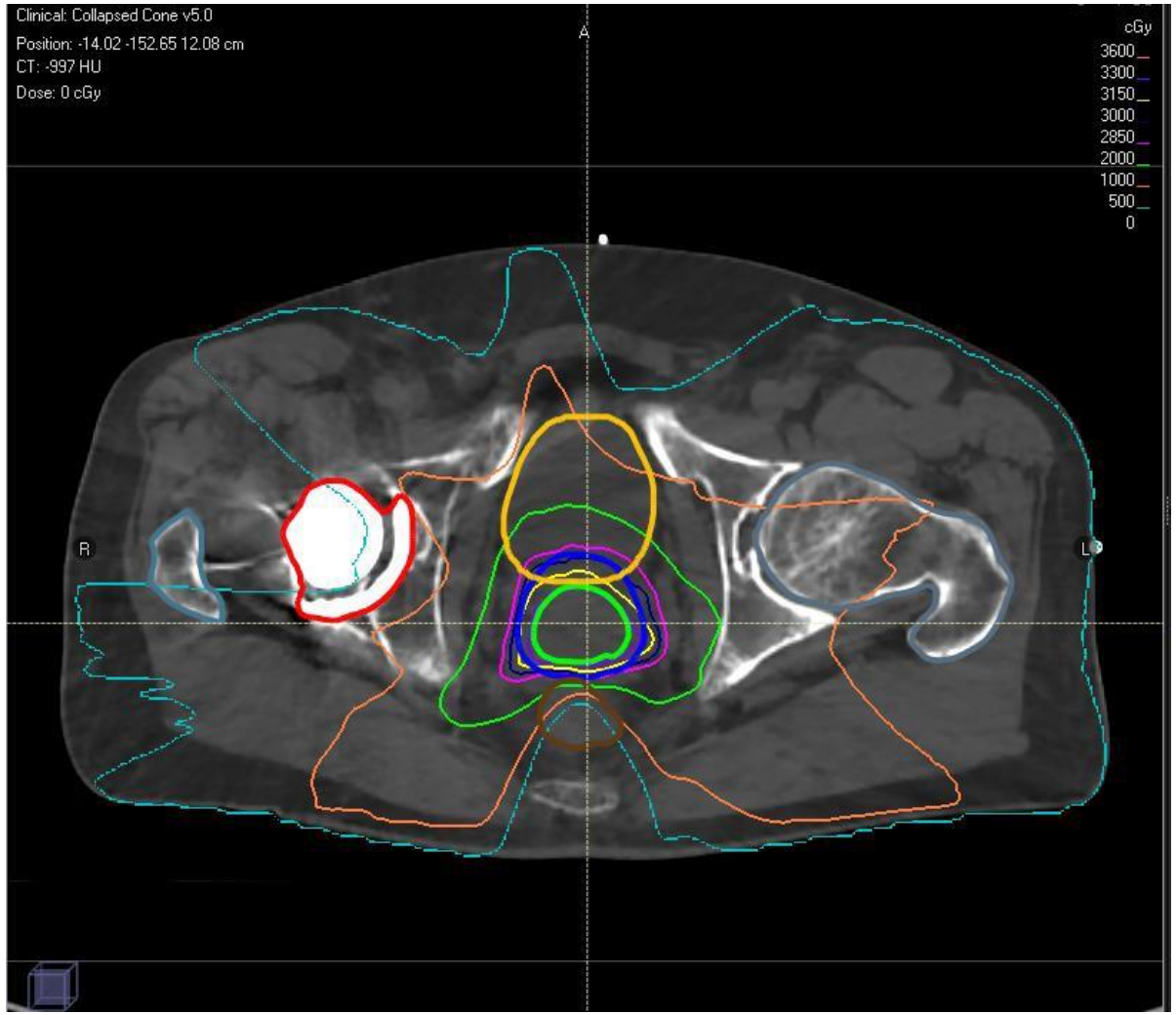
Use of TCP and NTCP models in the clinic

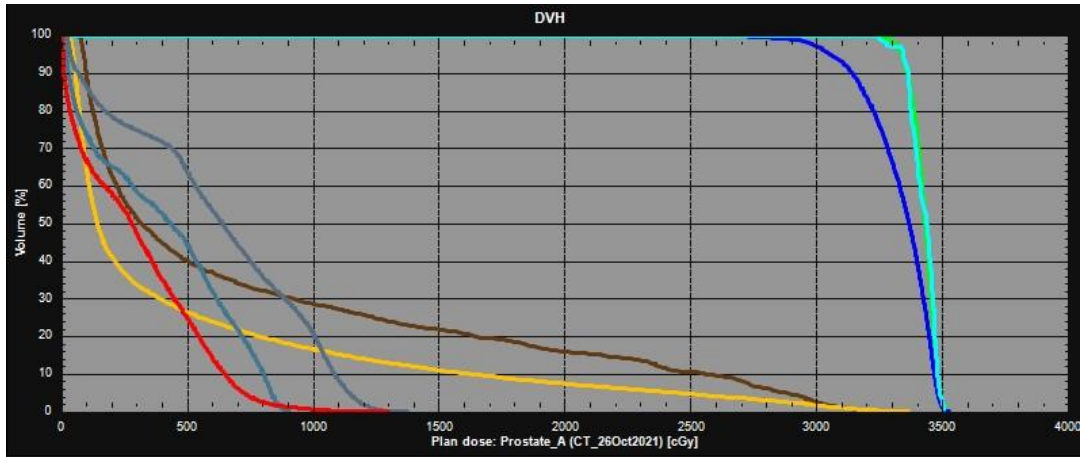
- Briefly review TCP and NTCP models
- Discuss AAPM Task Group report No. 166: The Use and QA of Biologically Related Models for Treatment Planning
- Discuss some benefits and challenges with using TCP and NTCP models as a part of treatment planning (i.e., optimization) and evaluation.
- Highlight the use of NTCP models for liver SBRT treatment planning (RTOG trial)

Radiation Therapy Treatment Process



Treatment Planning: Plan Evaluation





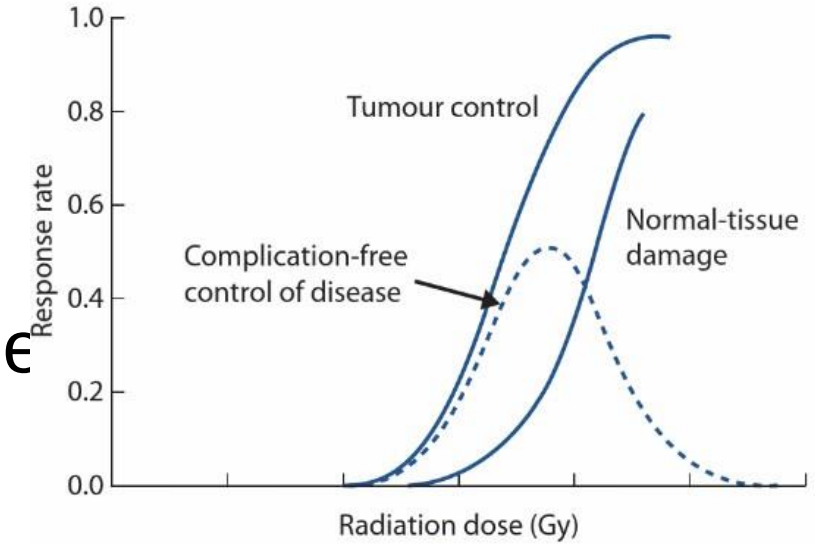
Beams (Current) | Control Points (Current) | BEV (Current)

Dose Statistics | Clinical Goals | Biological Response | Plan Fraction Schedule

Add physical... | Add biological... | Edit... | Copy | Delete | Load template... | Create template...

Priority	Dose	ROI/POI	Clinical goal	Value	Result	% o
	Plan dose: Prostate_A...	Bladder	At most 1500 cGy dose at 40.00 % volume	213 cGy	✓	0 %
	Plan dose: Prostate_A...	Bladder	At most 3000 cGy dose at 5.00 cm³ volume	2954 cGy	✓	0 %
	Plan dose: Prostate_A...	CTVp_3000	At least 3300 cGy dose at 95.00 % volume	3339 cGy	✓	0 %
	Plan dose: Prostate_A...	Femur_L	At most 1200 cGy dose at 5.00 % volume	1144 cGy	✓	0 %
	Plan dose: Prostate_A...	Femur_R	At most 1200 cGy dose at 5.00 % volume	836 cGy	✓	0 %
	Plan dose: Prostate_A...	*LargeBowel*	At most 1500 cGy dose at 5.00 cm³ volume		N/A	
	Plan dose: Prostate_A...	*LargeBowel*	At most 2500 cGy dose at 1.00 cm³ volume		N/A	
	Plan dose: Prostate_A...	PenileBulb	At most 2400 cGy dose at 50.00 % volume	197 cGy	✓	0 %
	Plan dose: Prostate_A...	PTVp_3000	At least 2850 cGy dose at 98.00 % volume	2967 cGy	✓	0 %
	Plan dose: Prostate_A...	PTVp_3000	At least 3000 cGy dose at 95.00 % volume	3055 cGy	✓	0 %
	Plan dose: Prostate_A...	PTVp_3000	At least a conformity index of 0.20 at 1500 cGy isodose	0.20	✓	0 %
	Plan dose: Prostate_A...	PTVp_3000	At least a conformity index of 0.80 at 3000 cGy isodose	0.80	✓	0 %

Part I: Use of Radiobiological models



- Probability of response as a function of dose
  - Tumor control probability (TCP)
  - Normal Tissue Complication Probability (NTCP)
- Models may be mechanistic (e.g., based on the LQ model) or empirical (functional form)
- Model parameters are fit from clinical/experimental data
- Can be used to compare different volumes of organs irradiated to different doses
- Relevant for a specific organ and a specific end-point
  - i.e., probability of ≥ grade 2 pneumonitis for partial lung irradiation

Part I: TCP Models

Number of clonogens (at start of tx)

$$\mathrm{TCP} = \text{Prob killing } \textit{all} \text{ clonogens} = (1 - \mathrm{SF})^{N_0}$$

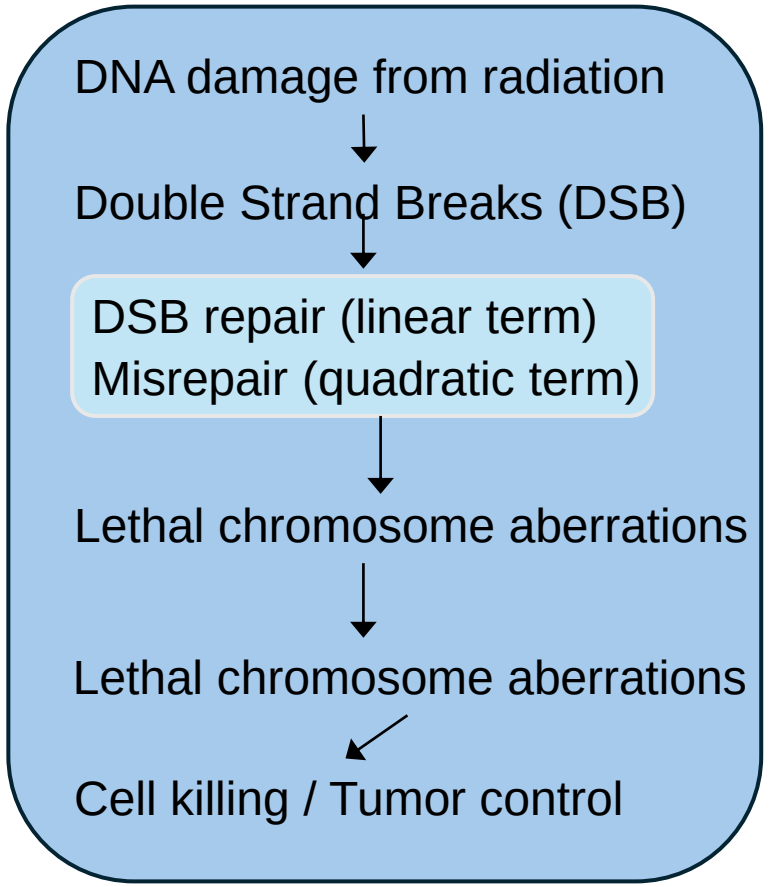
Prob that a single clonogen is killed (= 1 – prob it survives)

- When $N_0 \gg 1$ (typically assumed to be ~10^8 /cc of tumour),

$$\mathrm{TCP} \simeq e^{-N_0 \mathrm{SF}}$$

- Need a model for the clonogen survival fraction to compute TCP.

LQ model



$$\mathrm{SF} = e^{-\alpha D - \beta d \cdot D} \equiv e^{-\alpha \cdot \mathrm{BED}}$$

Biological Mechanisms

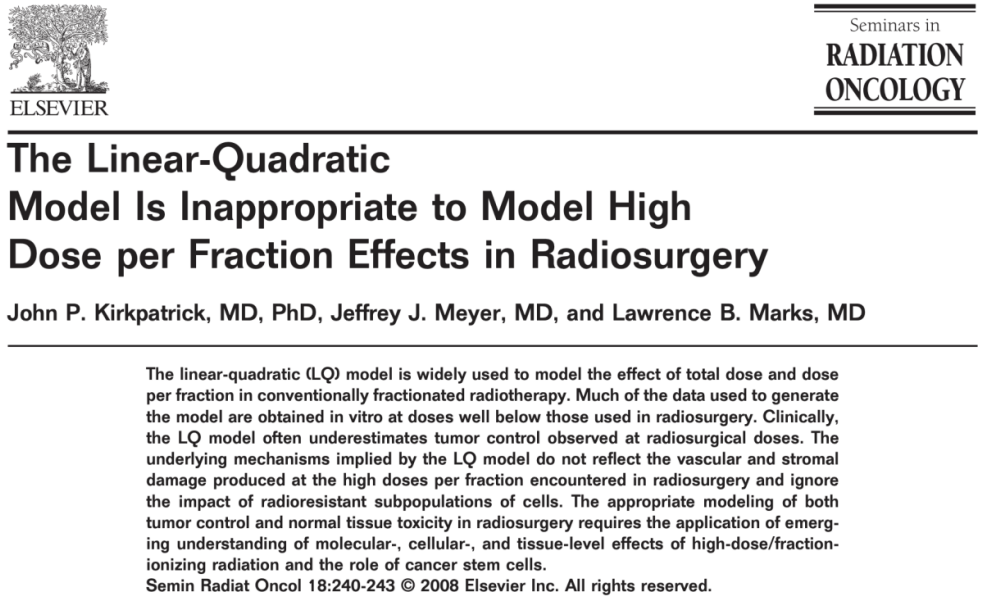
- α Term (Linear): Single radiation tracks → lethal lesions
- β Term (Quadratic): Two independent radiation tracks misrepair → lethal lesions
- Repair Rate (λ): Determines how quickly DSBs are repaired

α/β ratio describes tissue repair capacity (tumour and late responding tissues) under the assumption of full repair

Type	Dose Range (Gy)	LQ Model Fit?
In vitro	0–7	Excellent
In vitro	Up to ~15	Good
In vivo	2–18	Consistent

Isoeffect equation: $$\frac{D_2}{D_1} = \frac{d_1 + (\alpha/\beta)}{d_2 + (\alpha/\beta)}$$

LQ model validity at large doses/fraction



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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.

- Mechanistic and biologically based
- Simple: few parameters, practical to apply
- Predicts similar fractionation effects as other mechanistic models
- Strong predictive value for dose-rate and fractionation effects in lab studies
- Experimentally and theoretically validated up to ~10 Gy/fraction
- Reasonable use up to ~18 Gy/fraction
- No clinical evidence of major issues when used appropriately

Brenner et al. 2008, Semin Rdiat Oncol

α/β ratios for human normal tissues and tumors

Table 9.1 Fractionation sensitivity of human normal tissues and tumours

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Early reactions				
Skin	Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
	Erythema	12.3	1.8; 22.8	Bentzen *et al.* (1988)
	Dry desquamation	~8	N/A	Chogule and Supe (1993)
	Desquamation	11.2	8.5; 17.6	Turesson and Thames (1989)
Oral mucosa	Mucositis	9.3		
	Mucositis	15		
	Mucositis	~8		
Late reactions				
Skin/vasculature	Telangiectasia	2.8		
	Telangiectasia	2.6		
	Telangiectasia	2.8		
Subcutis	Fibrosis	1.7		
Breast	Cosmetic change in appearance	3.4		
	Induration (fibrosis)	3.1	1.8; 4.4	Yarnold *et al.* (2005)
Muscle/vasculature/ cartilage	Impaired shoulder movement	3.5	0.7; 6.2	Bentzen *et al.* (1989)
Nerve	Brachial plexopathy	<3.5*	N/A	Olsen *et al.* (1990)
	Brachial plexopathy	~2	N/A	Powell *et al.* (1990)
	Optic neuropathy	1.6	−7; 10	Jiang *et al.* (1994)

Mean Late 2.9 Gy
Mean Early 10.6 Gy
H&N, Lung tumors high
Breast , Prostate tumors low

Table 9.1 Fractionation sensitivity of human normal tissues and tumours

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Spinal cord	Myelopathy	<3.3	N/A	Dische *et al.* (1981)
Eye	Corneal injury	2.9	−4; 10	Jiang *et al.* (1994)
Bowel	Stricture/perforation	3.9	2.5; 5.3	Deore *et al.* (1993)
Bowel	Various late effects	4.3	2.2; 9.6	Dische *et al.* (1999)
Lung	Pneumonitis	4.0	2.2; 5.8	Bentzen *et al.* (2000)
	Lung fibrosis	3.1	−0.2; 8.5	Dubray *et al.* (1995)
		3.5	1.1; 5.9	Rezvani *et al.* (1991)
		4.0	3.3; 5.0	Stuschke and Thames (1999)
		3.8	0.8; 14	Maciejewski *et al.* (1986)
		0.8	−0.6; 2.5	Maciejewski *et al.* (1990)
		10.5	6.5; 29	Stuschke and Thames (1999)
		14.5*	4.9; 24	Rezvani *et al.* (1993)
		~13	'wide'	Robertson *et al.* (1993)
		6.6	2.9; ∞	Maciejewski *et al.* (1989)
		7.2	3.6; ∞	Maciejewski *et al.* (1989)
Nasopharynx		16	−11; 43	Lee *et al.* (1995)
Skin		8.5*	4.5; 11.3	Trott *et al.* (1984)
Prostate†		1.1	−3.3; 5.6	Bentzen and Ritter (2005)
Breast		4.6	1.1; 8.1	START Trialists Group (2008)
Oesophagus		4.9	1.5; 17	Geh *et al.* (2006)
Melanoma		0.6	−1.1; 2.5	Bentzen *et al.* (1989)
Liposarcoma		0.4	−1.4; 5.4	Thames and Suit (1986)

CL, confidence limit.
*Re-analysis of original published data.
†Several more estimates are available from comparisons of outcome after brachytherapy versus external-beam therapy.
Reference details are available from Søren Bentzen. See also Thames *et al.* (1990) and Table 13.2.

Basic Clinical Radiobiology, Fourth Edition, Joiner and Van der Kogel

Part I: NTCP Models

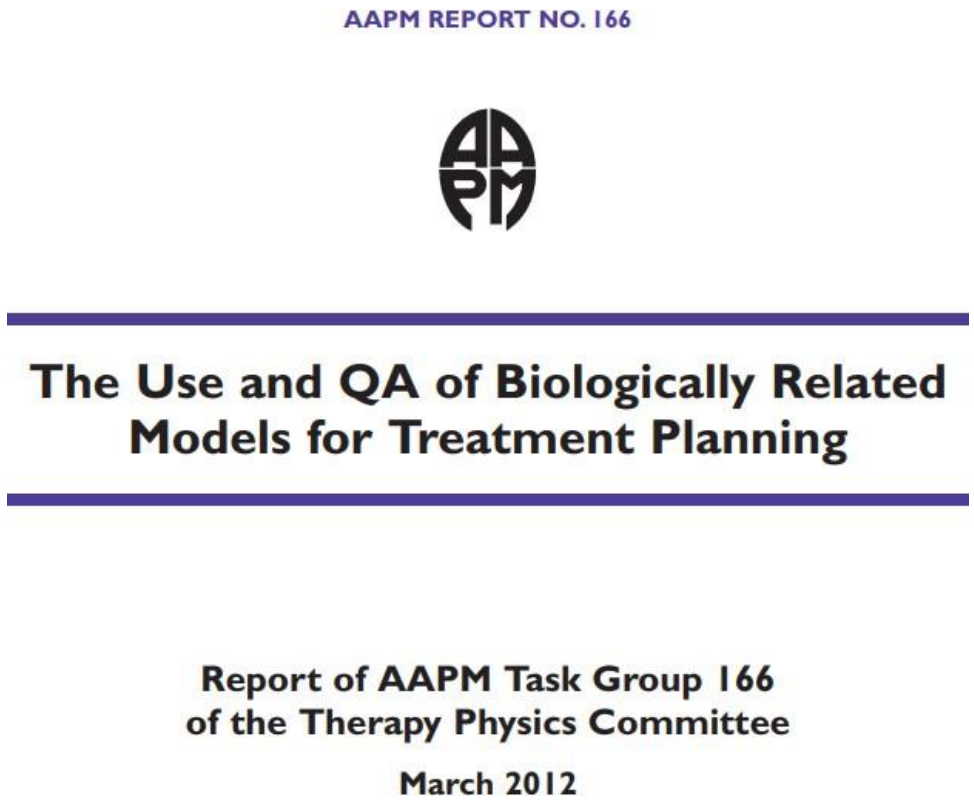
- LKB model (Kutcher & Burman, 1989)

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

$$t = (D - TD_{50}(V))/m * TD_{50}(V),$$

$$TD_{50}(1) = TD_{50}(V) * V^{-n},$$

Part I: AAPM TG-166


AAPM REPORT NO. 166

The Use and QA of Biologically Related Models for Treatment Planning

Report of AAPM Task Group 166
of the Therapy Physics Committee

March 2012

Part I: Use of Biological Models in Treatment Planning

Input: Heterogeneous 3D dose distribution or Dose-volume histogram (DVH): D_i

Output: Single number representing the patient outcome (ideally, related to TCP):

$$\mathrm{TCP}_{\mathrm{total}} = \prod_{i=1}^{N} \mathrm{TCP}(N_{0,i}, \mathrm{BED_i})$$

Used in Radiotherapy

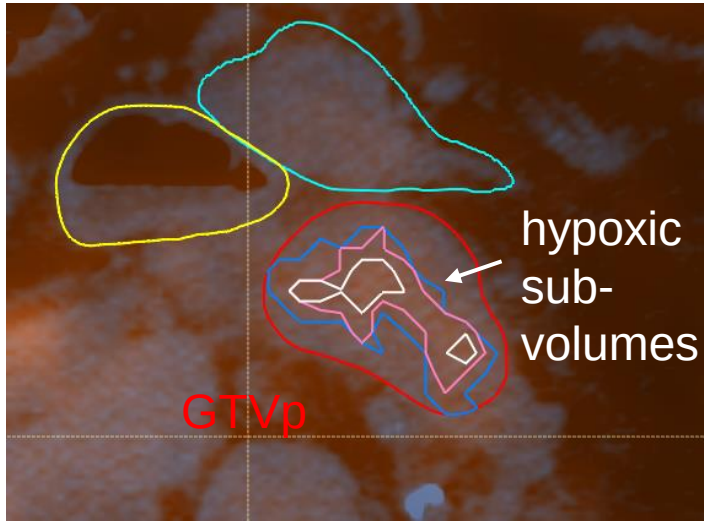
- Optimize treatment plans
- Evaluate treatment plans
- Compare different treatment plans

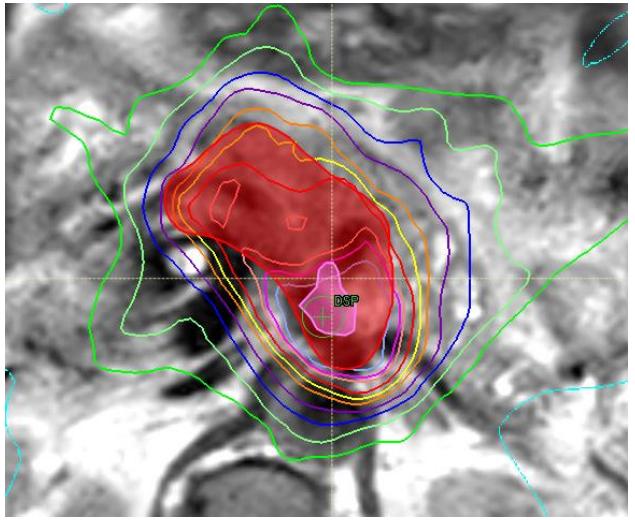
Part I: Use of Biological Models in Treatment Planning

Pros	Cons

Nonuniform dose to optimize TCP

- Ideally, deliver a spatially non-uniform dose D_i to the *i*-th "voxel" to accommodate nonuniform clonogen density ($N_{0,i}$ /V_i) and radiosensitivity (α_i, OER_i) to maximize TCP ("dose painting").
- *Can't do while minimizing dose to OARs.*
- More practically, "sub-volume" boosting. e.g., boost to hypoxia-PET avid regions of pancreatic tumours:





Hedge against (large) radiobiological uncertainty

- *Radbio-optimized planning must be ≥ SOC*:

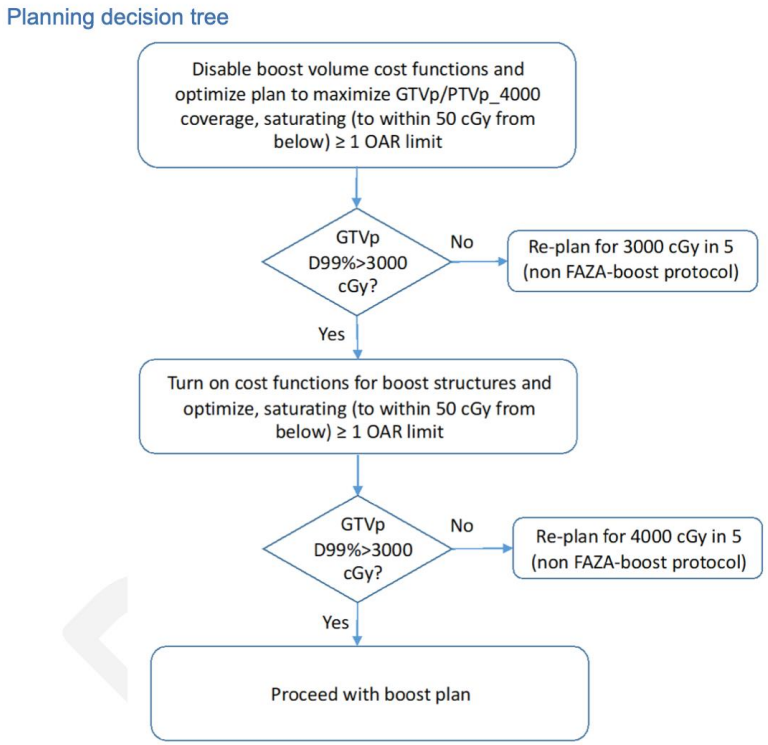
RADIATION MEDICINE PROGRAM
MRL Protocol – Treatment Planning

UHN Princess Margaret Cancer Centre

Site Group: UGI-Pancreas (FAZA Boost)

Go to page 2

Pancreas + simultaneous integrated boost (SIB) to hypoxic sub-volumes: 4500/5000/5400 cGy in 5 fractions. Unity IMRT only.



NTCP Modeling for Liver

Int. J. Radiation Oncology Biol. Phys., Vol. 13, pp. 103–109
Printed in the U.S.A.

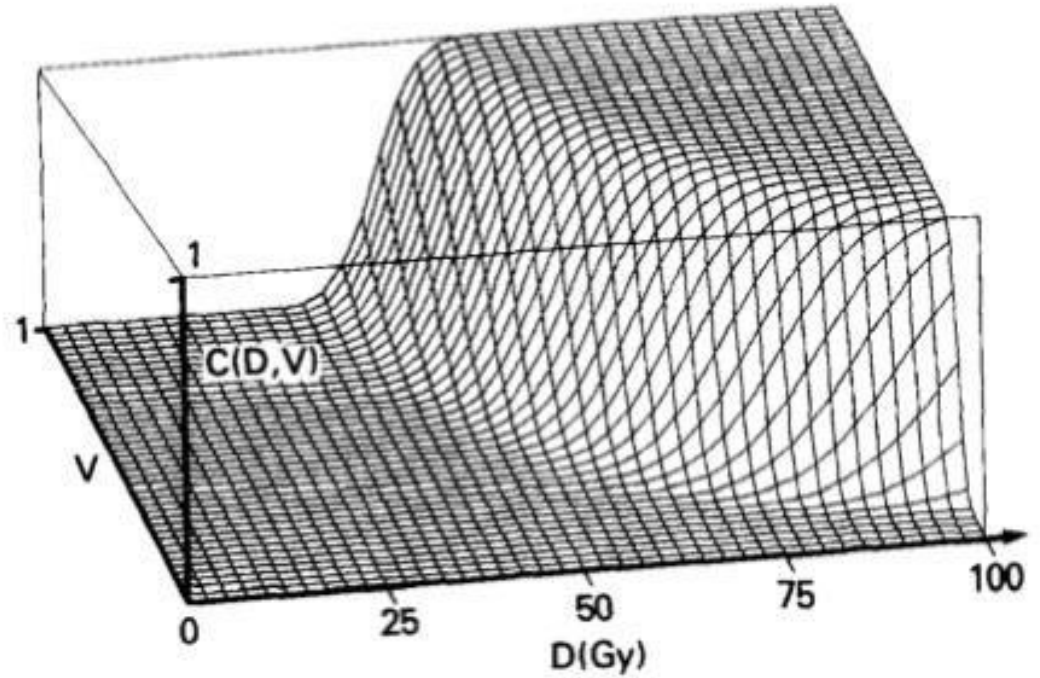
0360-3016/87 $3.00 + .00

● *Special Feature*

OPTIMIZATION OF RADIATION THERAPY, III: A METHOD OF ASSESSING COMPLICATION PROBABILITIES FROM DOSE-VOLUME HISTOGRAMS

JOHN T. LYMAN[1] AND ANTHONY B. WOLBARST[2]

[1] Lawrence Berkeley Laboratory, Bldg. 55, Room 127, Berkeley, CA 94720; and [2]Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892



(Lyman & Wolbarst, 1987)

APPENDIX

One possible representation of C(D, V)

Various functions sigmoidal in dose D and partial volume V can provide suitable analytic representations of the response of an organ to irradiation under the experimental conditions shown in Figure 2. One possibility is the integrated standard normal, or probit:

$$C(D, V) = C(t) = (2\pi)^{-1/2} \int_{-\infty}^{\infty} e^{-t'^2/2} dt',$$

where

$$t = [D - TD_{50/5}(V)]/\sigma(V).$$

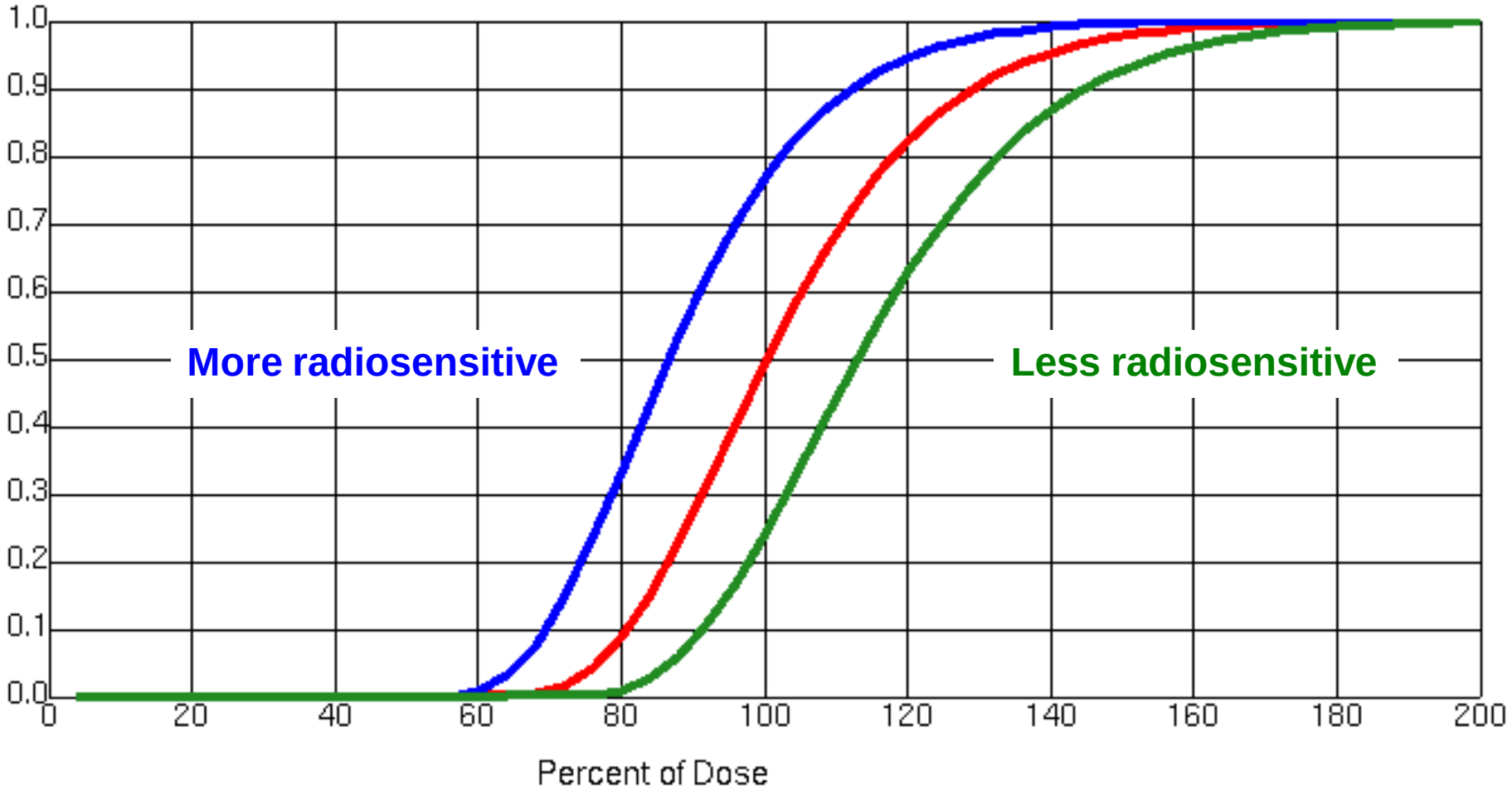
The normal deviate t represents the number of standard deviations the point (D, V) is away from $TD_{50/5}(V)$, the 5 year, 50% tolerance dose for the partial volume V. $TD_{50/5}(V)$ is taken to vary with V as

$$TD_{50/5}(V) = TD_{50/5}(1)/V^n;$$

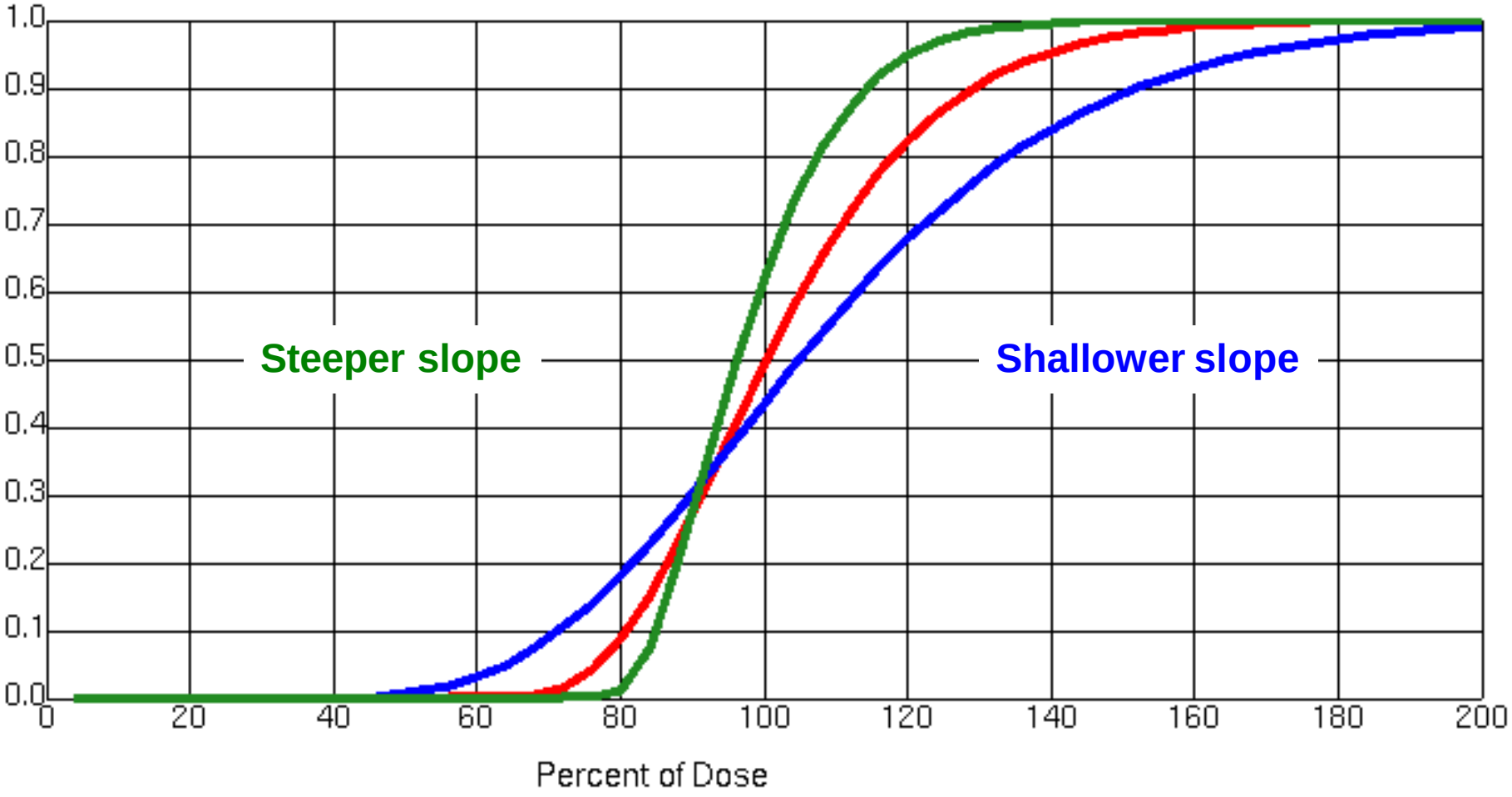
the use of a power law volume dependence for the tolerance dose is discussed in Refs. 3 and 9. $\sigma(V)$ is expressed as $\sigma(V) = m \cdot TD_{50/5}(V)$. C(D, V) is then fully parameterized by the tolerance dose for uniform irradiation of the entire organ $TD_{50/5}(1)$, the exponent n, and the coefficient m.

Figure 3, showing C(D, V) for human heart, was constructed with the above expressions using parameters ($TD_{50/5}$ = 41.9 Gy, n = 0.5, m = 0.1) determined from only four data points[6]; it is presented only to illustrate the formalism.

TD_{50}


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
20
40
60
80
100
120
140
160
180
200
Percent of Dose
More radiosensitive
Less radiosensitive

m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100
120
140
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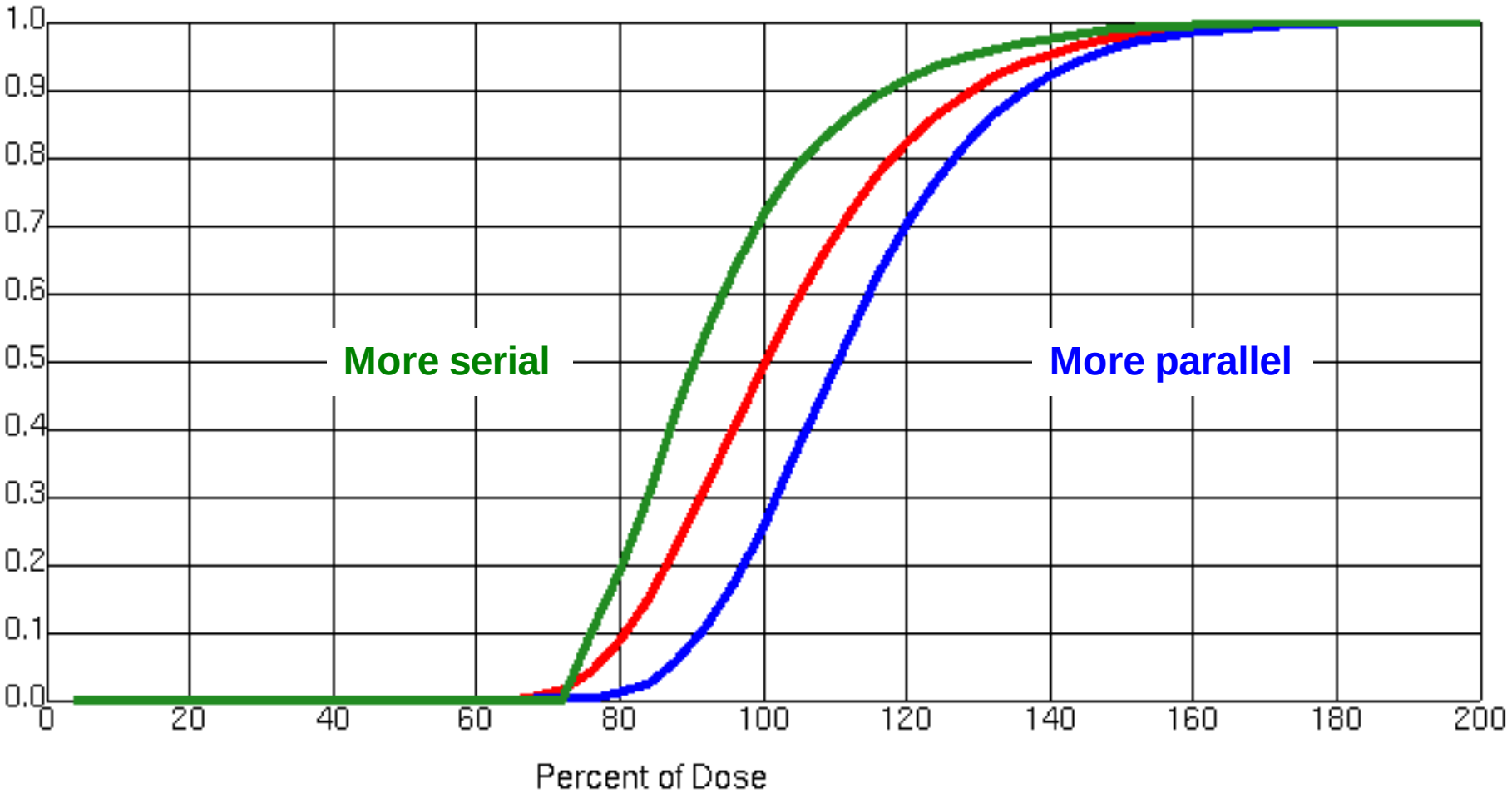
180
200
Percent of Dose
Steeper slope
Shallower slope

n


1.0
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0.4
0.3
0.2
0.1
0.0
0
20
40
60
80
100
120
140
160
180
200
More serial
More parallel
Percent of Dose

Int. J. Radiation Oncology Biol. Phys., Vol. 53, No. 4, pp. 810–821, 2002

0360-3016/02/$–see front matter

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PII S0360-3016(02)02846-8

CLINICAL INVESTIGATION **Normal Tissue**

ANALYSIS OF RADIATION-INDUCED LIVER DISEASE USING THE LYMAN NTCP MODEL

Laura A. Dawson, M.D., Daniel Normolle, Ph.D., James M. Balter, Ph.D.,
Cornelius J. McGinn, M.D., Theodore S. Lawrence, M.D., Ph.D., and Randall K. Ten Haken, Ph.D.

Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

To better describe the different risk of RILD in patients with primary hepatobiliary malignancies and those with liver metastases, another fit was completed in which the LKB model parameters n and m were fit to the entire group of patients treated with FUdR (169 patients), but the $TD_{50}(1)$ was separately fit for patients with primary hepatobiliary cancer [$TD_{50}(1)_{HB}$; 84 patients] and liver metastases [$TD_{50}(1)_{LM}$; 85 patients]. The parameters were as follows: n = 0.97 (95% CI 0.69–2.3), m = 0.12 (95% CI 0.07–0.25), $TD_{50}(1)_{HB}$ = 39.8 Gy (95% CI 38.8–41.1), and $TD_{50}(1)_{LM}$ = 45.8 Gy (95% CI 43.4–50.4; D = 66.0, $p > 0.99$). The two $TD_{50}(1)$ values were significantly different ($p < 0.02$). This indicates a higher tolerance of the liver to radiation for patients with liver metastases compared with those with primary hepatobiliary malignancies. On the basis of this analysis, an opportunity exists for higher doses to be

(Dawson et al., 2002)

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S94–S100, 2010

0360-3016/10/$–see front matter

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doi:10.1016/j.ijrobp.2009.06.092

RADIATION-ASSOCIATED LIVER INJURY

Charlie C. Pan, M.D.,* Brian D. Kavanagh, M.D., M.P.H.,† Laura A. Dawson, M.D.,‡ X. Allen Li, Ph.D.,§ Shiva K. Das, Ph.D.,‖ Moyed Miften, Ph.D.,† and Randall K. Ten Haken, Ph.D.*

From the *Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, MI; †Department of Radiation Oncology, University of Colorado, Aurora, CO; ‡Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; §Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI; ‖Department of Radiation Oncology, Duke University Medical Center, Durham, NC

6. MATHEMATICAL/BIOLOGICAL MODELS

The Lyman NTCP model has been applied by numerous groups. From the series referenced in Table 2, the range of estimates of the parameters generated among patients with Child-Pugh A or better liver function and no HBV infection are as follows: n, 0.86–1.1; m, 0.12–0.31; and TD50, 39.8–46.1 Gy (8, 21). For patients with HBV or Child-Pugh B dysfunction, the ranges are: n = 0.26–0.7, m = 0.4–0.43, TD50 = 23–50 Gy (3, 21). These patients with worse liver dysfunction likely have lower TD50 values within the previous range, though this needs to be clarified in future studies.

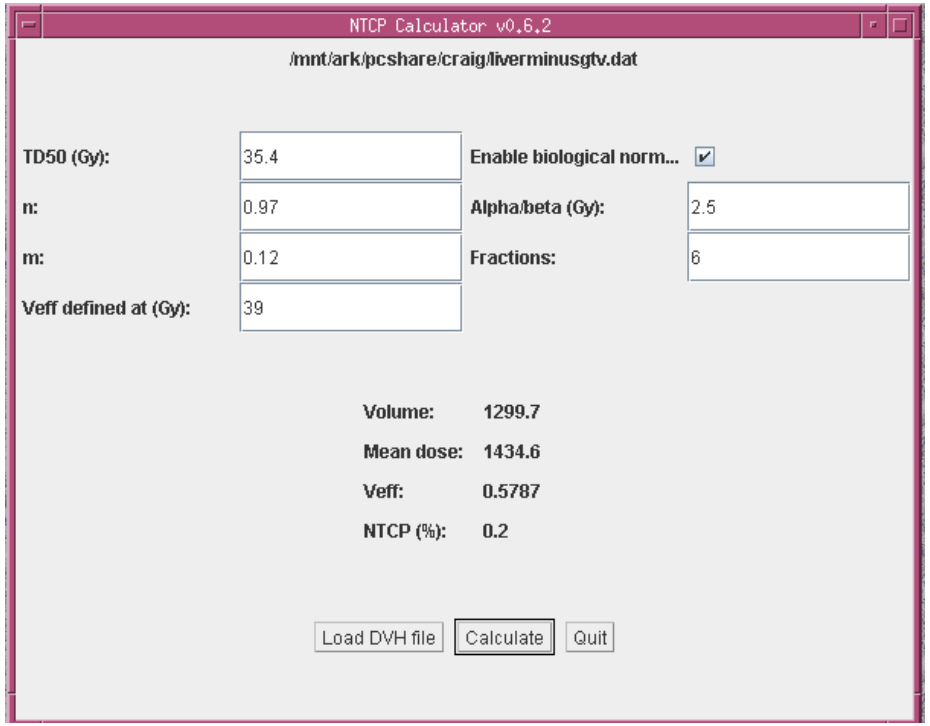
(Pan et al., 2010)

UM → PMH

- Started with UM parameters
- Made conservative radiobiological assumptions
  - α/β = 2.5 Gy
- Used LQ model to approximately convert TD50 from 1.5 Gy fractions
- Implemented “bioNTCP” approach
  - LQ conversion of DVH prior to calculation

PMH Liver Study Dose Allocation

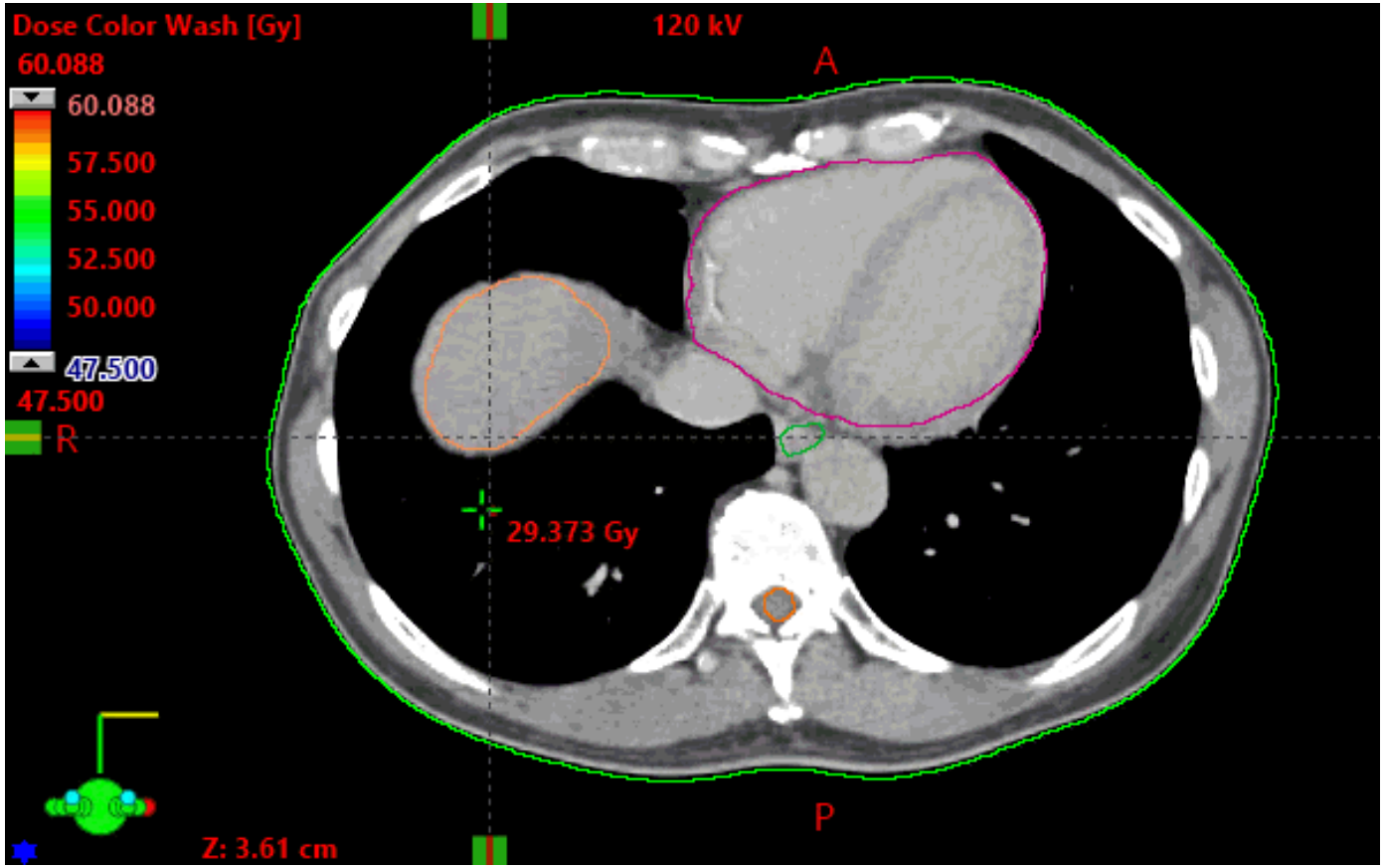
1. Plan is developed
2. Veff is calculated
3. Prescription is determined
4. Plan is modified
5. Repeat
6. Calculate NTCP
7. Modify prescription, if possible



RTOG 1112

V_{eff}	Mean Liver Dose (Gy)	Planned Prescription Dose (Gy)	If Mean Liver Dose is Exceeded at this Prescription
< 25%	13.0	50	Reduce to 45 Gy and re-evaluate
25 – 29%	15.0	45	Reduce to 40 Gy and re-evaluate
30 – 34%	15.0	40	Reduce to 35 Gy and re-evaluate
35 – 44%	15.5	35	Reduce to 30 Gy and re-evaluate
45 – 54%	16.0	30	Reduce to 27.5 Gy and re-evaluate
55 – 64%	17.0	27.5	Ineligible

Example RTOG1112 Treatment Plan



Predictors of Liver Toxicity

Parameter	Odds ratio(95% CI)	P value
Baseline CP score (6 vs. 5)	4.9 (1.5-16.1)	0.01
Baseline platelet count	0.9 (0.8-1.0)	0.02
Mean liver dose	1.3 (1.0-1.7)	0.02
D800cc	1.1 (1.0-1.2)	0.02

Velec et al, IJROBP 2017; 97: 939-946

		Mean Liver Dose (Gy)						
		15	16	17	18	19	20	21
D800cc (Gy)	5	0% (0/18)	0% (0/23)	0% (0/26)	3% (1/30)	6% (2/32)	6% (2/32)	6% (2/32)
	10	0 % (0/24)	0% (0/32)	0% (0/38)	4% (2/45)	6% (3/47)	6% (3/47)	6% (3/47)
	15	0% (0/26)	3% (1/36)	2% (1/43)	6% (3/53)	7% (4/58)	7% (4/59)	7% (4/59)
	20	0% (0/26)	3% (1/37)	4% (2/45)	7% (4/55)	10% (6/62)	11% (7/64)	12% (8/65)
	25	0% (0/26)	3% (1/37)	6% (3/47)	9% (5/57)	11% (7/65)	12% (8/67)	16% (11/70)
	30	0% (0/26)	3% (1/37)	6% (3/47)	9% (5/57)	11% (5/57)	13% (9/69)	18% (13/73)

Velec et al, IJROBP 2017; 97: 939-946

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ReRT in Practice - PART II
Bridging the Gap Between Art and Science

Monica Serban, PhD, MCCPM

April 11, 2025

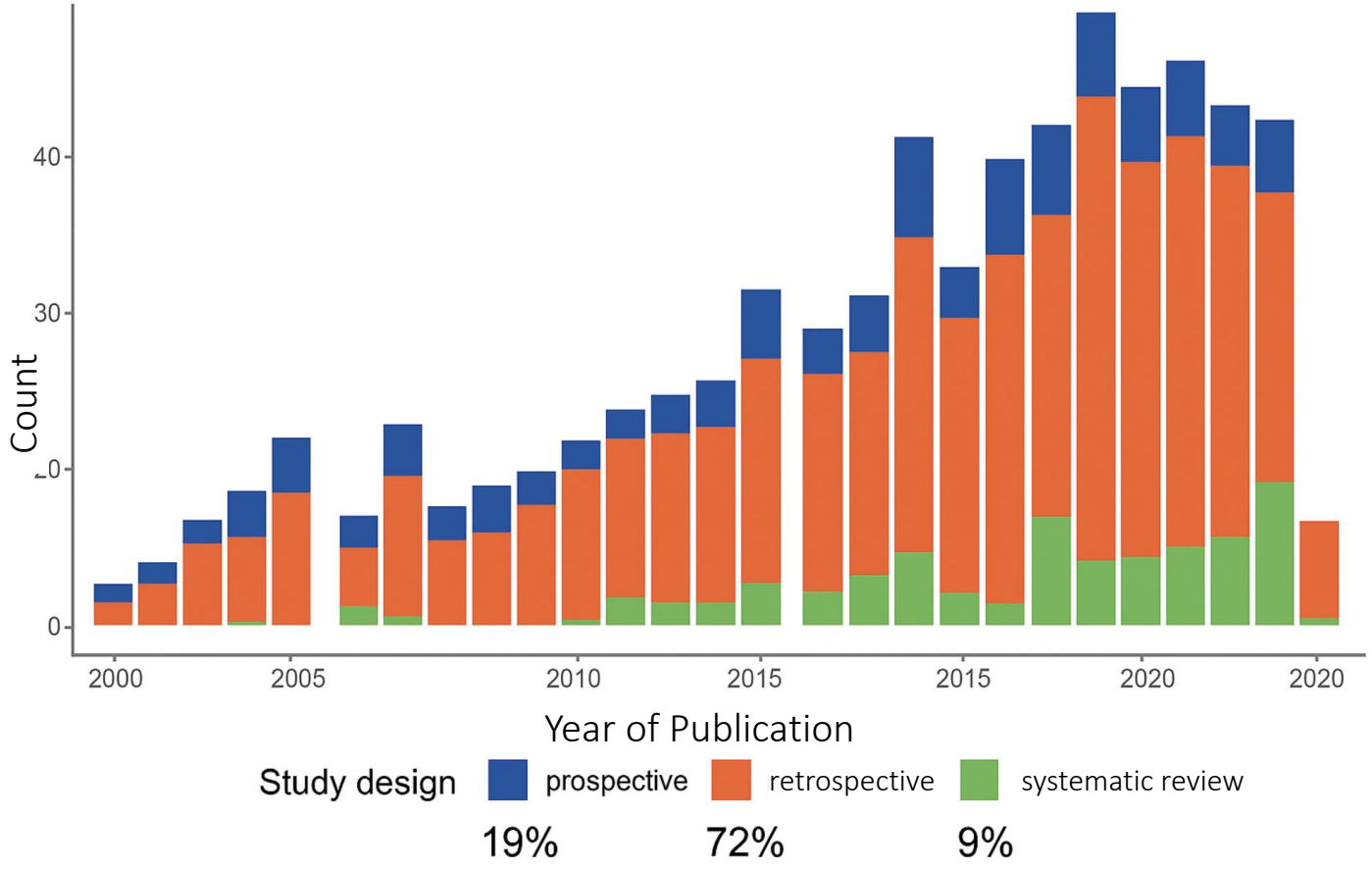
ReRT: A Growing Part of Clinical Practice

- As treatments improve and patients live longer, recurrences and second primaries are increasingly common.
- Re-irradiation is becoming a core part of modern radiation oncology
- Existing clinical and RT protocols are largely designed for de novo treatments and not reRT
- This shift introduces complex challenges we are not yet fully prepared to manage
- The radiation oncology community is actively working on developing guidelines

Learning Objectives

- Definition of reRT
- Patient Selection and Clinical Decision Making for reRT
- Evaluating Cumulative Doses to Normal Tissues
- Current clinical practice for dose accumulation and assessment
  - Limitations
  - Challenges
- Validity of the LQ Model
- Case examples of reRT, manual calculations

ReRT – Hot Topic with Low Level of Evidence

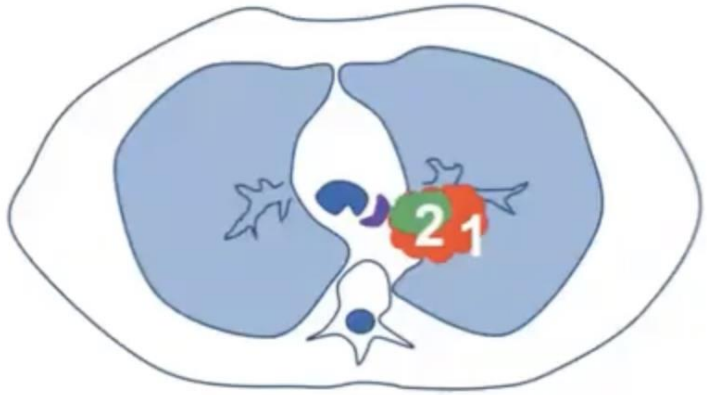


- Systematic review
- A lot of reRT publications in recent years
- Proportion of prospective data (in blue)
- Methodology for how to perform dose accumulation and report doses is limited
- Mixed cohorts, extremely heterogeneous populations
- Curative and palliative intent in the same series
- Changes is staging and normal tissue scoring
- No concise definition of reRT

Courtesy of N. Andratschke

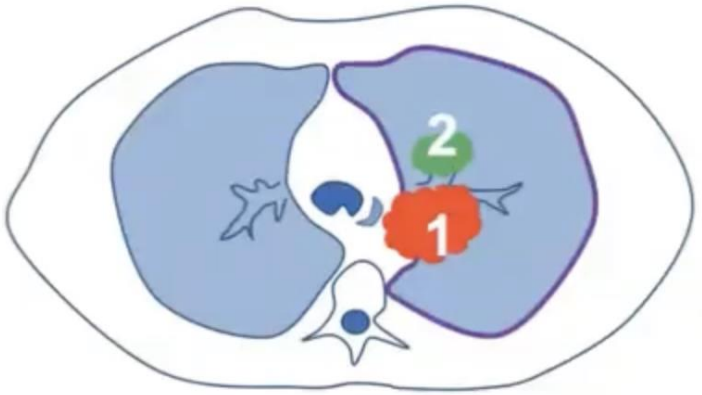
Clinical Scenarios for reRT

Full Overlap



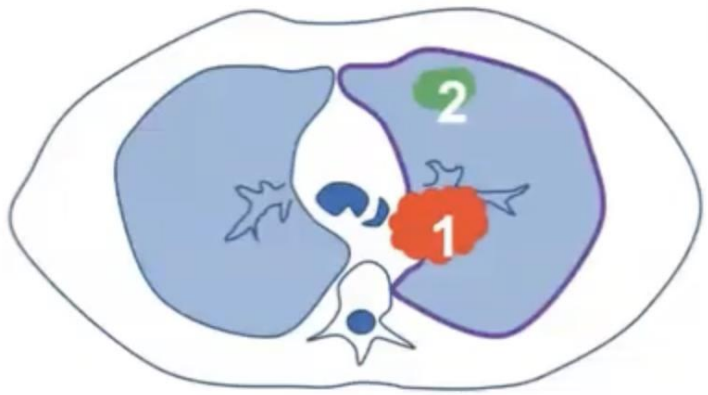
- 95% isodose lines (IDL) of the 1st and 2nd RT courses overlap

Partial Overlap



- No direct overlap of target volumes between the 1st and 2nd RT courses

No Overlap

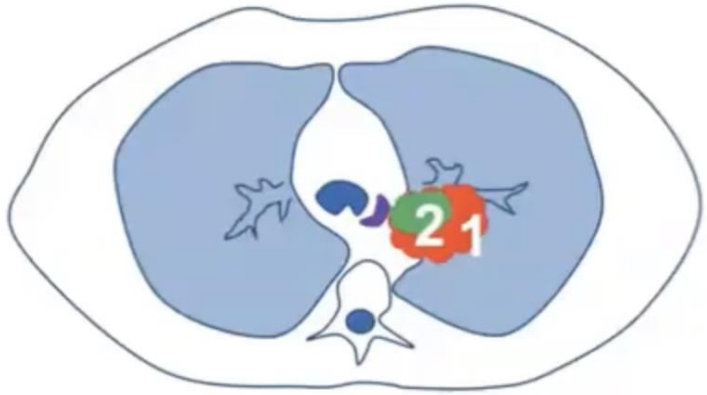


- Only 10% IDL of the 1st and 2nd RT courses overlap

Courtesy of J. Willman - ReCare Initiative

Clinical Considerations for reRT

Full Overlap



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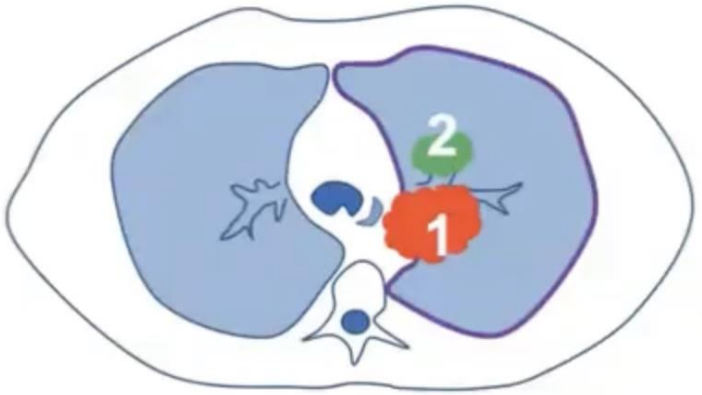

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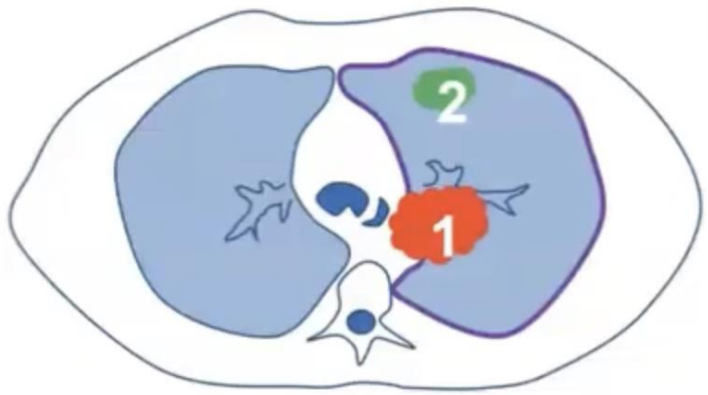


Time of recurrences is important

- Within 6 Months of Previous RT?
- Consider recovery from prior RT?
- Can we do high-dose reRT?

➢ Palliative intent still valid

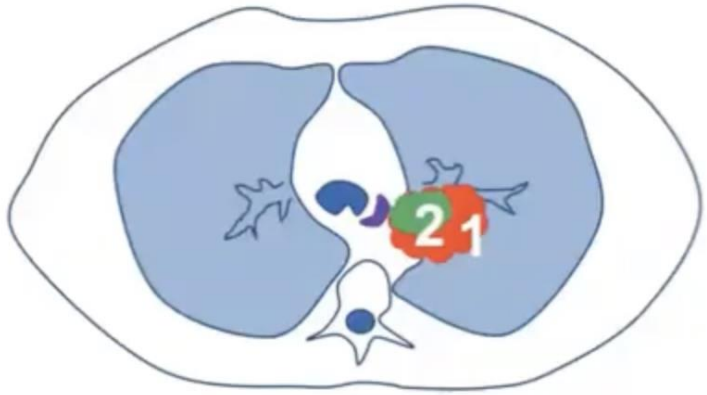
Irrespective of Time of Recurrence

- Assess for side effects from previous treatment
- Oncologic intent: palliative vs potentially curative

➢ Risk-adapted high-dose reRT may be possible

Toxicity Considerations for reRT

Full Overlap



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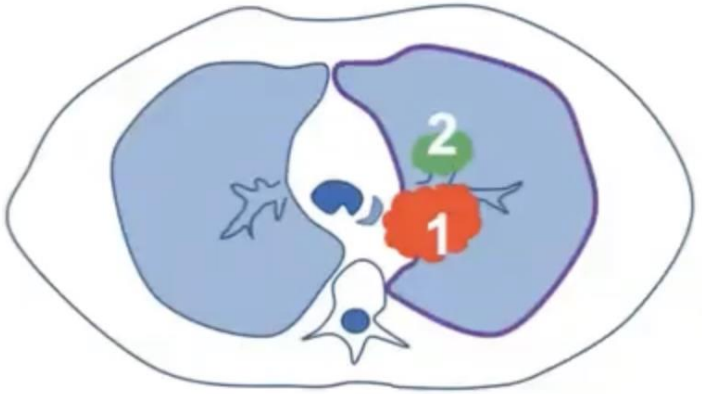
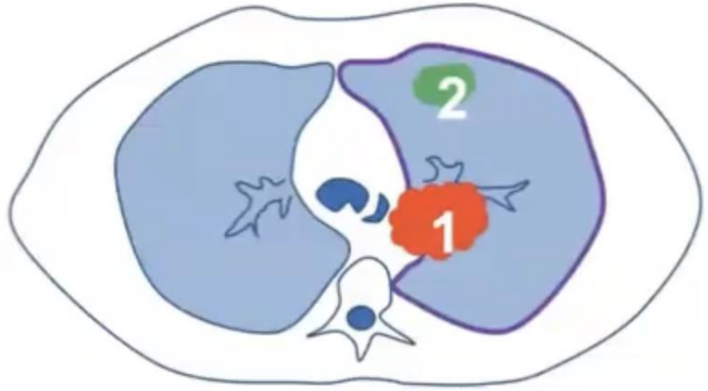


Cumulative max dose to serial organs

No Overlap



Cumulative dose spread to parallel organs – volume-based constraints

Courtesy of J. Willman - ReCare Initiative

Scope of the EORTC/ESTRO Delphi Consensus

European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making

Nicolaus Andratschke, Jonas Willmann*, Ane L Appelt, Najlaa Alyamani, Panagiotis Balermpas, Brigitta G Baumert, Coen Hurkmans, Morten Høyer, Johannes A Langendijk, Orit Kaidar-Person, Yvette van der Linden, Icro Meattini, Maximilian Niyazi, Nick Reynaert, Dirk De Ruysscher, Stephanie Tanadini-Lang, Peter Hoskin, Philip Poortmans, Carsten Nieder*

- What is reRT: searching for an universal terminology
- How can we better learn from the data: improving the reporting quality
- When do we consider high-dose reRT: applying best practices for the assessment of reRT (in absence of high-level evidence)

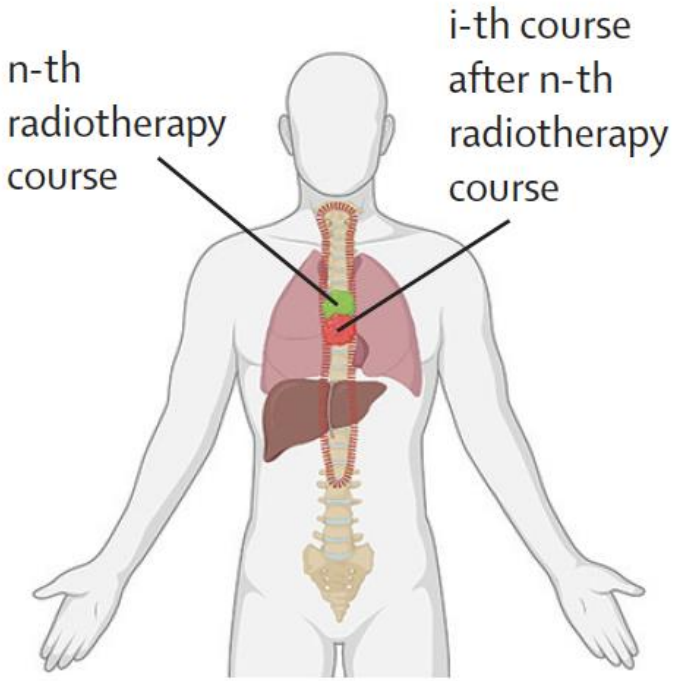
A Delphi Consensus Based Definition

"Re-irradiation is a new course of radiotherapy either to **a previously irradiated volume** (irrespective of concerns of toxicity) or **where the cumulative dose raises concerns of toxicity.**"

Andratschke et al. 2022, Lancet Oncol

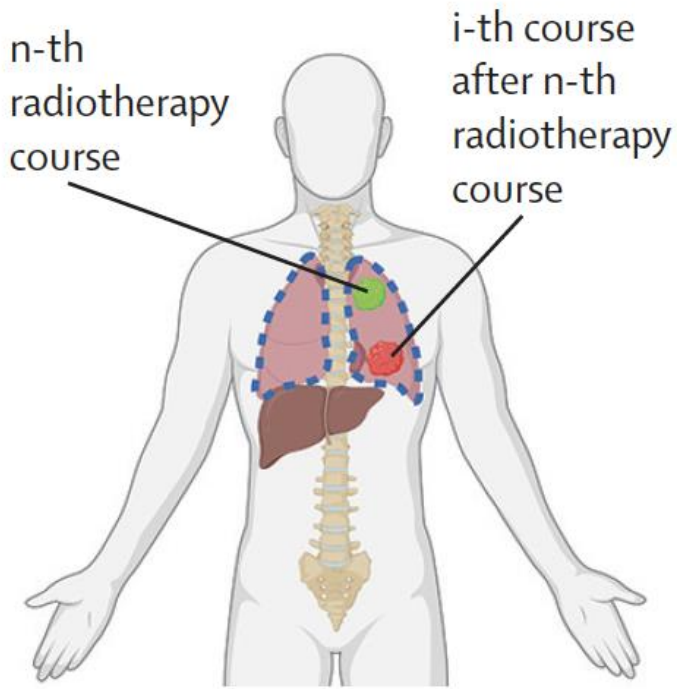
Types of ReRT

Re-irradiation Type I



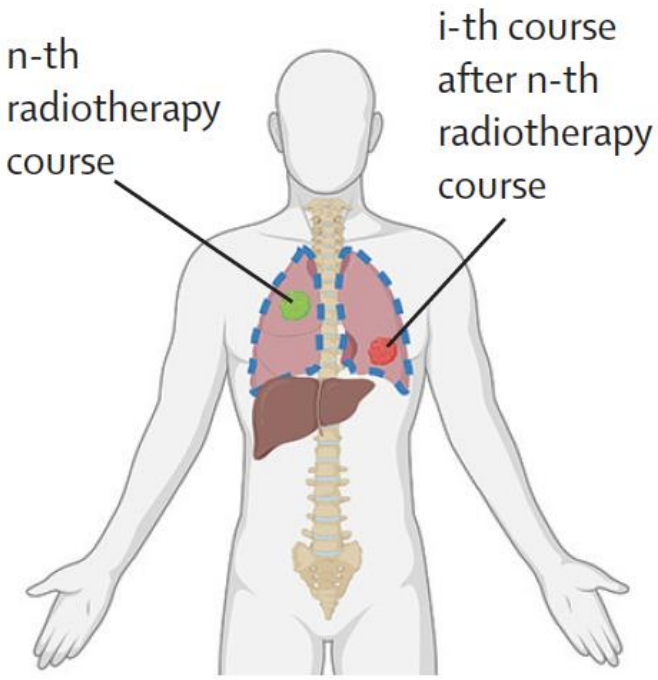
- Overlap of irradiated volumes
- With or without concern for toxicity from cumulative doses

Re-irradiation Type II



- No overlap of irradiated volumes
- Concern for toxicity from cumulative doses

Repeat Organ Irradiation

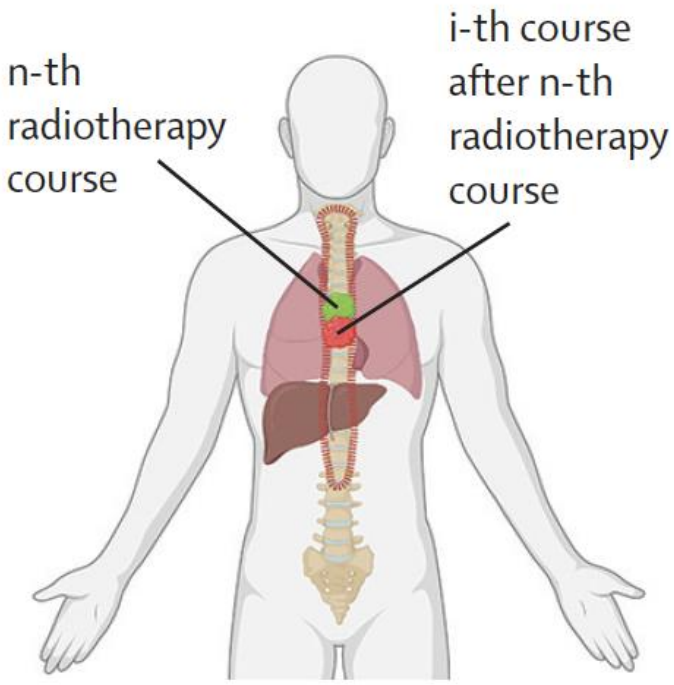


- No overlap of irradiated volumes
- No concern for toxicity from cumulative doses
- Target volumes in the same organ

Andratschke et al. 2022, Lancet Oncol

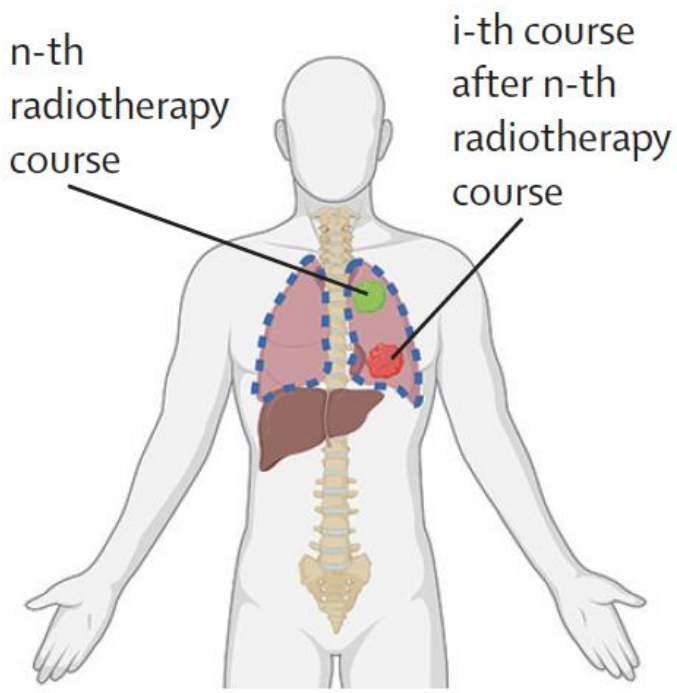
Types of ReRT

Re-irradiation Type I



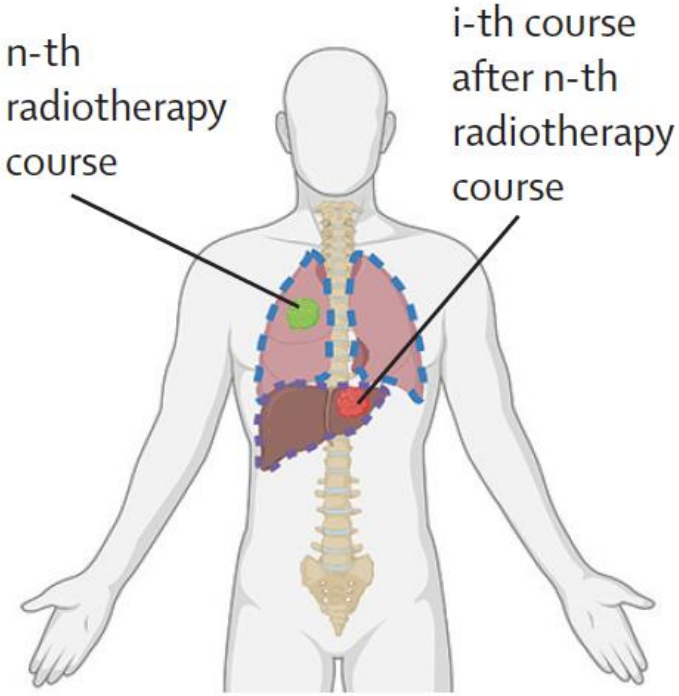
- Overlap of irradiated volumes
- With or without concern for toxicity from cumulative doses

Re-irradiation Type II



- No overlap of irradiated volumes
- Concern for toxicity from cumulative doses

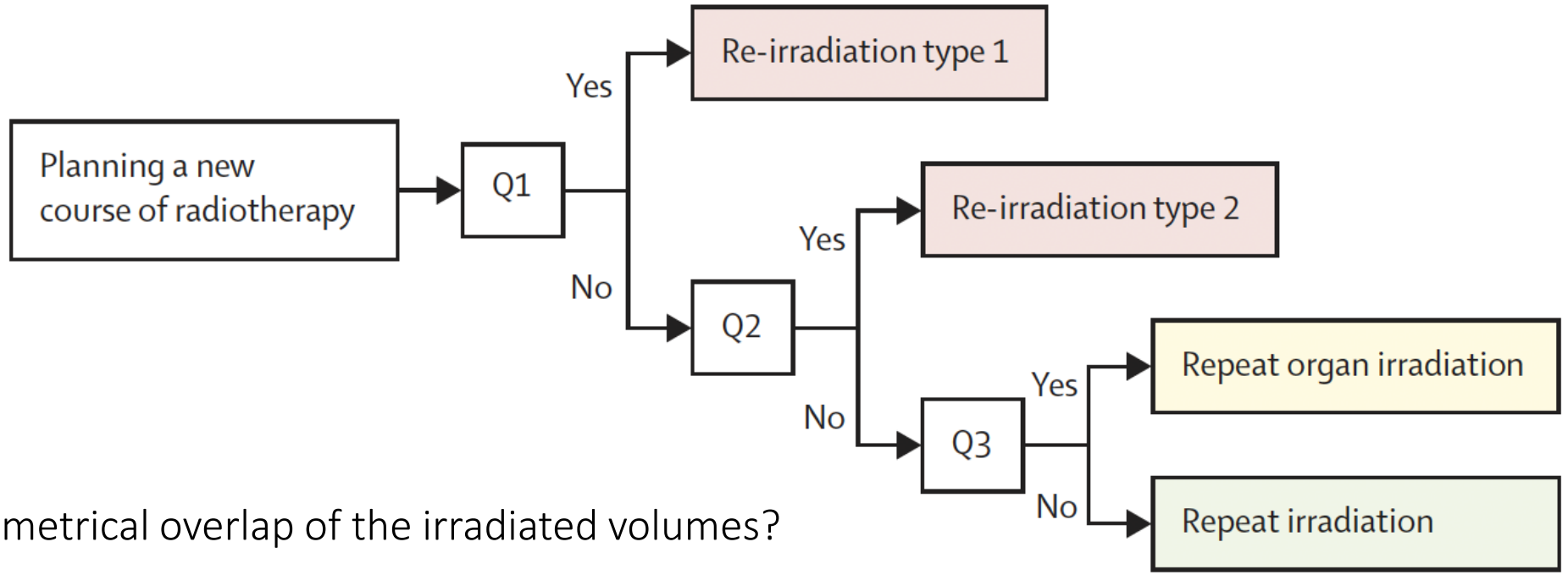
Repeat Irradiation



- No overlap of irradiated volumes
- No concern for toxicity from cumulative doses
- Target volumes in different organs

Andratschke et al. 2022, Lancet Oncol

Hierarchical question-based decision tree



Q1. Is there a geometrical overlap of the irradiated volumes?

Q2. Is there a concern for toxicity from the cumulative doses?

Q3. Are the target volumes of current and previous radiotherapy located in the same organ?

Andratschke et al. 2022, Lancet Oncol

Recommendations for clinical decision making

Interdisciplinary Management & Shared Decision-Making

- Consider treatment alternatives
- Assess life expectancy
- Evaluate patient's acceptance of risk
- Define treatment intent

Patient & Tumour-Specific Factors

- Performance status
- Estimated survival
- Persistent toxicity from first RT
- Time interval since first RT

Andratschke et al. 2022, Lancet Oncol

* Radiobiological Aspects

- Primary histology and response to first RT
- α/β values and cumulative EQD2
- Organ type: serial vs parallel

* Reirradiation-Specific Factors

- Availability of previous plans
- Dose overlap and cumulative dose
- Dose constraints for critical OARs
- Prioritization of dose constraints
- Tolerance and recovery
- Follow-up: imaging and clinical

Clinical decision Making for reRT

Radical --> Local Control

Palliative --> Symptoms Relief

Clinical Oncology 32 (2020) 688–703

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

ELSEVIER

Overview

Complex Clinical Decision-Making Process of Re-Irradiation

S. Armstrong, P. Hoskin

Mount Vernon Cancer Centre, Northwood, UK

Received 12 June 2020; received in revised form 20 July 2020; accepted 31 July 2020

Armstrong and Hoskin 2020, Clinical Oncology

Radical reRT

Optimize timing since initial treatment

- More time → better normal tissue recovery
- More time → higher risk of metastases

Minimize treated volume

Tailor dose fractionation:

- Smaller fractions → reduce late effects?
- Balance total dose: efficacy vs toxicity

Armstrong and Hoskin 2020, Clinical Oncology

Examples

- Prostate local recurrence
- Head and neck retreats
- Pelvic recurrence: uterus, cervix, rectum
- Metachronous oligometastases: liver, lung, brain

Considerations

- Choice of modality: EBRT vs SBRT vs BT

Palliative reRT

No delay in symptom relief

Focus on acute and medium-term morbidity

Volume defined by site of symptoms

Dose fractionation:

- Hypofractionation preferred
- Balance total dose: efficacy vs toxicity

Examples

- Bone metastasis (for pain relief)
- Recurrent spinal cord compression
- Dysphagia from esophageal recurrence
- NSCLC with recurrent hemoptysis
- Hematuria from bladder or prostate recurrence

Considerations

- Modality: EBRT vs SBRT vs BT

Armstrong and Hoskin 2020, Clinical Oncology

J Neurooncol (2014) 118:489–499
DOI 10.1007/s11060-013-1337-6

TOPIC REVIEW & CLINICAL GUIDELINES

The role of radiotherapy in the management of progressive glioblastoma

A systematic review and evidence-based clinical practice guideline

Samuel Ryu · John M. Buatti · Ann Morris · Steven N. Kalkanis · Timothy Charles Ryken · Jeffrey J. Olson

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Hot Topic

Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy: An ESTRO ACROP Delphi consensus

Barbara A. Jereczek-Fossa[a,b,1], Giulia Marvaso[a,b,1], Mattia Zaffaroni[a,*], Simone Giovanni Gugliandolo[a,c,d,2], Dario Zerini[a], Federica Corso[e,f], Sara Gandini[e], Filippo Alongi[g,h], Alberto Bossi[i], Philip Cornford[j], Berardino De Bari[k,l], Valérie Fonteyne[m], Peter Hoskin[n,o], Bradley R. Pieters[p], Alison C. Tree[q,r], Stefano Arcangeli[s], Donald B. Fuller[t], Ciro Franzese[u,v], Jean-Michel Hannoun-Levi[w], Guillaume Janoray[x,y], Linda Kerkmeijer[z], Young Kwok[aa], Lorenzo Livi[ab], Mauro Loi[ac], Raymond Miralbell[ad], David Pasquier[ae,af], Michael Pinkawa[ag], Nathaliel Scher[ah,ai], Marta Scorsetti[u,v], Mohamed Shelan[aj], Alain Toledano[ah,ai], Nicholas van As[ak], Andrea Vavassori[a], Thomas Zilli[al,am], Matteo Pepa[a,3], Piet Ost[m,3], on the behalf of the European Society for Radiotherapy, Oncology Advisory Committee on Radiation Oncology Practice (ESTRO ACROP)

Journal Pre-proof

American Radium Society™ Appropriate Use Criteria Systematic Review and Guidelines on Reirradiation for Non-small Cell Lung Cancer Executive Summary

Charles B. Simone II M.D. , Arya Amini M.D. , Indrin J. Chetty Ph.D. , J. Isabelle Choi M.D. , Stephen G. Chun M.D. , Jessica Donington M.D. , Martin J. Edelman M.D. , Kristin A. Higgins M.D. , Larry L. Kestin M.D. , Pranshu Mohindra M.D.,M.B.B.S. , Benjamin Movsas M.D. , George B. Rodrigues M.D. , Kenneth E. Rosenzweig M.D. , Igor I. Rybkin M.D.,Ph.D. , Annemarie F. Shepherd M.D. , Ben J. Slotman M.D.,Ph.D. , Andrea Wolf M.D. , Joe Y. Chang M.D.,Ph.D.

Seminars in Radiation Oncology
Volume 31, Issue 2, April 2021, Pages 124-132

Re-Irradiation of Recurrent Non-Small Cell Lung Cancer

Benjamin Hunter MBChB, MRes, PGDip, MRCP, FRCR * [1], Cathryn Crockett MBBCH, BAO, MRCP, FRCR † [2], Corrinne Faivre-Finn MD, PhD, FRCR †, Crispin Hiley MBChB(Hons), PhD, BSc(Hons), PGDip, MRCP, FRCR ‡ [1], Ahmed Salem MBBCH, PGCert, MSc, PhD, FRCR † [1]

APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE

Review Article

Thoracic reirradiation for lung cancer: a literature review and practical guide

C. Suzanne Drodge[1], Sunita Ghosh[2], Alysa Fairchild[1]

[1]Department of Radiation Oncology, [2]Department of Experimental Oncology, Cross Cancer Institute, Edmonton, Alberta, Canada

Correspondence to: Dr. Alysa Fairchild, BSc, MD, FRCPC. Department of Radiation Oncology, Cross Cancer Institute, 11560 University Avenue, Edmonton, AB T6G 1Z2, Canada. Email: alysa@ualberta.ca.

Critical Review

International Recommendations on Reirradiation by Intensity Modulated Radiation Therapy for Locally Recurrent Nasopharyngeal Carcinoma

Wai Tong Ng, FRCR,* Yoke Lim Soong, FRCR,† Yong Chan Ahn, MD,‡ Hussain AlHussain, FRCPC,§ Horace C.W. Choi, PhD,* June Corry, FRANZCR,‖ Vincent Grégoire, MD,¶ Kevin J. Harrington, FRCR,# Chao Su Hu, MD, Kenneth Jensen, PhD,†† Dora L. Kwong, FRCR,‡‡ Johannes A. Langendijk, MD,§§ Quynh Thu Le, MD,‖‖ Nancy Y. Lee, MD,¶¶ Jin Ching Lin, MD,## Tai Xiang Lu, MD,*** William M. Mendenhall, MD,††† Brian O'Sullivan, FRCR,‡‡‡ Enis Ozyar, MD,§§§ Jian Ji Pan, MD,‖‖‖ Lester J. Peters, FRANZCR,¶¶¶ Sharon S. Poh, FRCR,† David I. Rosenthal, MD,### Giuseppe Sanguineti, MD,**** Yungan Tao, MD,†††† Joseph T. Wee, FRCR,† Sue S. Yom, MD,‡‡‡‡ Melvin L.K. Chua, FRCR,† and Anne W.M. Lee, FRCR§§§§**

HyTEC Organ-Specific Paper: Spinal Cord

Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy

Arjun Sahgal, MD,* Joe H. Chang, MBChB, PhD,* Lijun Ma, PhD,† Lawrence B. Marks, MD,‡ Michael T. Milano, MD, PhD,§ Paul Medin, PhD,‖ Andrzej Niemierko, PhD,¶ Scott G. Soltys, MD,# Wolfgang A. Tomé, PhD, C. Shun Wong, MD,* Ellen Yorke, PhD,†† Jimm Grimm, PhD,‡‡ and Andrew Jackson, PhD††**

Radiotherapy and Oncology 118 (2016) 122–130

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

s study on salvage brachytherapy for prostate cancer herapy, a Uro-GEC study

ley R. Pieters[a], György Kovács[b], Peter J. Hoskin[c]

msterdam, Amsterdam, The Netherlands; [b] Interdisciplinary Brachytherapy Unit, University of Lübeck, Germany; and [c] Mount Vernon Cancer

Radiotherapy and Oncology 164 (2021) 104–114

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ation

national Delphi consensus for pelvic stereotactic ablative rapy re-irradiation

in[a,b,*], Katharine Aitken[c,d], Filippo Alongi[e,f], Stefano Arcangeli[g], Eliot Chadwick[h], ang[i], Patrick Cheung[j], Christopher Crane[k], Matthias Guckenberger[l], cja Jereczek-Fossa[m,n], Sophia C. Kamran[o], Rémy Kinj[p], Mauro Loi[q], Anand Mahadevan[r], Massaccesi[s], Lucas C. Mendez[t], Rebecca Muirhead[u], David Pasquier[v,w], Antonio Pontoriero[x], pratt[y], Yat Man Tsang[z], Michael J. Zelefsky[k], John Lilley[a], Peter Dickinson[a], Maria A. Hawkins[aa], ıry[a,b], Louise J. Murray[a,b]

Radiation Oncology UNIVERSITY OF TORONTO | Temerty Medicine | UHN Princess Margaret Cancer Centre

Clinical and Experimental Radiobiology Course 2025

Evaluating Doses to Normal Tissue

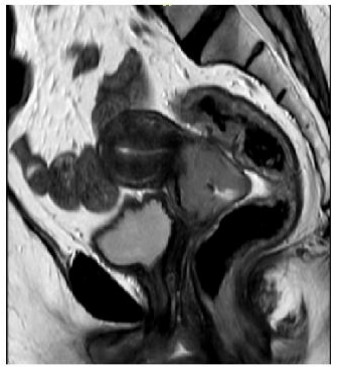
More Complex

Less Complex

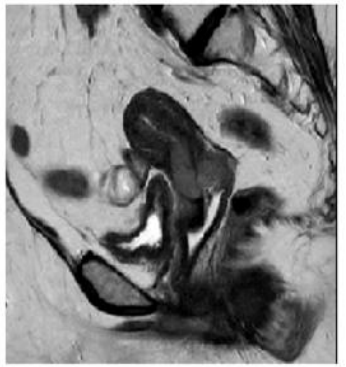
- EQD2 Dose Summation based on Deformable Image Registration
- Physical Dose Transfer
- Isodose Line Transfer

} based on Rigid Image Registration

- Sum of Maximum OAR doses
- Sum of Dose Prescriptions



Diagnosis



1st Recurrence

What is Considered Best Practice?

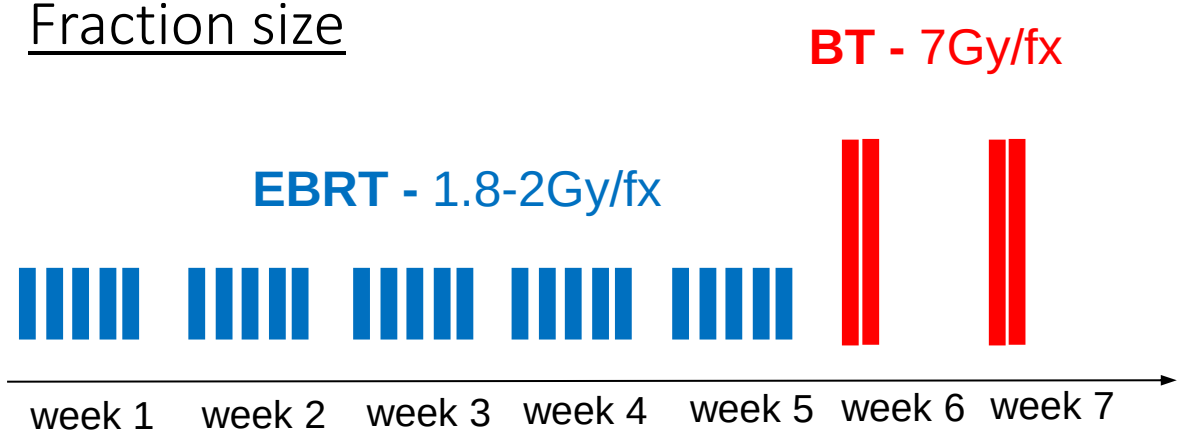
"If high-dose reRT is considered, access to full information on previous treatments, including imaging, treatment plans, and dose distributions is strongly recommended for assessing cumulative dose summation.

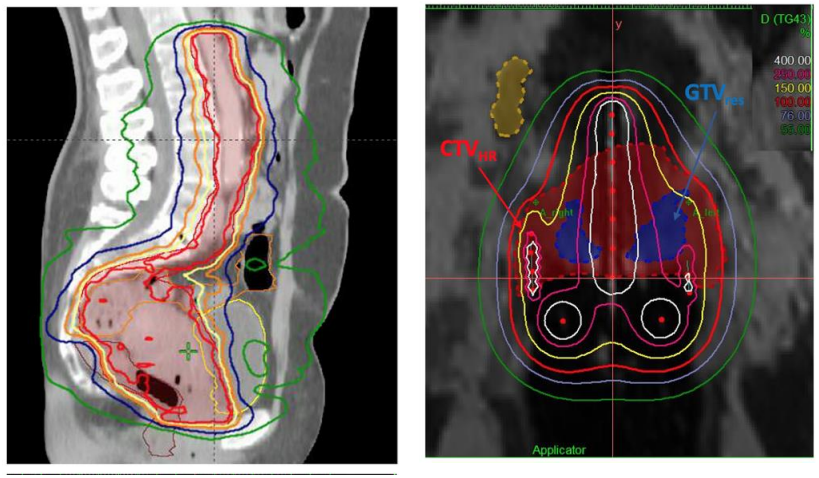
Biologically equieffective doses (eg, EQD2 or BED) should be calculated when doing dose summations of treatment plans"

Andratschke et al. 2022, Lancet Oncol

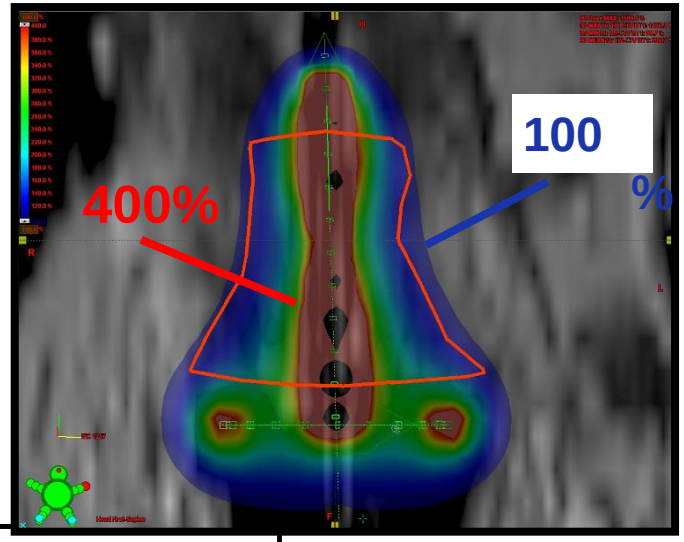
Dose Accumulation Considerations

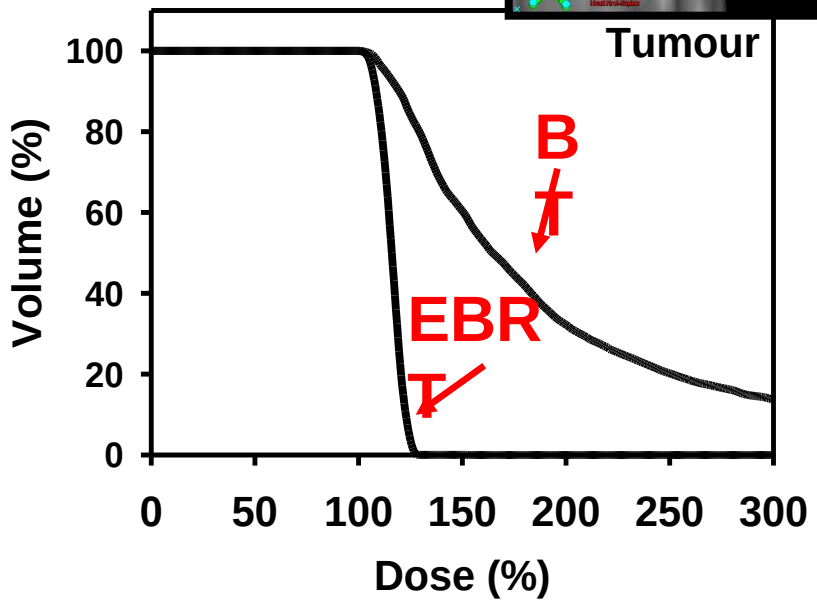
Fraction size





Dose gradient





To put variable fractionations onto equal footing,

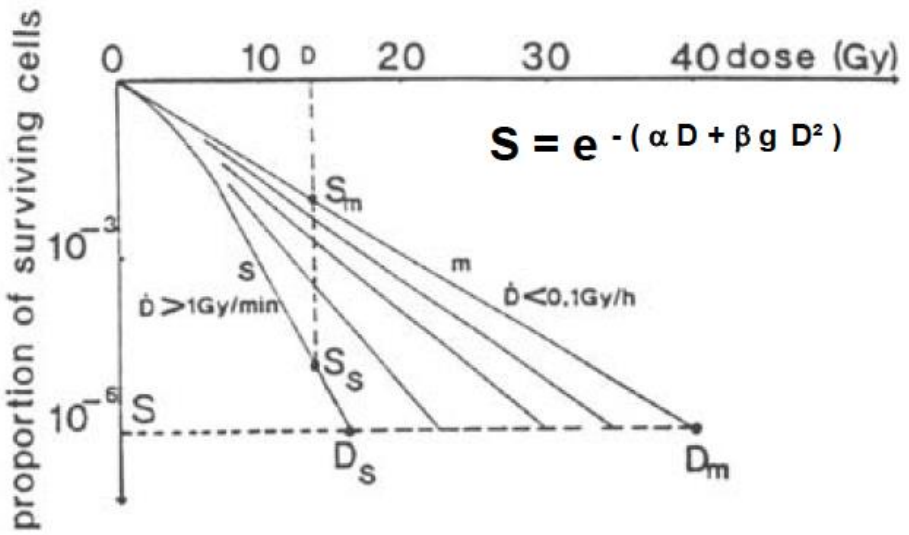
a biological dose correction is needed

From Absorbed to Biologically Equieffective Dose Linear Quadratic Model

$$BED = nd\left[1 + g\frac{d}{\alpha/\beta}\right]$$

BED – virtual dose value that produces the same biological effect as the physical dose with an infinite low dose rate

n – number of equal fractions
d – dose per fraction
g – repair function depending on:
- half time for cell repair $T_{1/2}$
- fractionation



Practical Manual of Brachytherapy, Pierquin/Marinello

The Equieffective Absorbed Dose Concept – EQDX

- The "equieffective" absorbed dose: concept used for comparing the clinical effects of physical doses delivered to the PTV and OARs using two or more different fractionation schedules

$$\mathrm{EQDX}_{\alpha/\beta} = D \cdot \frac{d + \alpha/\beta}{X + \alpha/\beta}$$

α/β is an endpoint- and radiation quality-specific parameter that describes the effect of changes in dose per fraction

- **Equieffective dose**s are defined as absorbed doses that, when delivered under specified but different conditions produce the **same probability of a specific radiation effect or endpoint.**
- Why EQD2? – Because of the large body of clinical experience gathered with fractions of 2 Gy, it is common to assume a reference protocol using photons in 2 Gy fractions in the EQDX formula and define EQD2 as "EQuivalent Dose in 2 Gy fractions".

Bentzen et al., 2012 Radiotherapy and Oncology

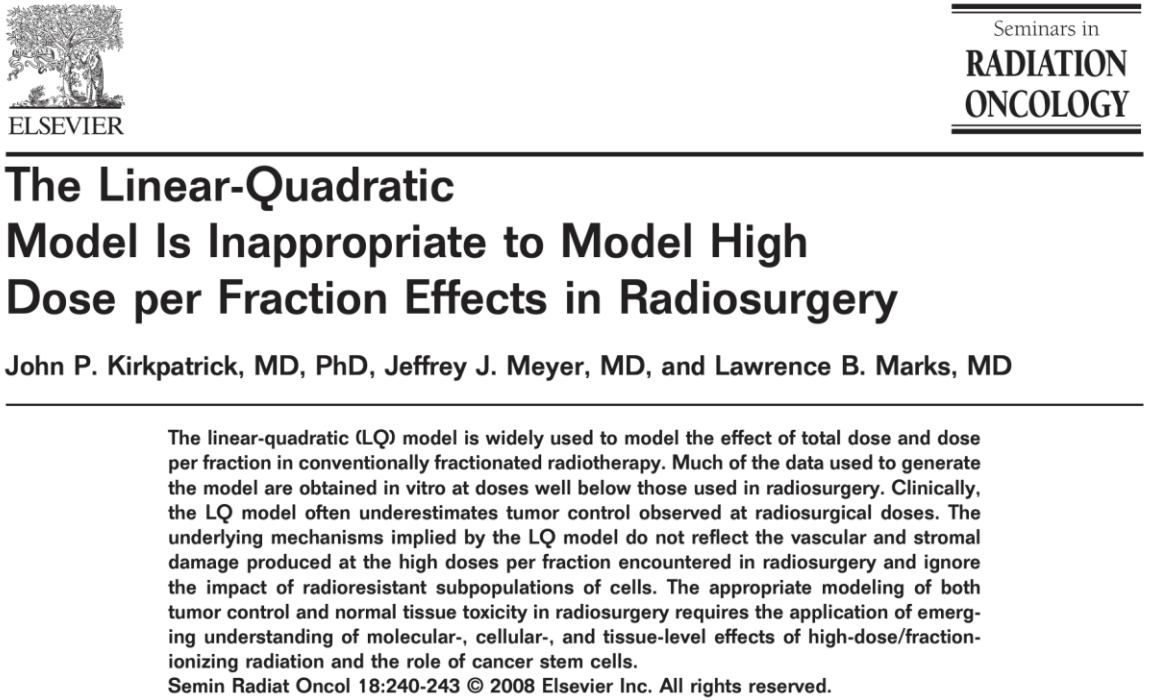
2-Gy Fraction Conditions

- LQ model gives biological equivalence for
  1. Classical LDR brachytherapy (50 cGy/h) with $T_{1/2}$ = 1.5 h
  2. Conventional external beam therapy with 2 Gy/fraction

- Calculated BED are normalized to conventional EBRT with 2 Gy fractions

$$\mathrm{EQD2} = \mathrm{nd}\,\frac{\left[1+\frac{\mathrm{d}}{\alpha/\beta}\right]}{1+\frac{2}{\alpha/\beta}} = \mathrm{nd}\,\frac{\mathrm{d}+\alpha/\beta}{2+\alpha/\beta}$$

LQ model validity at large dc



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

- Mechanistic and biologically based
- Simple: few parameters, practical to a
- Predicts similar fractionation effects a
- Strong predictive value for dose-rate and fractionation effects in lab studies
- Experimentally and theoretically validated up to ~10 Gy/fraction
- Reasonable use up to ~18 Gy/fraction
- No clinical evidence of major issues when used appropriately

Brenner et al. 2008, Semin Rdiat Oncol

α/β ratios for human normal tissues and tumors

Table 9.1 Fractionation sensitivity of human normal tissues and tumours

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Early reactions				
Skin	Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
	Erythema	12.3	1.8; 22.8	Bentzen *et al.* (1988)
	Dry desquamation	~8	N/A	Chogule and Supe (1993)
	Desquamation	11.2	8.5	
Oral mucosa	Mucositis	9.3	5.8	
	Mucositis	15	−1	
	Mucositis	~8	N/	
Late reactions				
Skin/vasculature	Telangiectasia	2.8	1.7	
	Telangiectasia	2.6	2.2	
	Telangiectasia	2.8	−0	
Subcutis	Fibrosis	1.7	0.6	
Breast	Cosmetic change in appearance	3.4	2.3	
	Induration (fibrosis)	3.1	1.8; 4.4	Yarnold *et al.* (2005)
Muscle/vasculature/ cartilage	Impaired shoulder movement	3.5	0.7; 6.2	Bentzen *et al.* (1989)
Nerve	Brachial plexopathy	<3.5*	N/A	Olsen *et al.* (1990)
	Brachial plexopathy	~2	N/A	Powell *et al.* (1990)
	Optic neuropathy	1.6	−7; 10	Jiang *et al.* (1994)

Table 9.1 Fractionation sensitivity of human normal tissues and tumours

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Spinal cord	Myelopathy	<3.3	N/A	Dische *et al.* (1981)
Eye	Corneal injury	2.9	−4; 10	Jiang *et al.* (1994)
Bowel	Stricture/perforation	3.9	2.5; 5.3	Deore *et al.* (1993)
Bowel	Various late effects	4.3	2.2; 9.6	Dische *et al.* (1999)
Lung	Pneumonitis	4.0	2.2; 5.8	Bentzen *et al.* (2000)
		3.1	−0.2; 8.5	Dubray *et al.* (1995)
		3.5	1.1; 5.9	Rezvani *et al.* (1991)
		4.0	3.3; 5.0	Stuschke and Thames (1999)
		3.8	0.8; 14	Maciejewski *et al.* (1986)
		0.8	−0.6; 2.5	Maciejewski *et al.* (1990)
		10.5	6.5; 29	Stuschke and Thames (1999)
		14.5*	4.9; 24	Rezvani *et al.* (1993)
		~13	'wide'	Robertson *et al.* (1993)
		6.6	2.9; ∞	Maciejewski *et al.* (1989)
Tonsil		7.2	3.6; ∞	Maciejewski *et al.* (1989)
Nasopharynx		16	−11; 43	Lee *et al.* (1995)
Skin		8.5*	4.5; 11.3	Trott *et al.* (1984)
Prostate†		1.1	−3.3; 5.6	Bentzen and Ritter (2005)
Breast		4.6	1.1; 8.1	START Trialists Group (2008)
Oesophagus		4.9	1.5; 17	Geh *et al.* (2006)
Melanoma		0.6	−1.1; 2.5	Bentzen *et al.* (1989)
Liposarcoma		0.4	−1.4; 5.4	Thames and Suit (1986)

CL, confidence limit

Mean Late 2.9 Gy
Mean Early 10.6 Gy
H&N, Lung tumors high
Breast , Prostate tumors low

Basic Clinical Radiobiology, Fourth Edition, Joiner and Van der Kog

α/β ratio describes tissue repair capacity (tumour and late responding tissues) under the assumption of full repair

Evaluating Doses to Normal Tissue

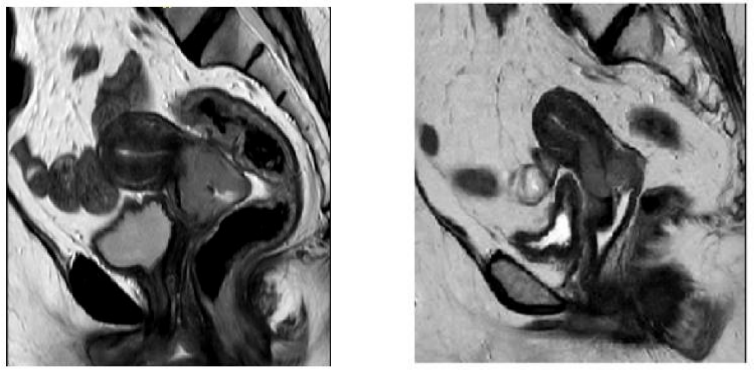
More Complex

Less Complex

- EQD2 Dose Summation based on Deformable Image Registration
- Physical Dose Transfer
- Isodose Line Transfer

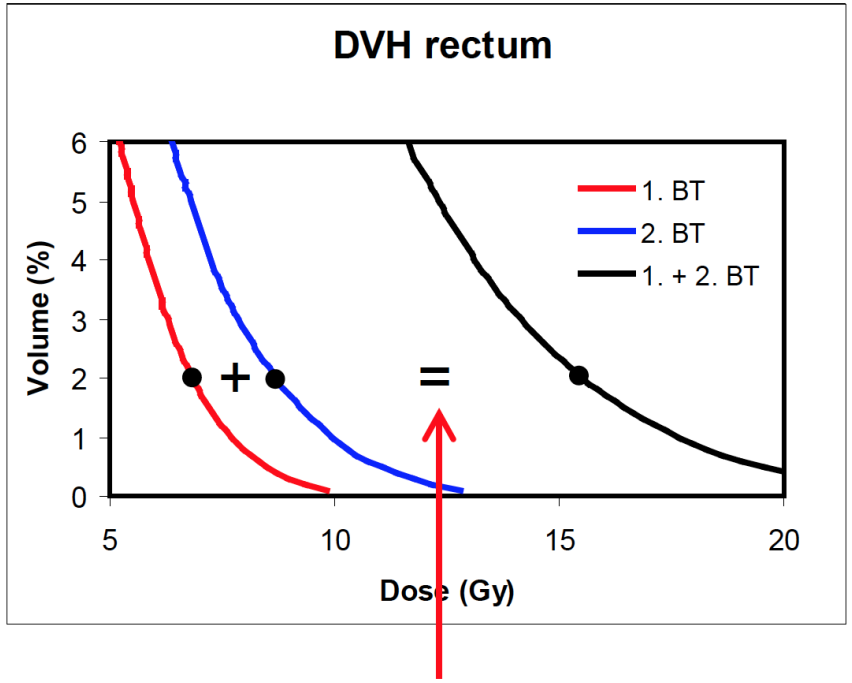
} based on Rigid Image Registration

- Sum of Maximum OAR doses
- Sum of Dose Prescriptions



1st Recurrence

DVH Parameter Addition: Worst Case Scenario



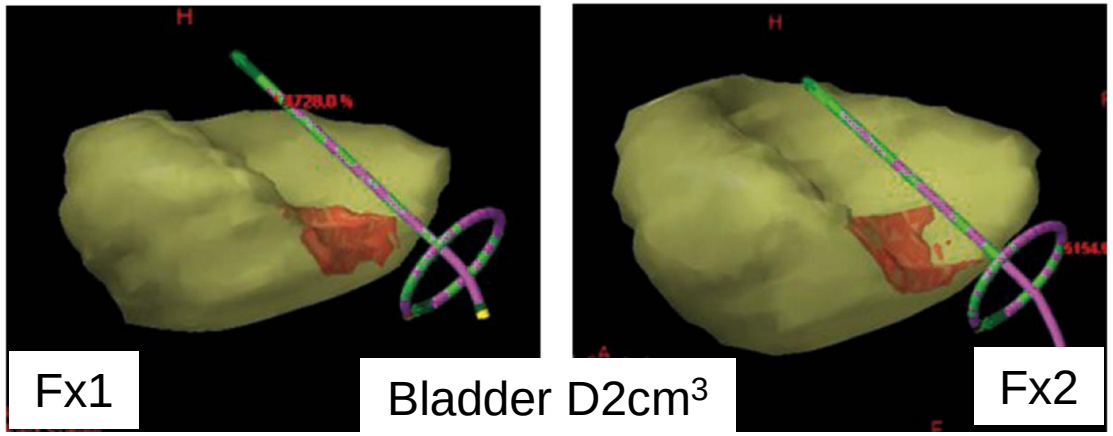
Approximation: DVH Addition

Is adding a DVH parameter a correct assumption?

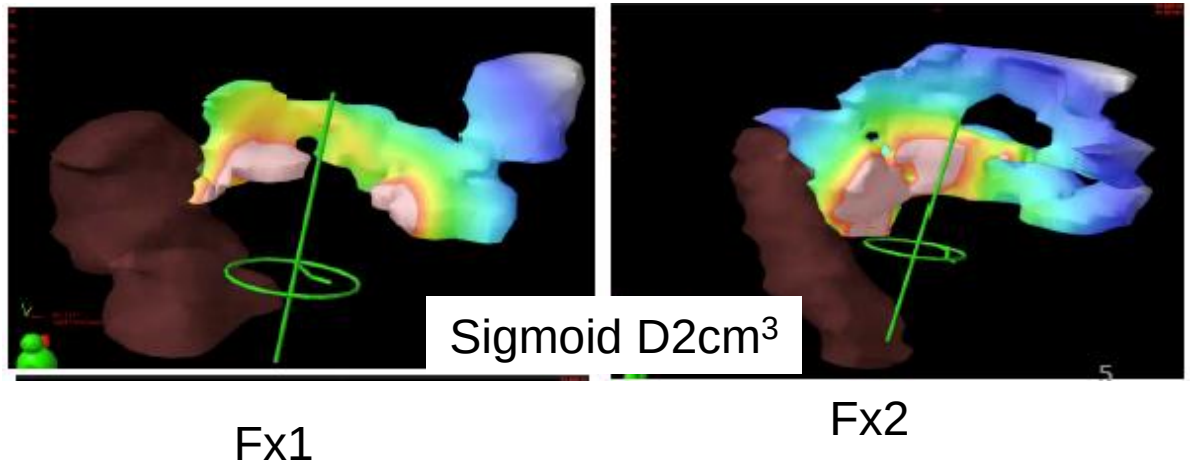
EQD2 Direct Dose Summation – Does it work?

Worst Case Scenario:

- Assumes hot spots in the organ are at the same location across fractions
- Limited to max doses, hot spot doses (e.g., D2cm^3)
- Hotspots cannot explain the entire morbidity dose-effects

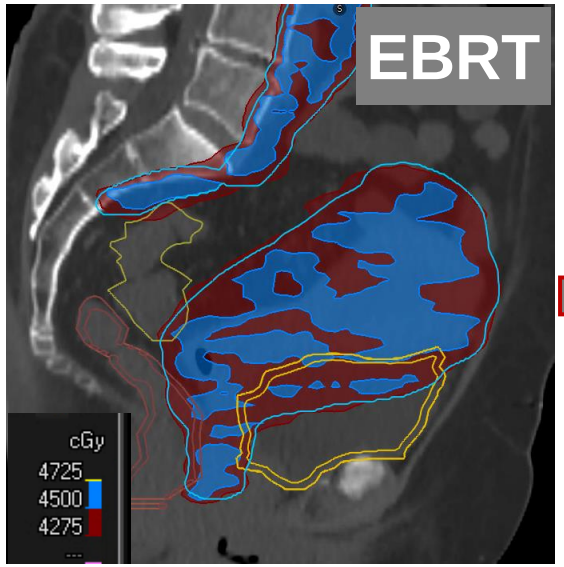


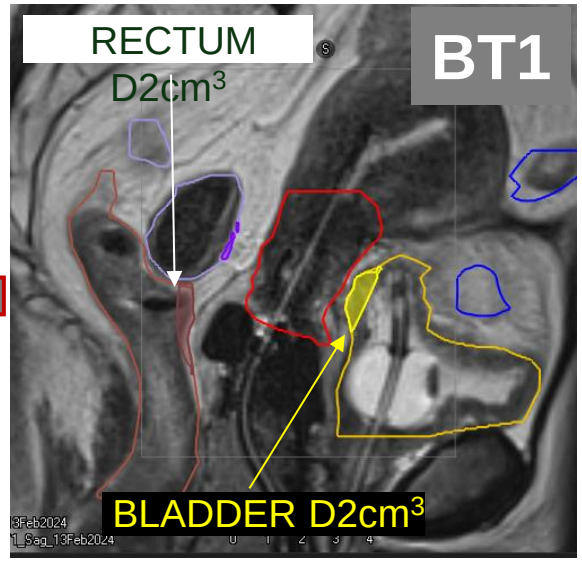
Mahantshetty et al., Brachytherapy 2017

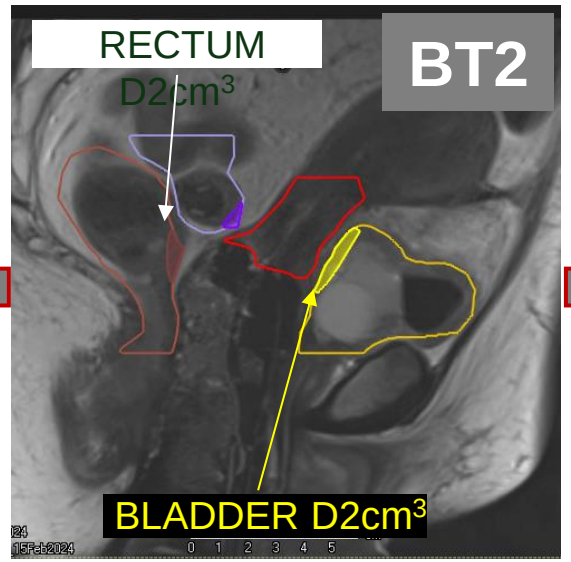


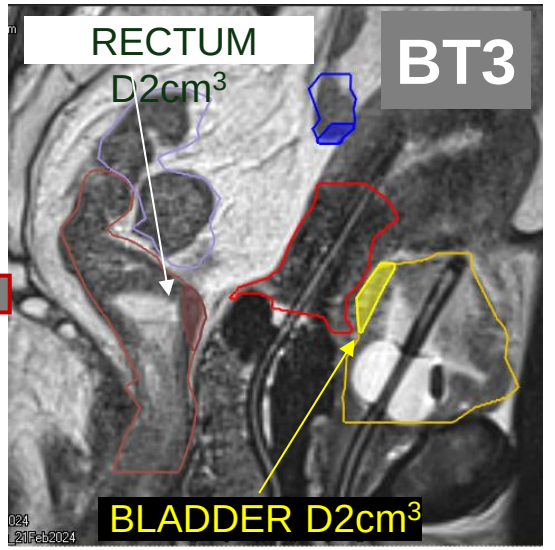
Courtesy of Dr. Kari Tanderup

EQD2 Direct Dose Summation – Does it work?





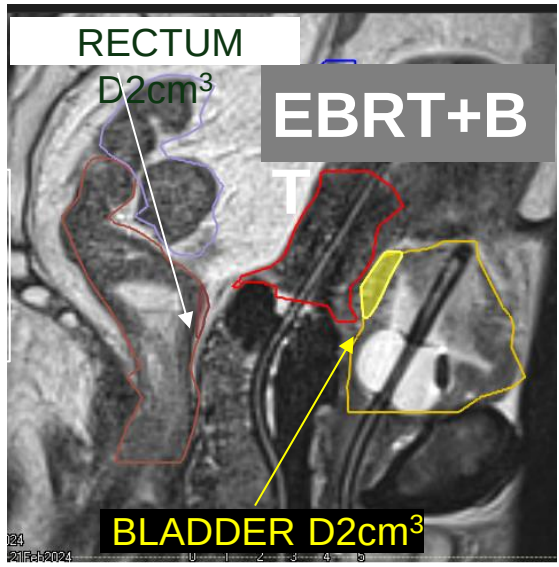




DIRECT DOSE SUMMATION **DIR*-based 3D DOSE SUMMATION**

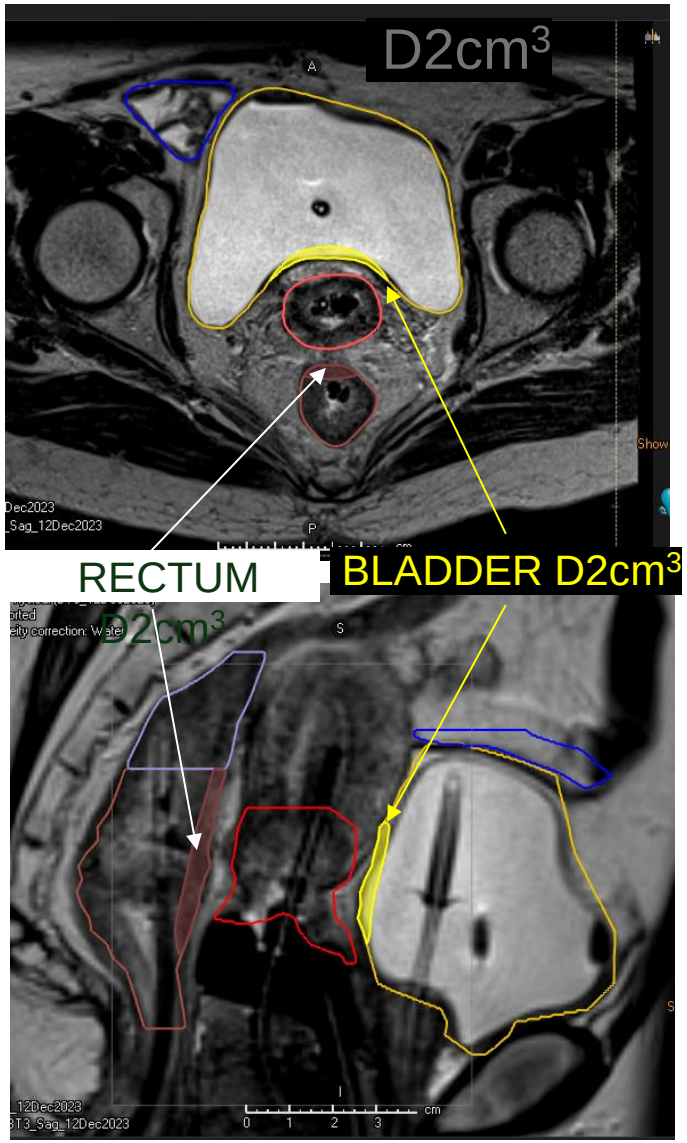
Bladder D2cm³	72Gy $EQD2_3$	71Gy $EQD2_3$
Rectum D2cm³	51Gy $EQD2_3$	48Gy $EQD2_3$
Sigmoid D2cm³	68Gy $EQD2_3$	68Gy $EQD2_3$

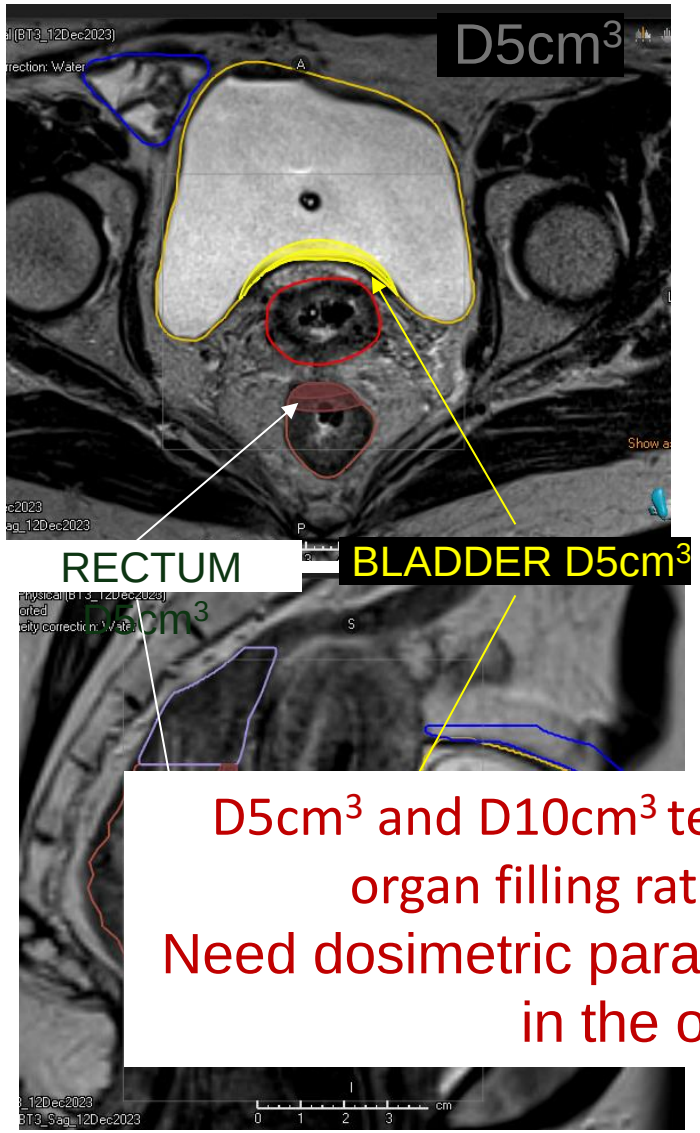
=

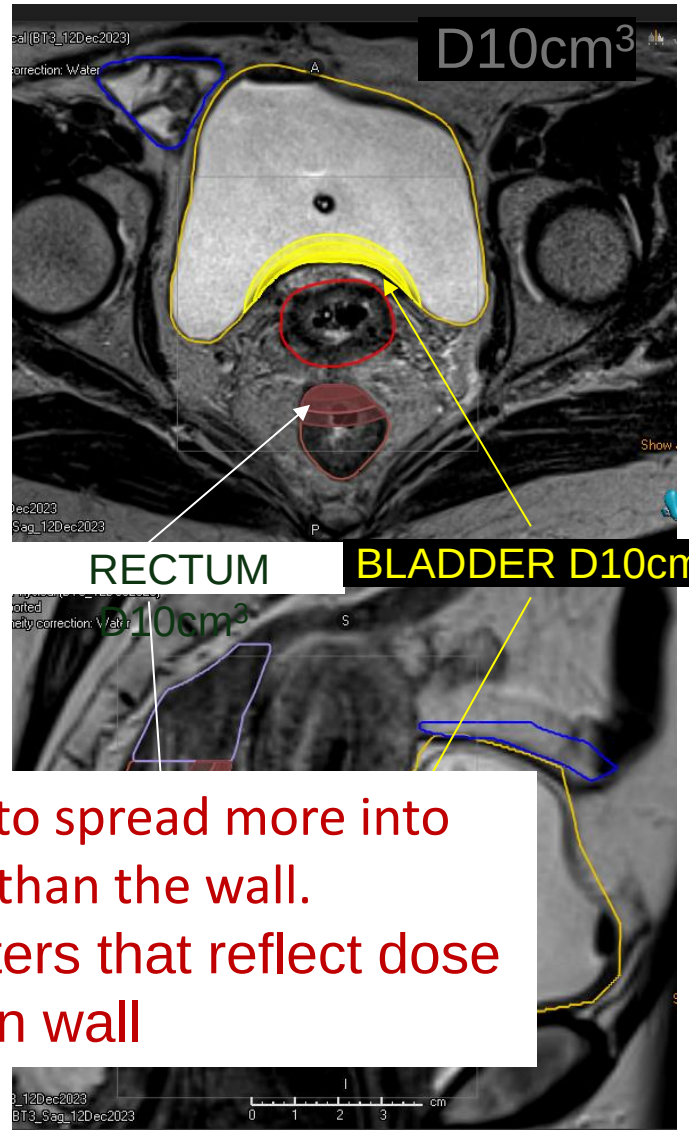


Hybrid intensity/contour-based algorithm to deform images and map doses in RS

Organ volumes irradiated with intermediate doses







D5cm^3 and D10cm^3 tend to spread more into organ filling rather than the wall.
Need dosimetric parameters that reflect dose in the organ wall

Evaluating Doses to Normal Tissue

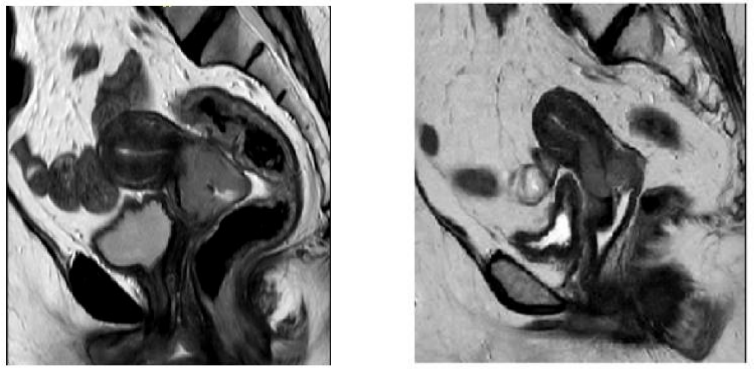
More Complex

Less Complex

- EQD2 Dose Summation based on Deformable Image Registration
- Physical Dose Transfer
- Isodose Line Transfer

based on Rigid Image Registration

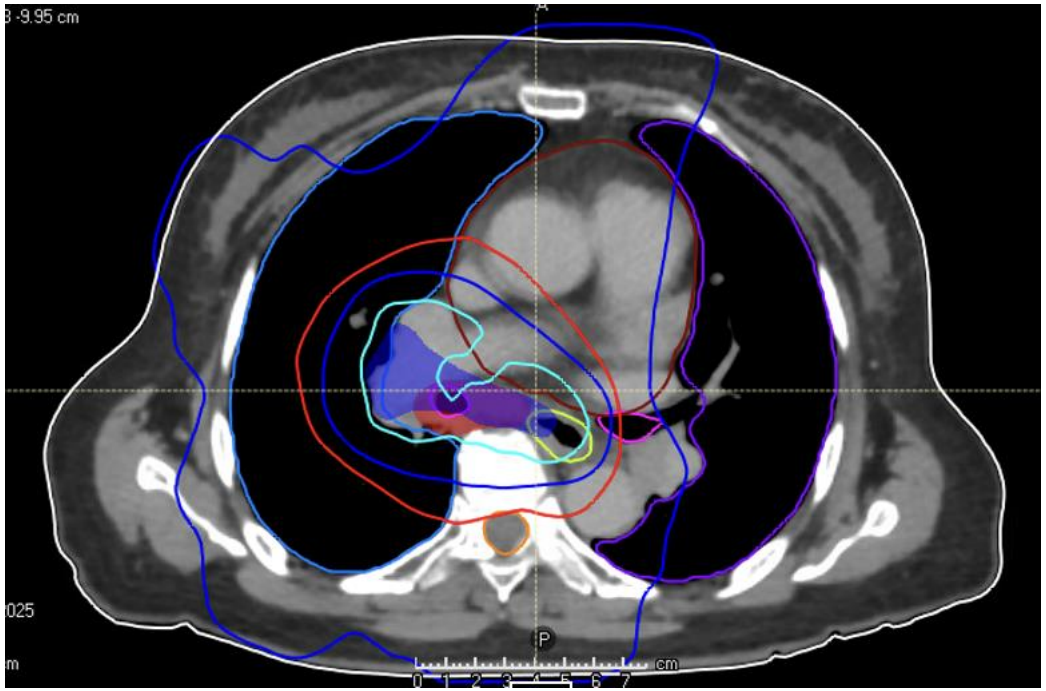
- Sum of Maximum OAR doses
- Sum of Dose Prescriptions

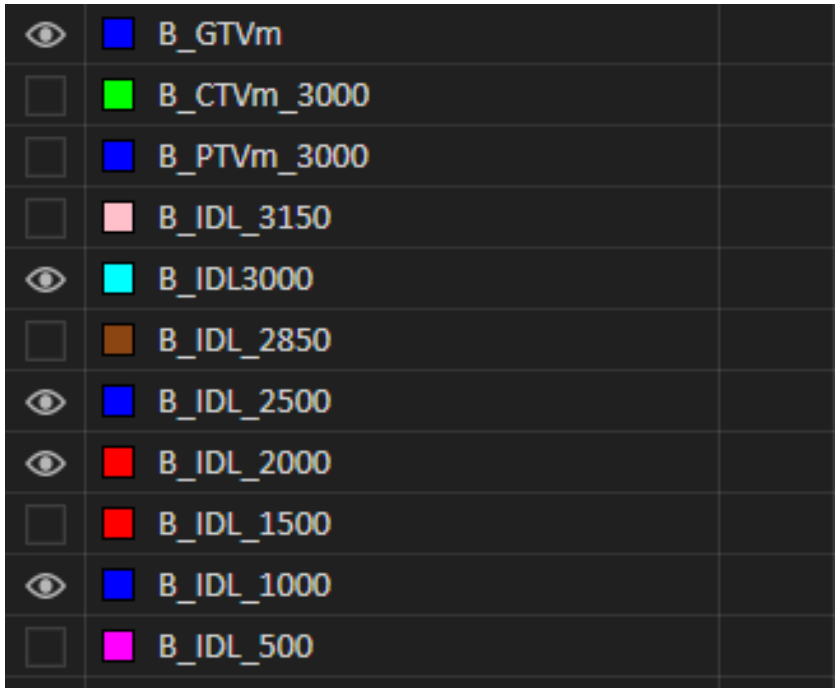


1st Recurrence

Isodose Line Transfer

- Isodose lines (IDLs) are converted to iso-contours representing clinically relevant doses
- Iso-contours are transferred to the current scan via rigid registration
- Prior dose is assessed only at contour locations—no full 3D dose distribution available





Evaluating Doses to Normal Tissue

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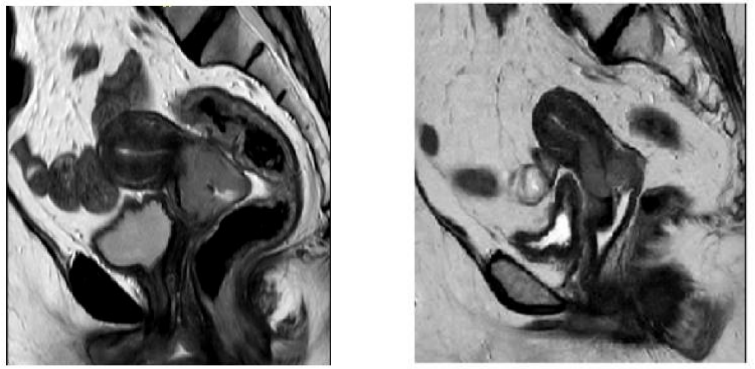
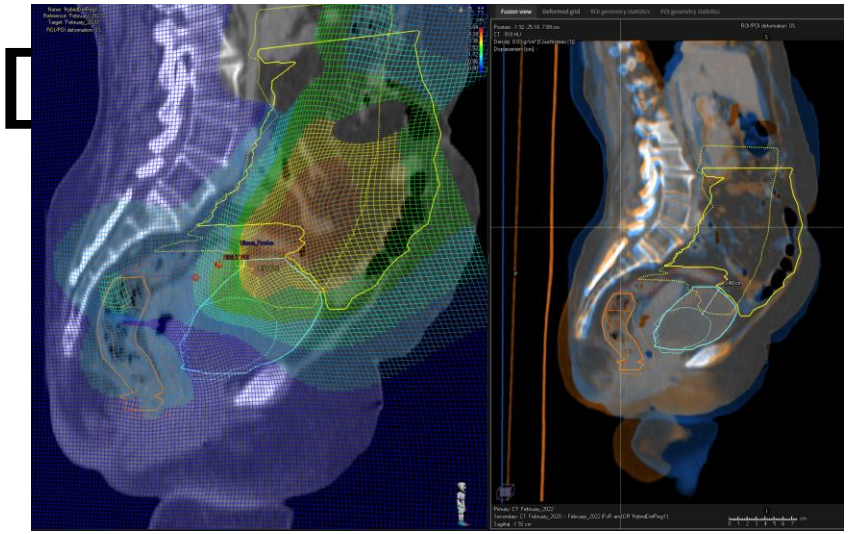
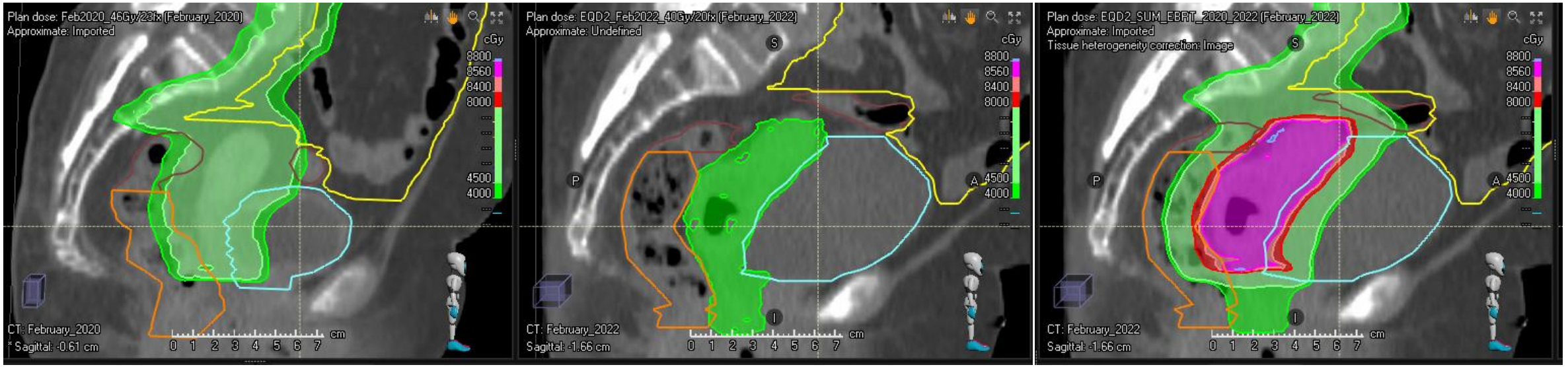


1st Recurrence

Dose Summation based on D



- 3D dose distribution is converted to EQD2 on a voxel-by-voxel basis
- DIR to align the previous and current scans
- DIR used to transfer the previous dose distribution onto the current scan



2020 scan | 2022 scan | 2022 scan SUM dose

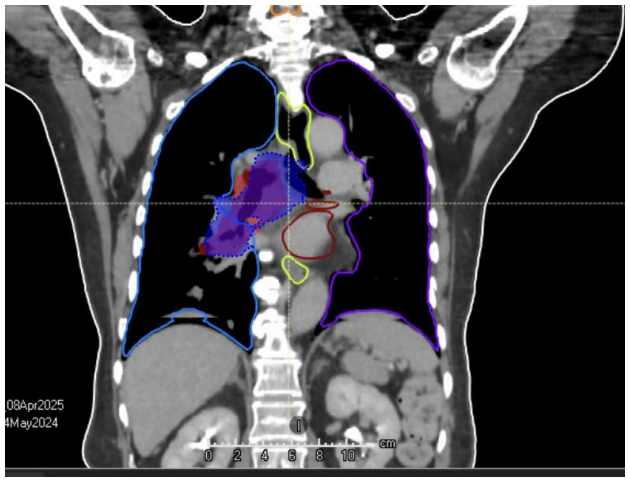
Case Examples

Case – 177 y/o F, Submand Gland AdenoCa, T2N0

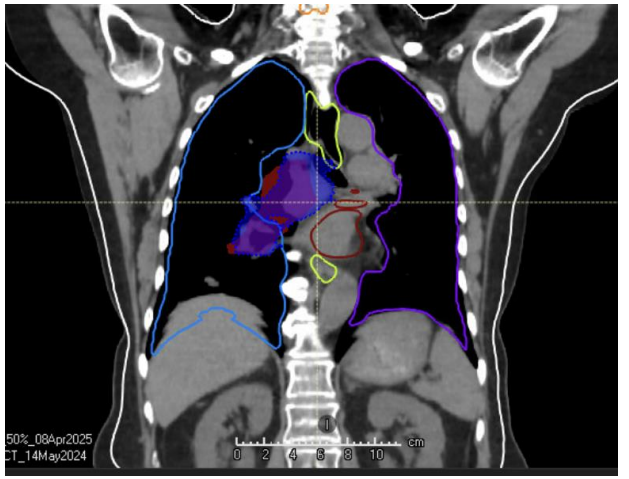
- Sept 2021: Submandibular Gland, Adenocarcinoma
  - H&N VMAT 66Gy/33 fx
- May 2024: Mediastinum met
  - Main bronchus IMRT 30Gy/10fx
- June 2024: Pelvic bone met
  - Pelvic VMAT 25Gy/5fx

Intent to treat with

- April 2025: Recurrence mediastinum met
  - Main bronchus VMAT 25Gy/5fx



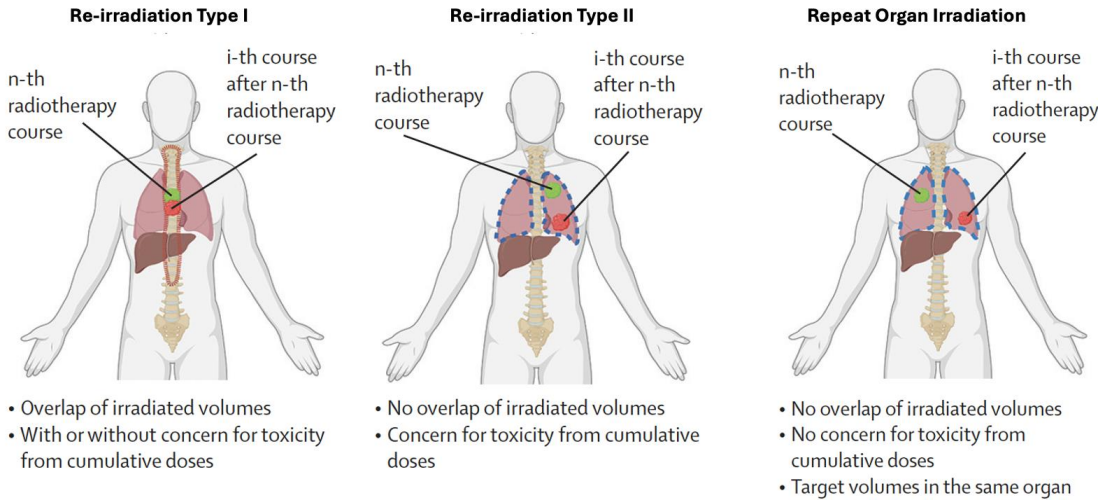
May 2024



April 2025

Cases 1

- What reRT type is being performed?
- What are the radiobiology parameters and tolerance doses you are using?
- Are you considering tumour or organs at risk (if so, what organs)?
- What method/model are you using to compare and add dose from different fractionations?



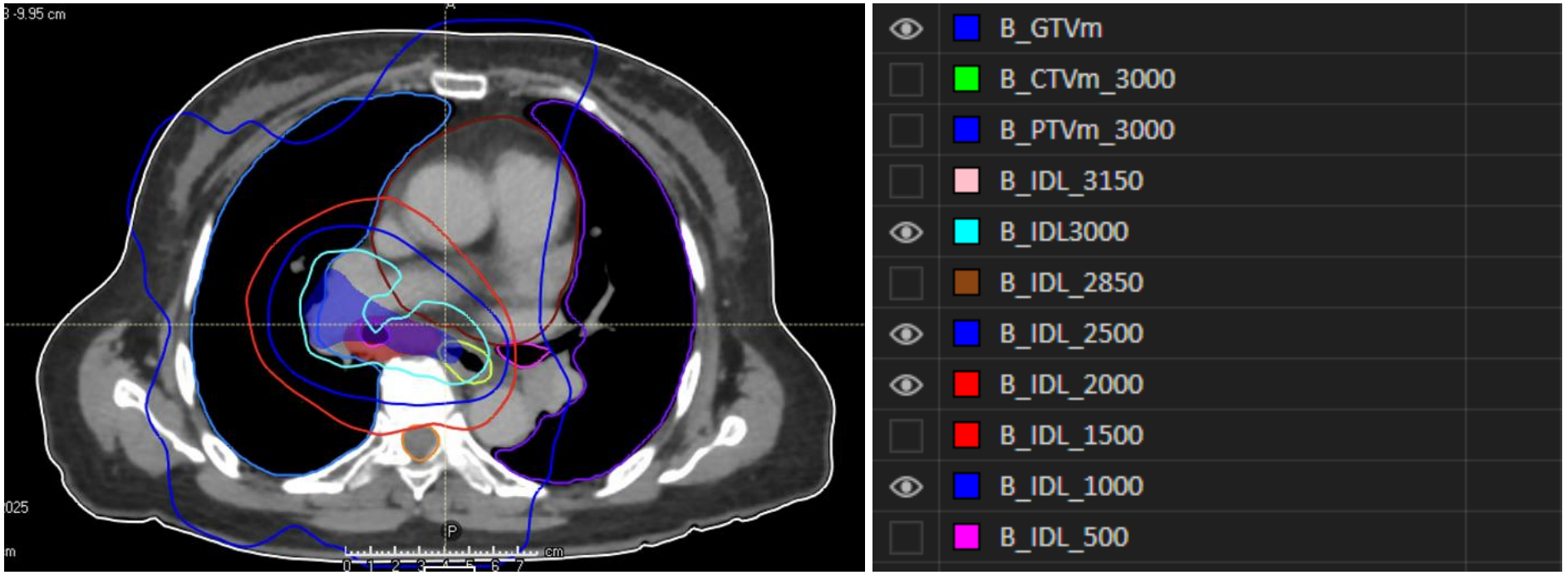
ReRT of Recurrent Non-Small Cell Lung Cancer Tolerances

OAR	Reference	Study Type	N	Time Interval*	Dose Constraint†	G3-4 Toxicity	G5 Toxicity	Notes
Lungs	Liu et al	Retrospective	72	>12m	V20<30-35%	14	1	
	Meijneke et al	Retrospective	20			0	0	2 patients V20>40%
Heart	Sumita et al	Retrospective	21	>24m	70Gy (Dmax)	0	0	1 G3 pneumonitis only
	Meijneke et al	Retrospective	20			0	0	7 patients >70Gy
Great vessels	Evans et al	Retrospective	35	>12m	Aorta <120Gy (D1cc)	0	2	Assumes 50% recovery at 1 year
	Feddock et al	Prospective	17		Pulmonary artery <110Gy (Dmax)	0	2	Both associated with LR
Esophagus	Binkley et al	Retrospective	38	>12m	100Gy (Dmax)	1 (at 75Gy)	0	3 patients >75Gy (1G2)
	Meijneke et al	Retrospective	20			0	0	8 patients >70Gy
Trachea	Binkley et al	Retrospective	38	>12m	100Gy (Dmax)	0	0	6 patients >100Gy
	Meijneke et al	Retrospective	20			0	0	7 patients >70Gy
PBT	Feddock et al	Prospective	17	>12m	<105Gy (Dmax)	0	0	
Brachial plexus	Chen et al	Retrospective	43	>24m	95Gy (Dmax) >24m, 80Gy (Dmax) <24m	NR	NR	
Spinal cord	Nieder et al	Retrospective	38	>6m	67.5Gy (Dmax)—non-SBRT	1	0	3% risk of RM if <75Gy and >6m
	Sahgal et al	Retrospective	14	>5m	75Gy (Dmax)—SBRT	5	0	SBRT ≤50% total dose

Hunter et al., 2021 Semin Radiat Oncol

Isodose Line Transfer

- Isodose lines (IDLs) are converted to iso-contours representing clinically relevant doses
- Iso-contours are transferred to the current scan via rigid registration
- Prior dose is assessed only at contour locations—no full 3D dose distribution available



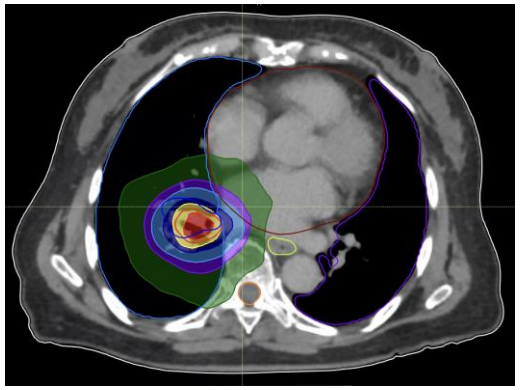
Organ Doses from Previous RT (30Gy/10fx)

Organ	DVH Metirc	Dose (Gy)	# Fractions
Spinal Canal	Dmax	21.5	10
Esophagus	Dmax	31.8	10
Heart	Dnax	30.0	10

Anything else?

- Remaining Dose Allowed in EQD2 = [OAR Dose Limit in EQD2] – [Dose to OAR from Prior Tx in EQD2]
- Then, convert back to physical dose so the dosimetrist can use in the treatment planning systems (very few planning systems allow planning input in EQD2)

Current RT (25Gy/5fx)



Organ	DVH Metric	Dose (Gy $EQD2_3$)	Remaining Dose (Gy $EQD2_3$)	Dose (Gy)
Spinal Canal	Dmax	22		
Esophagus	Dmax	39		
Heart	Dnax	38		

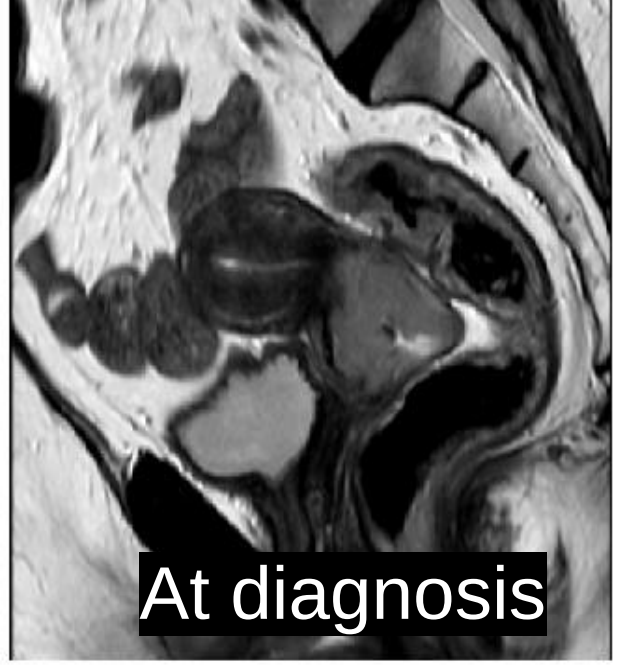
Priority	Dose	ROI/POI	Clinical goal	Value	Result
1	Plan dose: Thorax_SBR...	Heart	At most 2625 cGy dose at 0.00 % volume	2623 cGy	✓
1	Plan dose: Thorax_SBR...	Heart	At most 3200 cGy dose at 10.00 cm³ volume	1882 cGy	✓
	Plan dose: Thorax_SBR...	Esophagus	At most 1600 cGy dose at 0.10 cm³ volume	1592 cGy	✓
	Plan dose: Thorax_SBR...	SpinalCanal	At most 1200 cGy dose at 0.10 cm³ volume	1139 cGy	✓

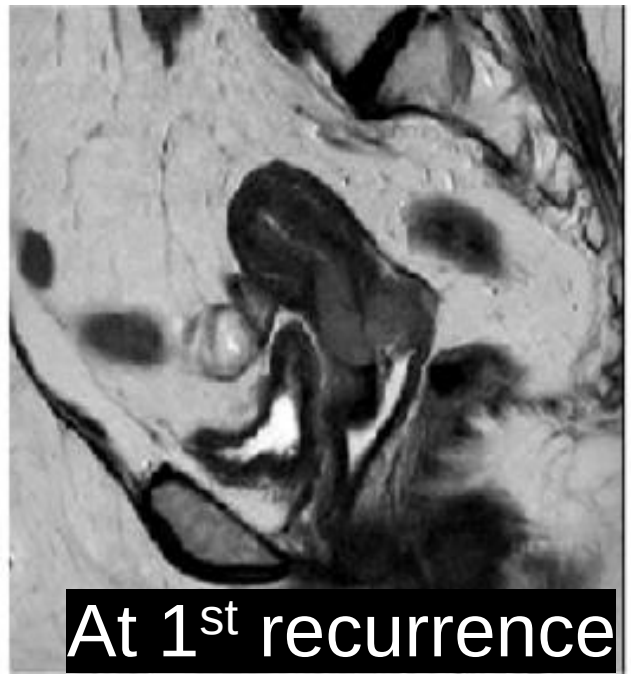
Case 2 – 56 y/o F Ca Cervix IIIC1

- Dec 2019: Primary malignancy and diagnosis
- Feb 2020: 1st course RT :
  - Pelvic IMRT 46Gy/23fx
  - Concomitant chemo: Cisplatin 40 mg/m2 weekly, 4 cycles
  - BT defaulted due to covid pandemic

Intent to treat with

- Feb 2022: 2nd course RT (local recurrence)
  - Pelvic IMRT 40Gy/20fx and
  - 4fx of HDR BT, Venezia applicator

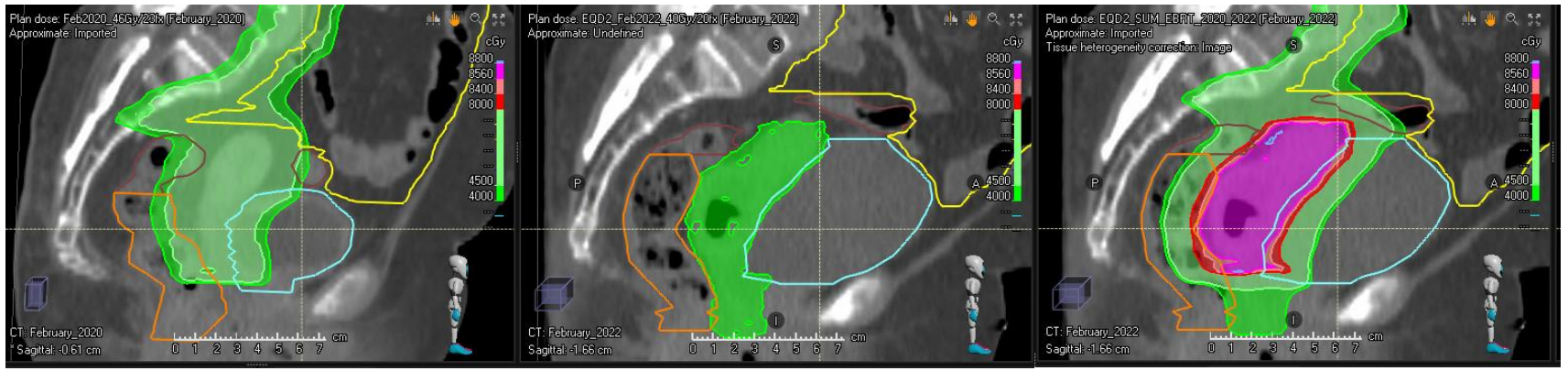




Courtesy of Dr. Supriya Chopra

Cases 2

- What reRT type is being performed?
- What are the radiobiology parameters and tolerance doses you are using?
- Are you considering tumour or organs at risk (if so, what organs)?
- What method/model are you using to compare and add dose from different fractionations?



2020 scan 2022 scan 2022 scan SUM dose

ReRT after SBRT in Abdominal or Pelvic Region Tolerances

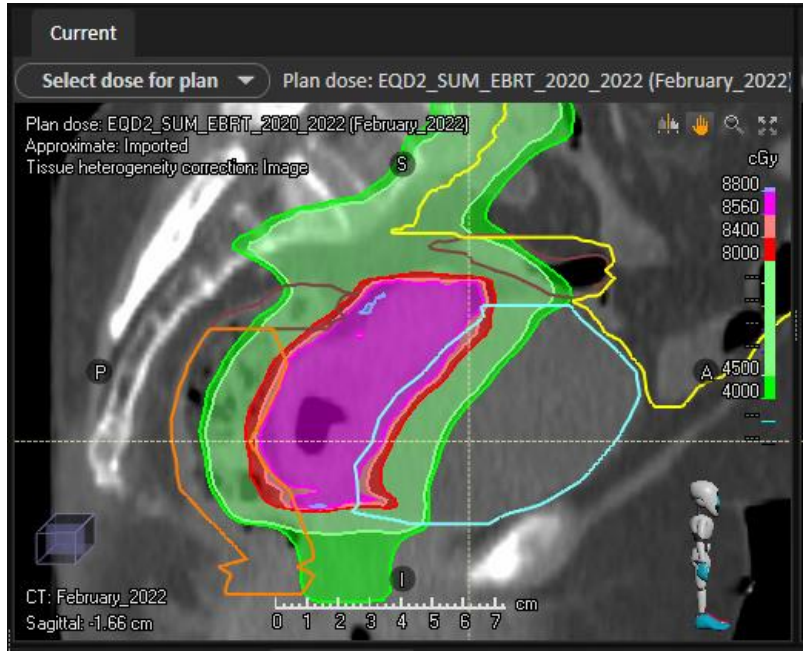
Cumulative dose (EQD2 / $\alpha/\beta = 3$ Gy) given to the organs at risk after stereotactic re-irradiation.

	Median	Mean	Min	Max	No. of patients
Bowel	98	97	56	144	18
Rectum	104	103	65	129	10
Bladder	113	116	79	235	13

Abusaris et al., 2012 Technology in cancer research and Treatment

Dose summation (EQD2)

- Doses in EQD2 added by:
  - Direct addition of D2ccc doses (“worst case scenario”)
  - DIR-based 3D dose summation



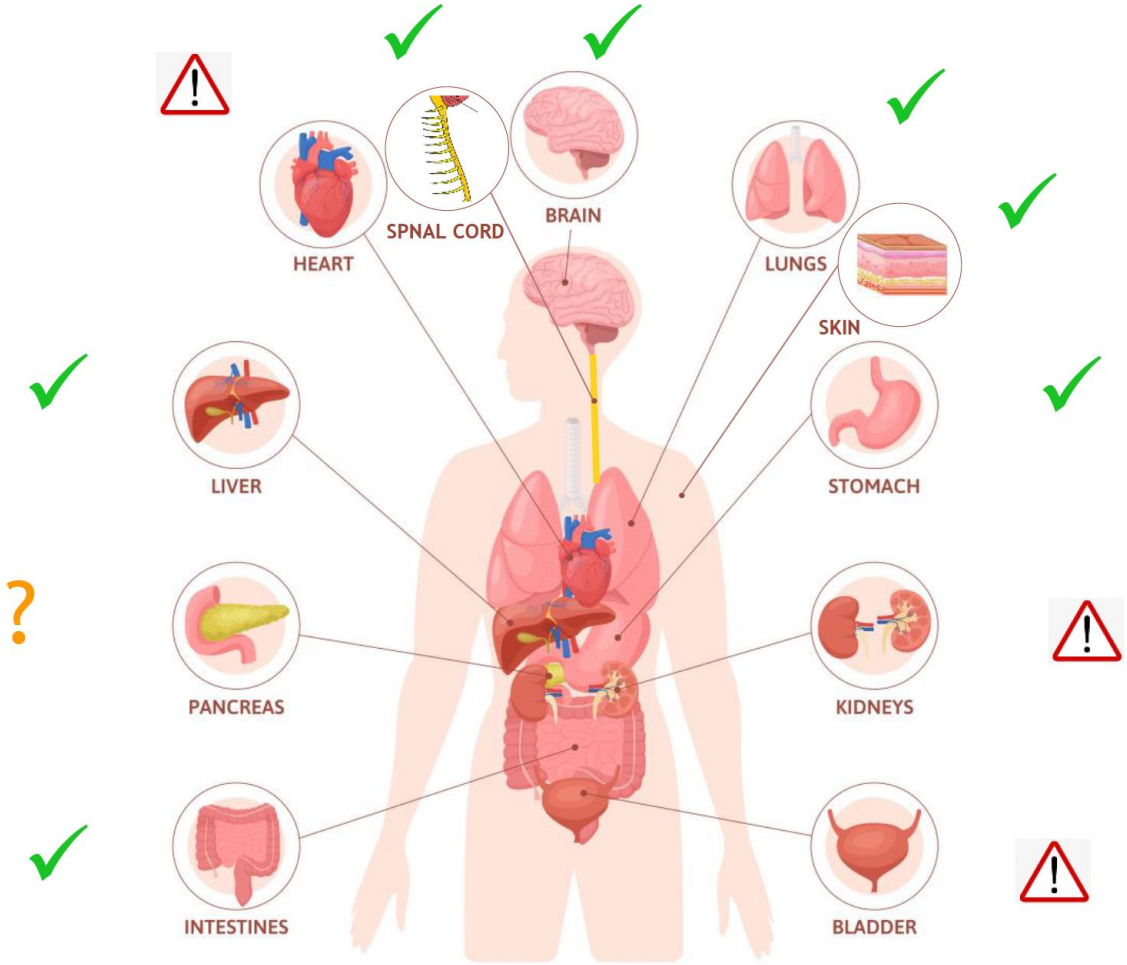
EQD2 cumulative dose from 1st and 2nd courses of RT

Patient , ID-number	Tata_ReRT_01					Symptoms:	Cystitis Gr 3	Mar-23					
Prior Courses/Plans Names	Pelvic IMRT 2020	Pelvic IMRT 2022	HDR BT 2022										
Date	01-Feb-20	01-Feb-22	01-Feb-22										
Prescribed Dose (Gy)	46	40	28										
No. of fx	23	20	4										
	☑	☑	☐										
OAR Name	Metric^	Pelvic IMRT 2020 Physical Dose (Gy)	Pelvic IMRT 2022 Physical Dose (Gy)	HDR BT 2022 EQD2 Dose (Gy EQD2)	Pelvic IMRT 2020 EQD2 (Gy EQD2)	Discount	Pelvic IMRT 2020 Adjusted EQD2 (Gy EQD2)	Pelvic IMRT 2022 EQD2 (Gy EQD2)	HDR BT 2022 EQD2 (Gy EQD2)	SUM EBRT DA SUM EBRT EQD2 (Gy EQD2)	SUM DA* SUM EQD2 (Gy EQD2)	SUM EBRT DIR SUM EBRT TPS EQD2 (Gy EQD2)	SUM DIR** SUM TPS EQD2 (Gy EQD2)
Bladder	D2cc	46.52	40.37	38.5	46.7	0.0	46.7	40.5	38.5	87.2	**125.7**	87.0	**125.5**
Rectum	D2cc	46.2	39.54	22.1	46.3	0.0	46.3	39.4	22.1	85.6	**107.7**	84.7	**106.8**
Sigmoid	D2cc	46.04	38.09	16.6	46.1	0.0	46.1	37.4	16.6	83.4	**100.0**	83.9	**100.5**

Limitations

- No validated dose discounts to OARs to account for the time elapsed between irradiations
- Sparse data for OARs tolerances in the context of ReRT
- Target BT dose reporting to periphery (e.g., D90%, D98%)
  - No understanding of the high dose volumes within the target
  - LQ model validated up to 10Gy/fx
  - Tumor shrinkage

When asked whether the panelists have a "rule of thumb" for how much dose they would forgive based on the duration of time that has passed from an initial course of radiation, there was no consensus with a wide range from not forgiving any dose to responses like 10% per year.



https://www.freepik.com/

Physician objectives for composite EQD_{2Gy} doses from summed plan that includes discounted prior doses and final plan for this course. Note:

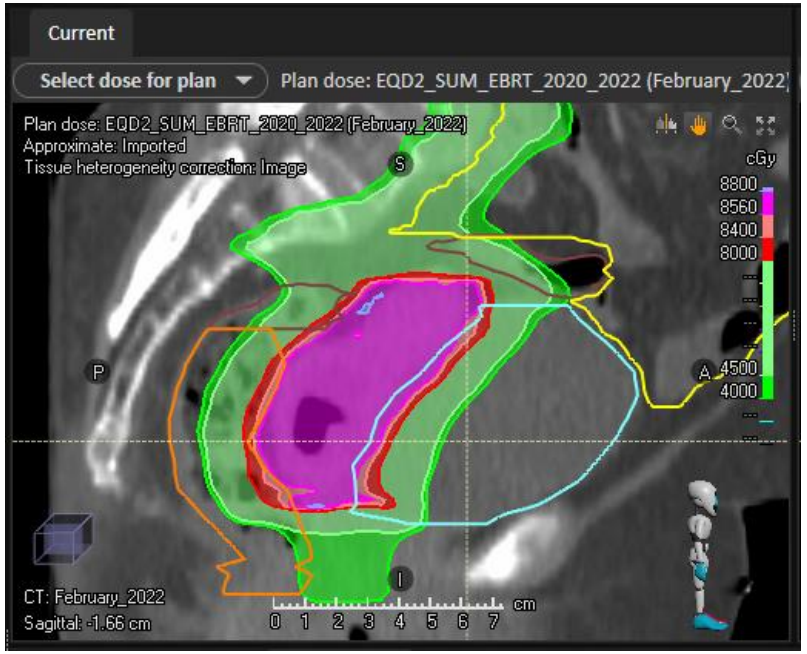
- **Volumetric limits cannot be assessed without composite plans. Biocorrected DVH's may be requested for further information.**
- **Dose limits given in EQD2, which may differ substantially from physical dose**

Generic, Serial

	OAR Name	α/β (Gy)	Dose limit Max to 0.1cc (EQD2) (Gy)	Previous dose discount (%) [0% means no discount] For >3 years, 50% discount suggested			
				< 3 mo	3-6 mo	6 mo – 1 yr	1 – 3 yrs
☐	Bladder	2.5	85	0	10	25	50
☐	Brachial Plexus	2.5	70	0	10	25	50
☐	Brain (report V100EQD2Gy[cc])	2.5	100	0	10	25	50
☐	Brainstem	2.5	64	0	10	25	50
☐	Cauda Equina	2.5	60	0	10	25	50
☐	Colon	2.5	70	0	10	25	50
☐	Duodenum	2.5	54	0	0	25	25
☐	Esophagus	2.5	70	0	10	25	50
☐	Great Vessels	2.5	100	0	10	25	50
☐	Heart	2.5	70	0	10	25	50
☐	Kidneys	2.5	ALARA	0	0	0	0

Dose summation (EQD2)

- Doses in EQD2 added by:
  - Direct addition of D2ccc doses (“worst case scenario”)
  - DIR-based 3D dose summation



EQD2 cumulative dose from 1st and 2nd courses of RT

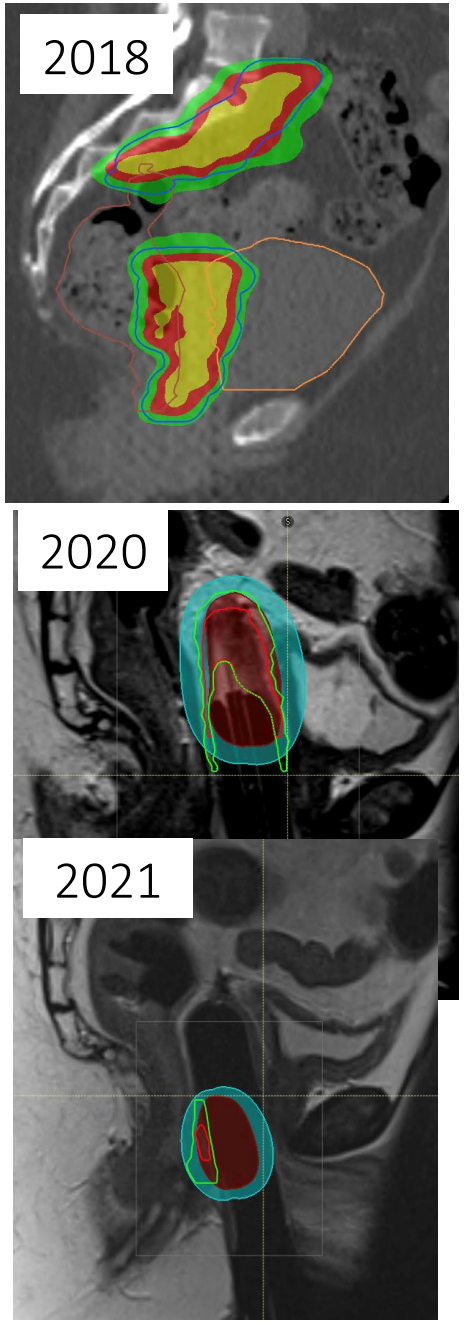
Patient , ID-number	Tata_ReRT_01					Symptoms:	Cystitis Gr 3	Mar-23					
Prior Courses/Plans Names	Pelvic IMRT 2020	Pelvic IMRT 2022	HDR BT 2022										
Date	01-Feb-20	01-Feb-22	01-Feb-22										
Prescribed Dose (Gy)	46	40	28										
No. of fx	23	20	4										
	☑	☑	☐										
OAR Name	Metric^	Pelvic IMRT 2020 Physical Dose (Gy)	Pelvic IMRT 2022 Physical Dose (Gy)	HDR BT 2022 EQD2 Dose (Gy EQD2)	Pelvic IMRT 2020 EQD2 (Gy EQD2)	Discount	Pelvic IMRT 2020 Adjusted EQD2 (Gy EQD2)	Pelvic IMRT 2022 EQD2 (Gy EQD2)	HDR BT 2022 EQD2 (Gy EQD2)	SUM EBRT DA EQD2 (Gy EQD2)	SUM DA* SUM EQD2 (Gy EQD2)	SUM EBRT DIR SUM EBRT TPS EQD2 (Gy EQD2)	SUM DIR** SUM TPS EQD2 (Gy EQD2)
Bladder	D2cc	46.52	40.37	38.5	46.7	0.5	23.4	40.5	38.5	63.9	**102.4**	87.0	**125.5**
Rectum	D2cc	46.2	39.54	22.1	46.3	0.5	23.1	39.4	22.1	62.5	**84.6**	84.7	**106.8**
Sigmoid	D2cc	46.04	38.09	16.6	46.1	0.5	23.0	37.4	16.6	60.4	**77.0**	83.9	**100.5**

Case 3 – 49 y/o F AdenoCa Cervix 1B1

- Jul 2018 : 1st course RT Post-Op Adjuvant EBRT
  - Pelvic VMAT 45Gy/25fx
- Feb 2020: 2nd course RT (upper-vagina recurrence)
  - 4fx of HDR BT, cylinder applicator, 8.5Gy/fx

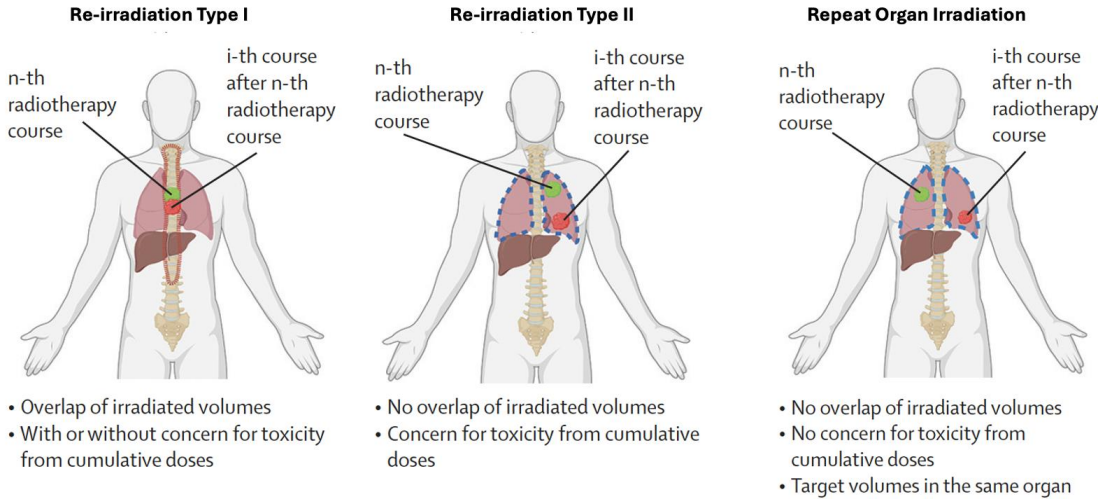
Intent to treat with

- Jun 2021: 3nd course RT (lower-vagina recurrence)
  - 5fx of HDR BT, cylinder applicator, 7Gy/fx



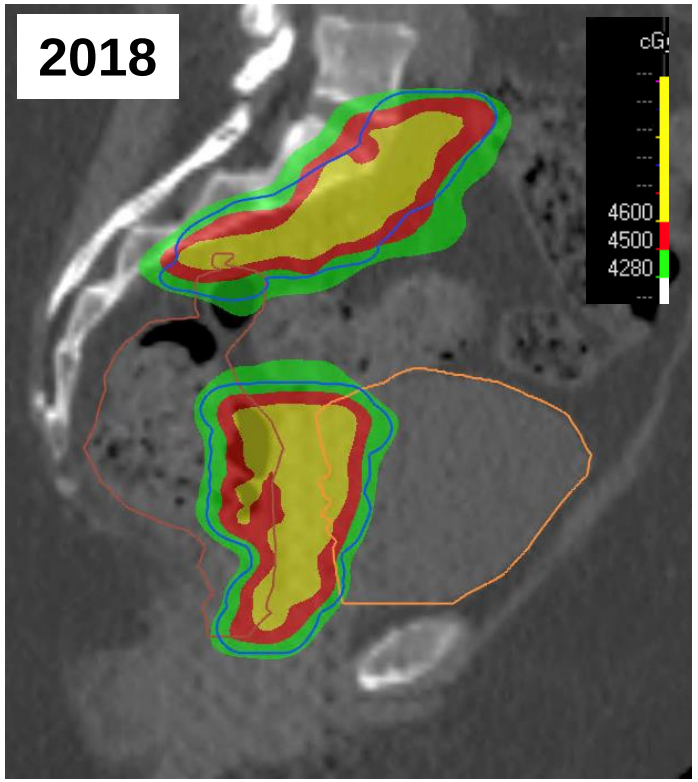
Case 3

- What reRT type is being performed?
- What are the radiobiology parameters and tolerance doses you are using?
- Are you considering tumour or organs at risk (if so, what organs)?
- What method/model are you using to compare and add dose from different fractionations?



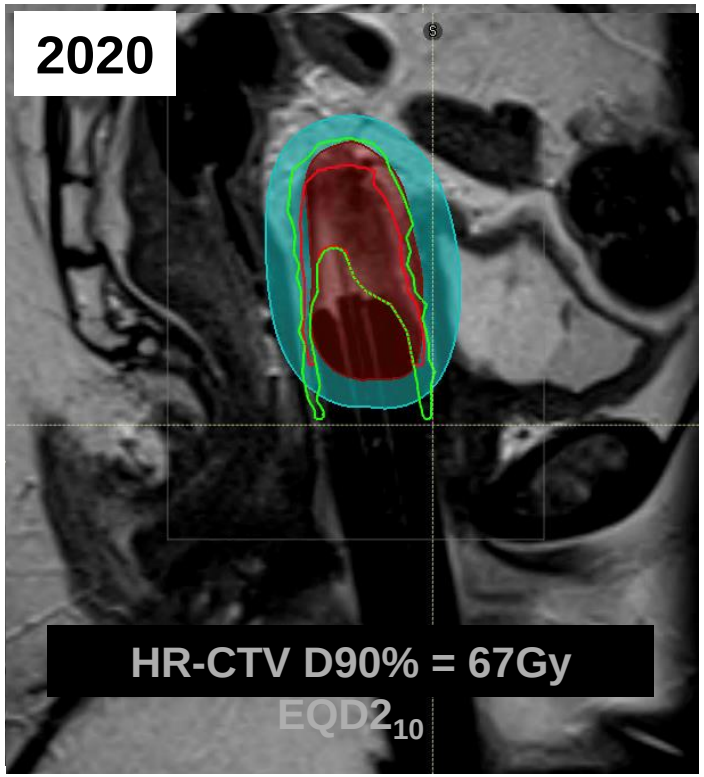
Dose summation (EQD2)

Post-Op Adjuvant EBRT



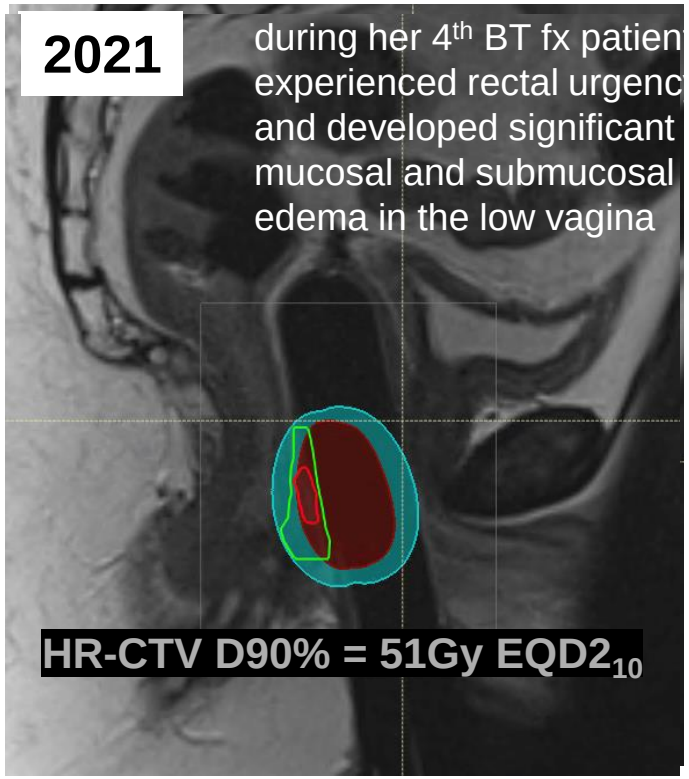
EBRT 45Gy/25fx

1st Recurrence upper vagina



HDR IC/IS BT 8.5Gyx4fx

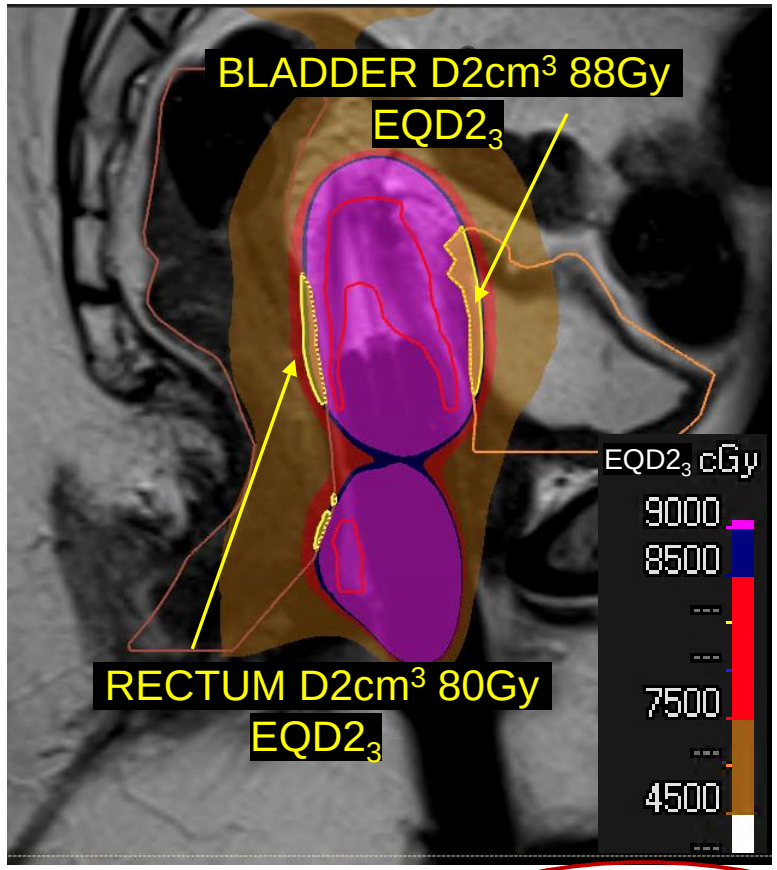
2nd Recurrence lower vagina

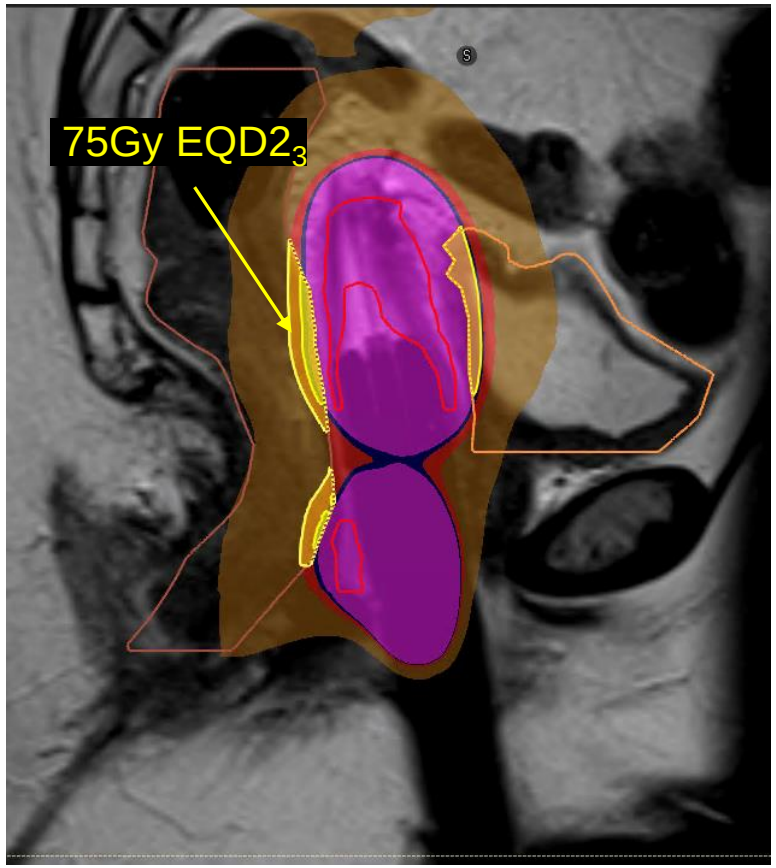


HDR IC BT 7Gyx5fx

Courtesy of Dr. Michael Milosevic

Direct addition vs DIR-based 3D dose summation





	DIRECT DOSE ADDITION	3D DIR-based DOSE ADDITION
BLADDER D2cm³	87Gy EQD2₃	88Gy EQD2₃
RECTUM D2cm³	78Gy EQD2₃	80Gy EQD2₃

Clinically used

Repair to OAR due to time elapsed between treatments not taken into account!!! No dose discounts!

We’d love your feedback!

Lecture Evaluation

Program Evaluation