Can dose indices predict toxicity?

The vision of a medical physicist
Prostate treatments

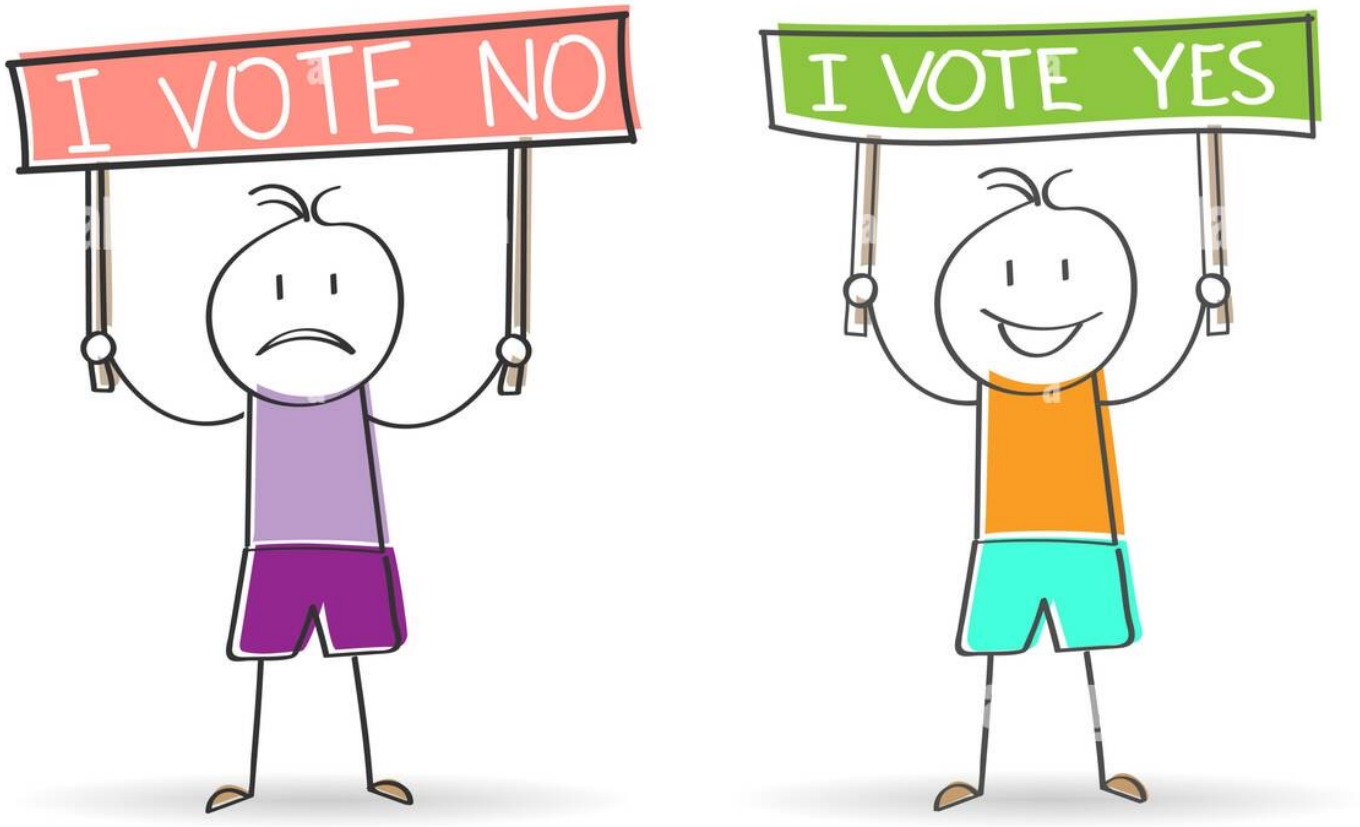
Núria Jornet

Servei de Radiofísica i Radioprotecció

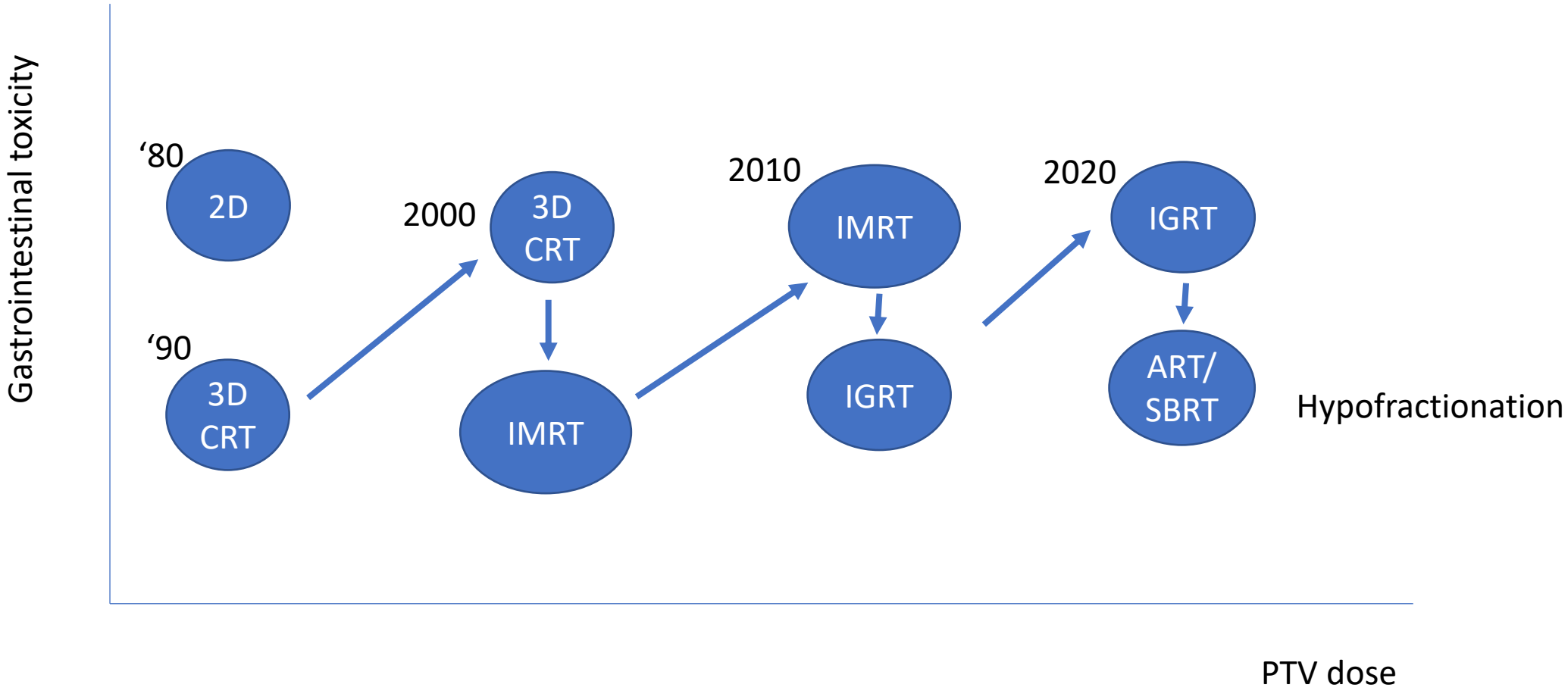
Hospital de la Santa Creu i Sant Pau

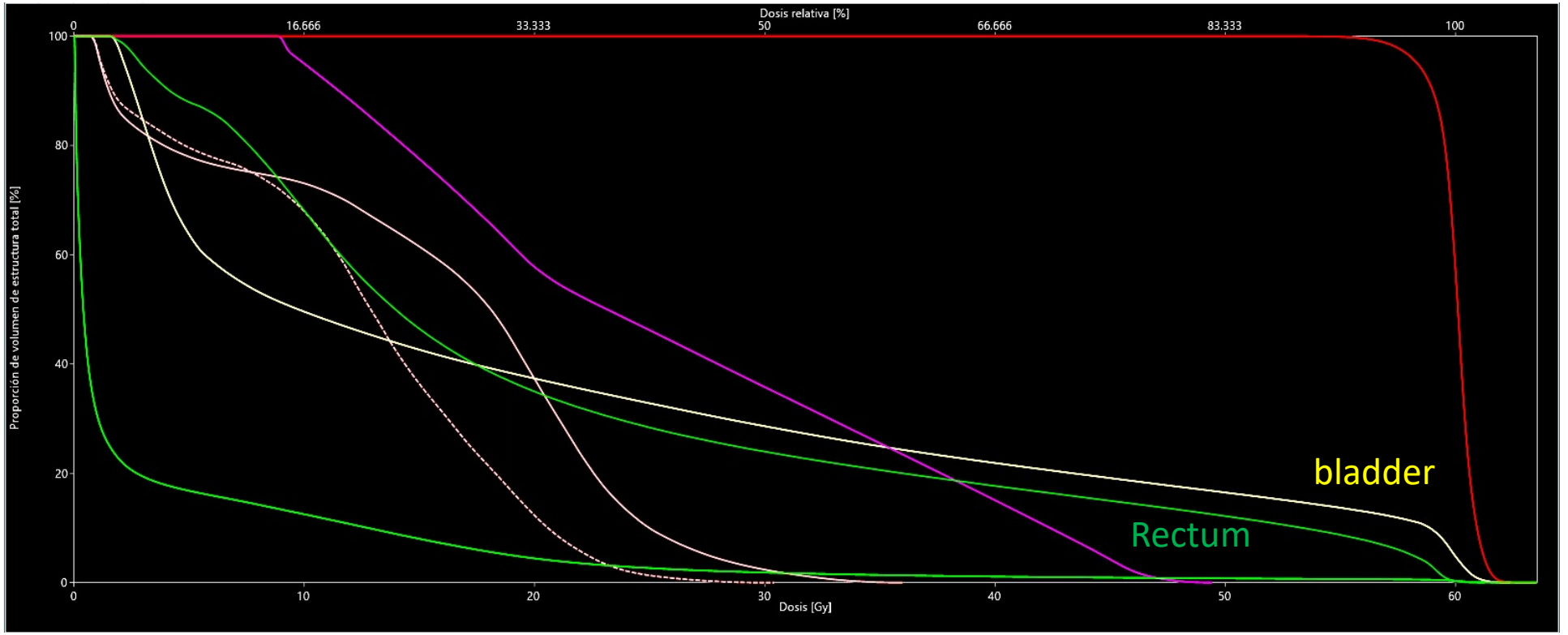
Barcelona

Do you think that dose indices can predict rectal and genitourinary toxicity?



Some historical background on prostate RT





1. DVH?
2. Dose distribution: Planning vs Reality
3. What else?

DVH: The holly grial

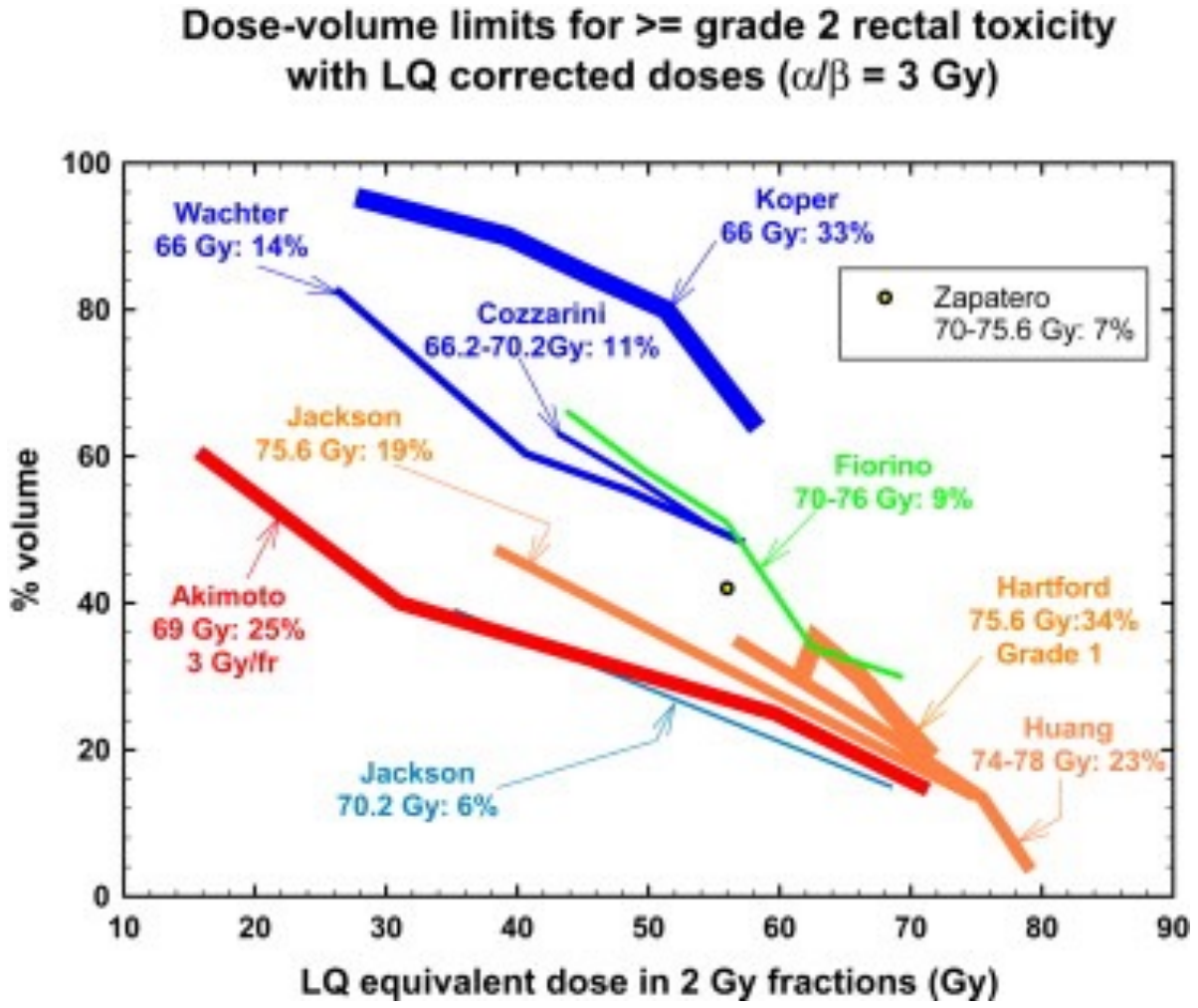
Dosis por fracción [Gy]	Número de fracciones	Dosis total [Gy]	Volumen objetivo
2.000	28	56.000	PTVp_5600
2.500		70.000	PTVp_7000

Órgano	Límite		
RECTE	Dosis máx	<	
	Dosis media	<	
	V30	<	80%
	V40	<	60%
	V50	<	50%
	V58	<	40%
	V62	<	30%
	V65	<	15%
	V68	<	10%
	V71	<	5%
	isosoai 45 Gy	<	1/2 recte post
	Isodosi 30 Gy	<	paret post recte

DVH: The holly grial

1. Model parameters were based on patients treated mostly without IMRT or daily localization

2. Most of the studies used 1.8- or 2-Gy fractions.



Agreement that going over V70>20% 30% of patients will develop grade 2 or more toxicity

At lower prescription doses, larger volumes must be exposed to intermediate doses before substantial toxicity is seen.

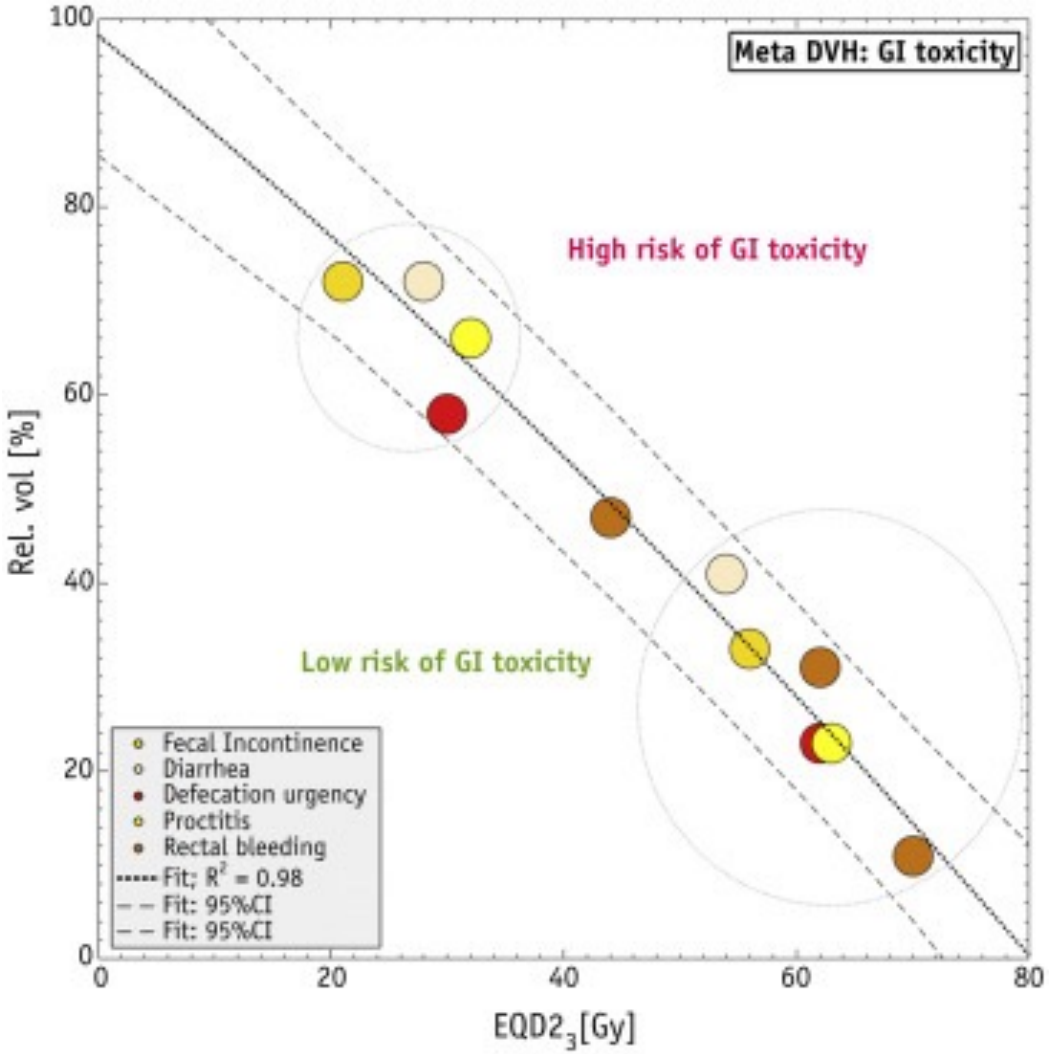
DVH: The holly grial

Rectum DVH constraints for prescriptions up to 79.2 Gy in standard 1.8- to 2-Gy fractions

V50<50%	V60<35%	V65<25%	V70<20%	V75<10%

Toxicity probability
Grade ≥2 late rectal toxicity to <15%
Grade ≥3 late rectal toxicity to <10%

DVH: The holly grial



DVH constraints revisited in 2018

New techniques included (VMAT and IMRT)

IGRT standard practice

EBRT

Maximum nominal total dose 80 Gy

Dose per fraction 1,8-3 Gy

Alfa/Beta 3

Still:

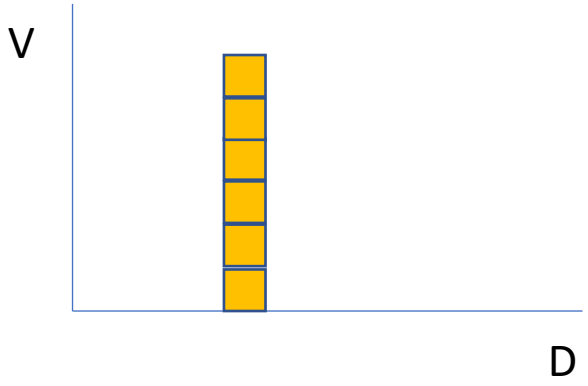
No, SBRT treatments

No, focal treatments

No protons

Caroline E. Olsson, Andrew Jackson, Joseph O. Deasy, Maria Thor,
A Systematic Post-QUANTEC Review of Tolerance Doses for Late Toxicity After Prostate Cancer Radiation Therapy,
International Journal of Radiation Oncology*Biology*Physics,
Volume 102, Issue 5, 2018, Pages 1514-1532,

DVH: Loss of spatial information

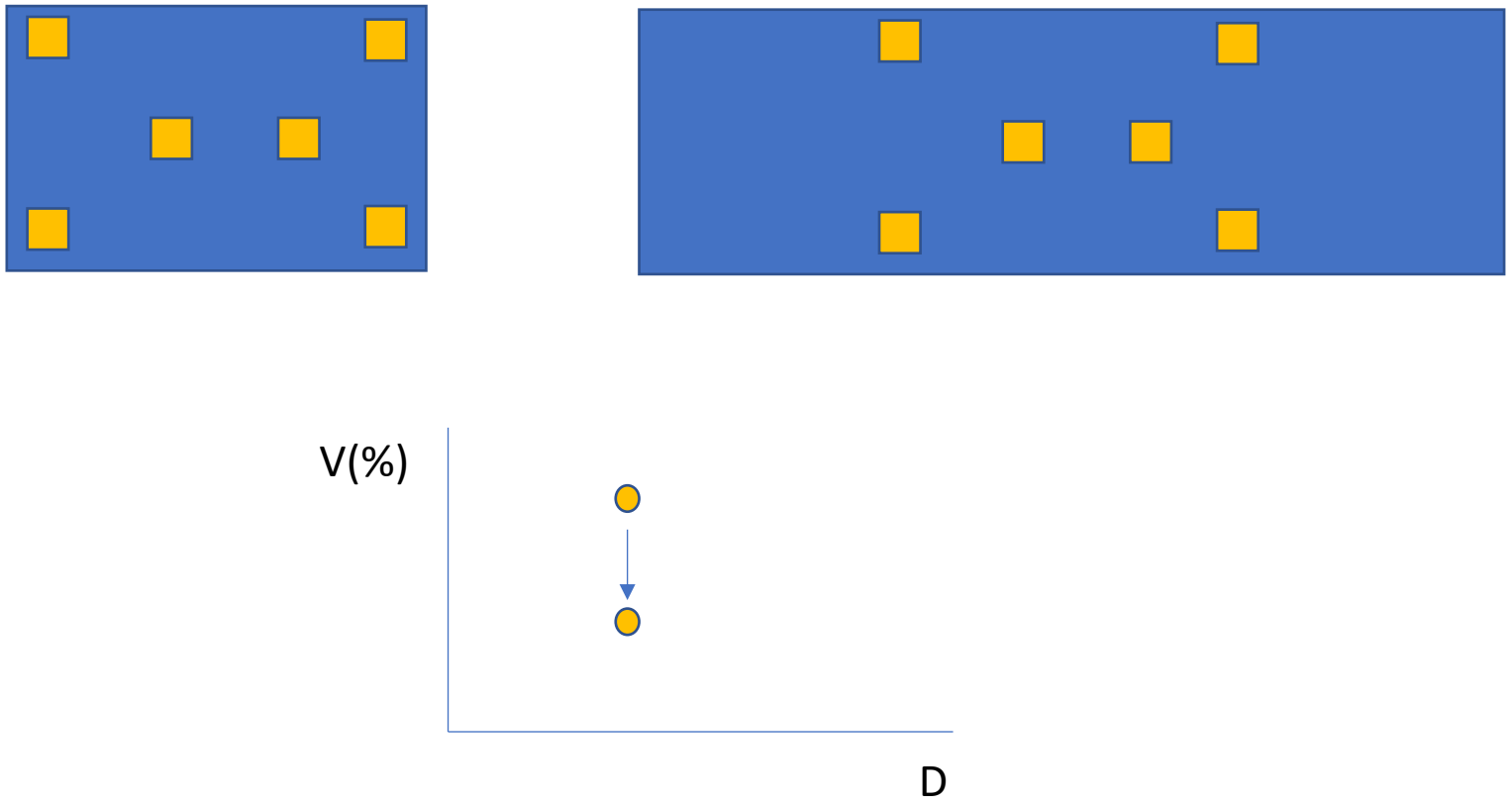


Evidence of the effect of spatial distribution

- Animal data: colon radiation damage in rats depends on SIZE AND SHAPE OF IRRADIATED SURFACE (Trott et al. Strahlenther. Onkol., 1995)

- Human data: No topographical distribution has been collected. The knowledge of process of damage is incomplete and so NTCP models...

DVH: Delineation of structures has a high impact

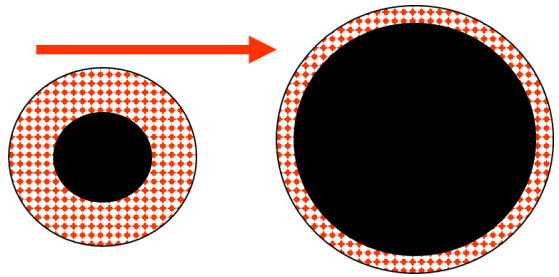


DVH: Would it be more relevant a dose-surface histogram for bladder and rectum?

Most studies date from 2000-2005 where 3DCRT was the standard of treatment

DVH: NDWH and NDSH including stretching and curving (2000)

Mackay et al., (BJR, 70, ‘97) :‘the number of sensitive cells in the rectal wall may be the same whether the rectum is full or empty’



No conclusive results on DSH improved the fits of NTCP models with respect DVH

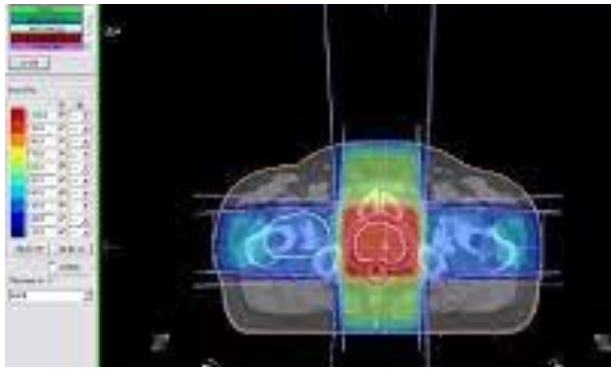
3DCRT techniques…

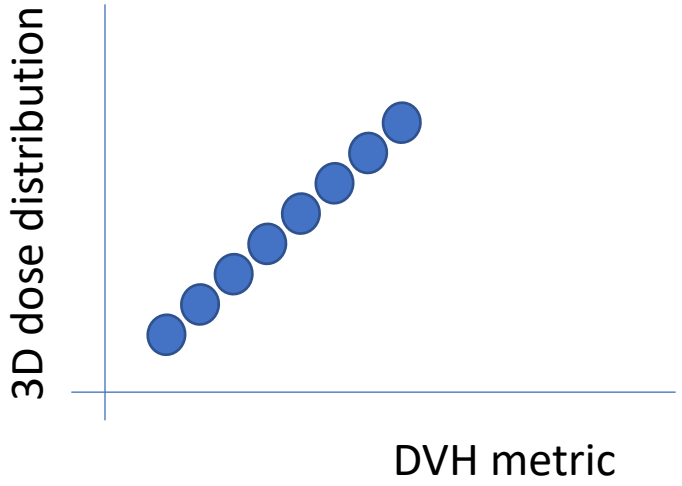
📖 Meijer et al., IJROBP 45(4), 1999

Developed a method to derive the inner rectal surface by contouring the outer rectal surface. Taking into account stretching and curving

How robust are DVH end points to changes in treatment techniques?

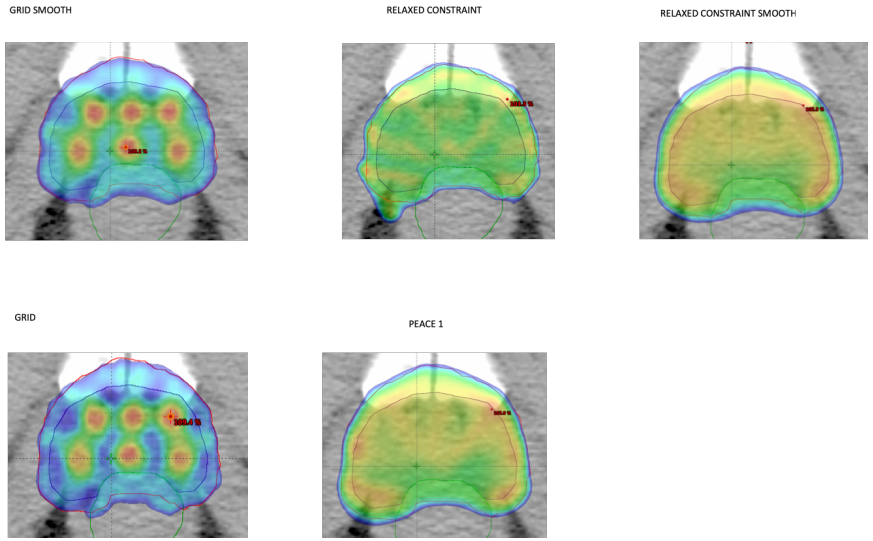
- At a point in time the treatment technique where very similar
- Dose distributions where very similar
- DVH even if loss spatial information described in fact similar spatial dose distributions

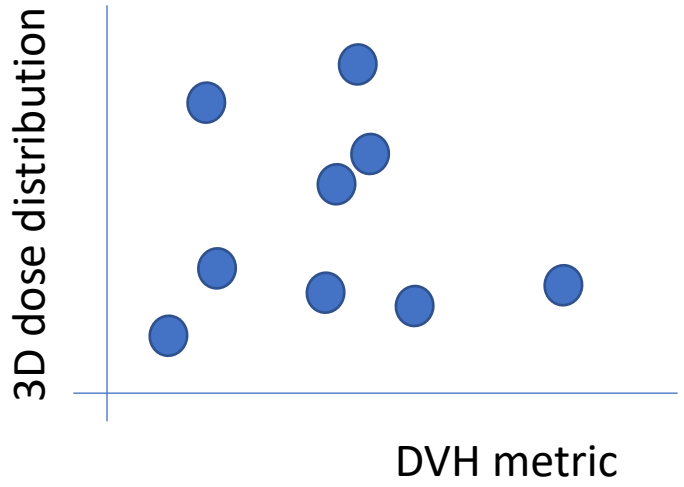




How robust are DVH end points to changes in treatment techniques?

- Different techniques
- Introduction of IMRT/VMAT
- The same two histograms can hide completely 3D dose distributions





What else:

Better metrics to describe the dose distribution

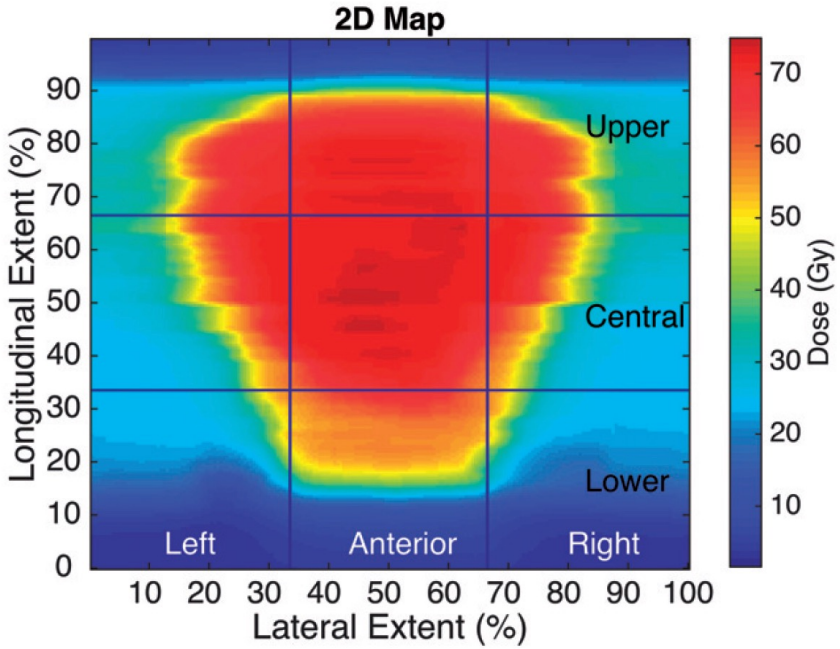
Better correlated to toxicity?

spatial-based models resulted in models with the overall highest discriminative ability than DVH and SVH

200 patients treated with 3DCRT
Prescribed dose =78 Gy (2Gy fraction)
Daily kV image guidance with implanted fiducial markers

Margin: 7mm in all directions, except cranio-caudal 9 mm

PRO- gastrointestinal toxicity



- Significant relations were found.
- Defecation urgency and faecal leakage were explained by high doses at the central/upper and central areas, respectively
- Emptying difficulties were explained by longitudinal extensions of intermediate doses.

Oscar Casares et al . Acta Oncologica 2017

VoxTox Study (2015):
How to assess dose deliverd to rectum without loosing spatial information

10 prostate patients
Planning study
Recalculation on weekly CBCT

DSMs are able to identify differences between DA and planned dose that cannot be appreciated from DVHs alone

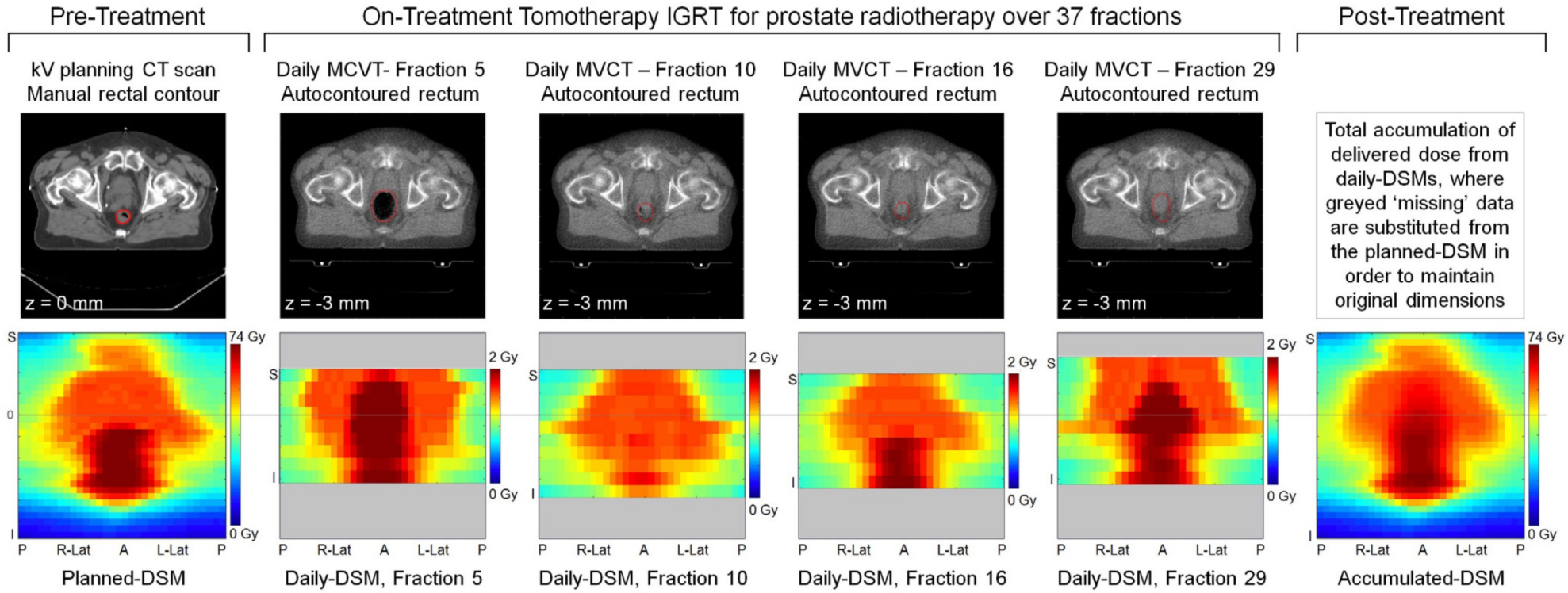
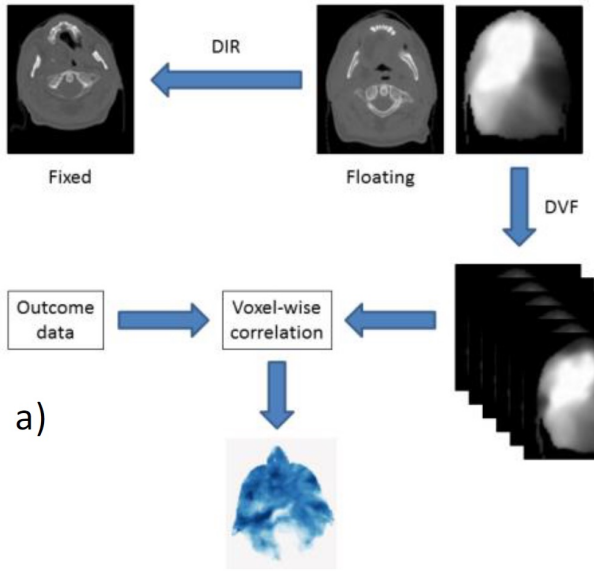
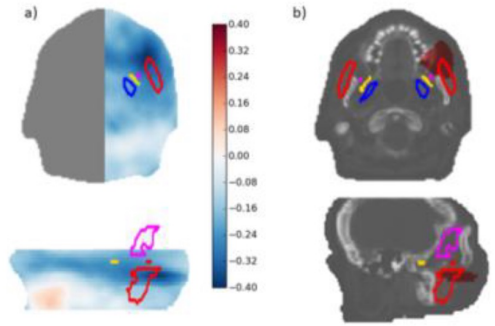


Fig. 1. Generation of planned, daily and accumulated dose surface maps.

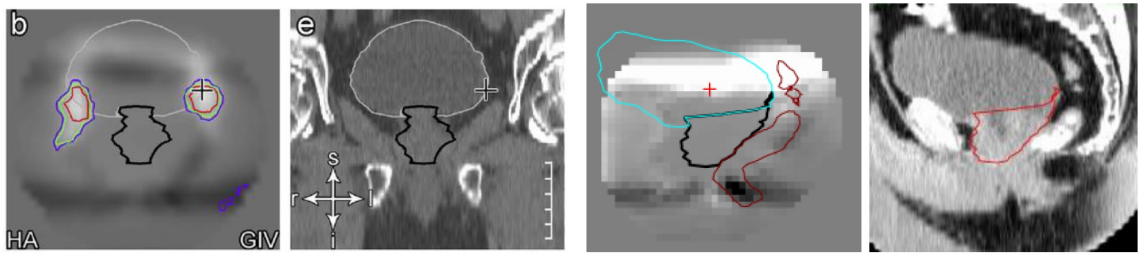
:o high doses

Scaife JE, Thomas SJ, Harrison K, Romanchikova M, Sutcliffe MPF, Forman JR, et al. Br J Radiol 2015; 88: 20150243



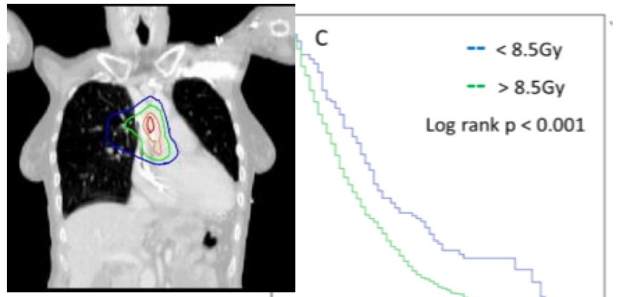


b)



c)

d)



e)

Courtesy of Laura Cella and Marcel van Herk

Planning vs reality :

Are we 100% sure that DVH metrics match what the patient receives?

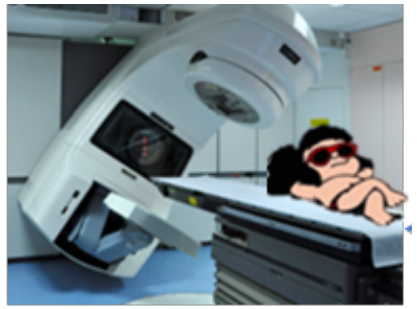
Patient-specific QA

Plan TPS

Plan Check
DVH metrics
Plan parameters

Independent dose calculation
Point doses
3D dose calculation

Pre-treatment verification
Treatment Unit

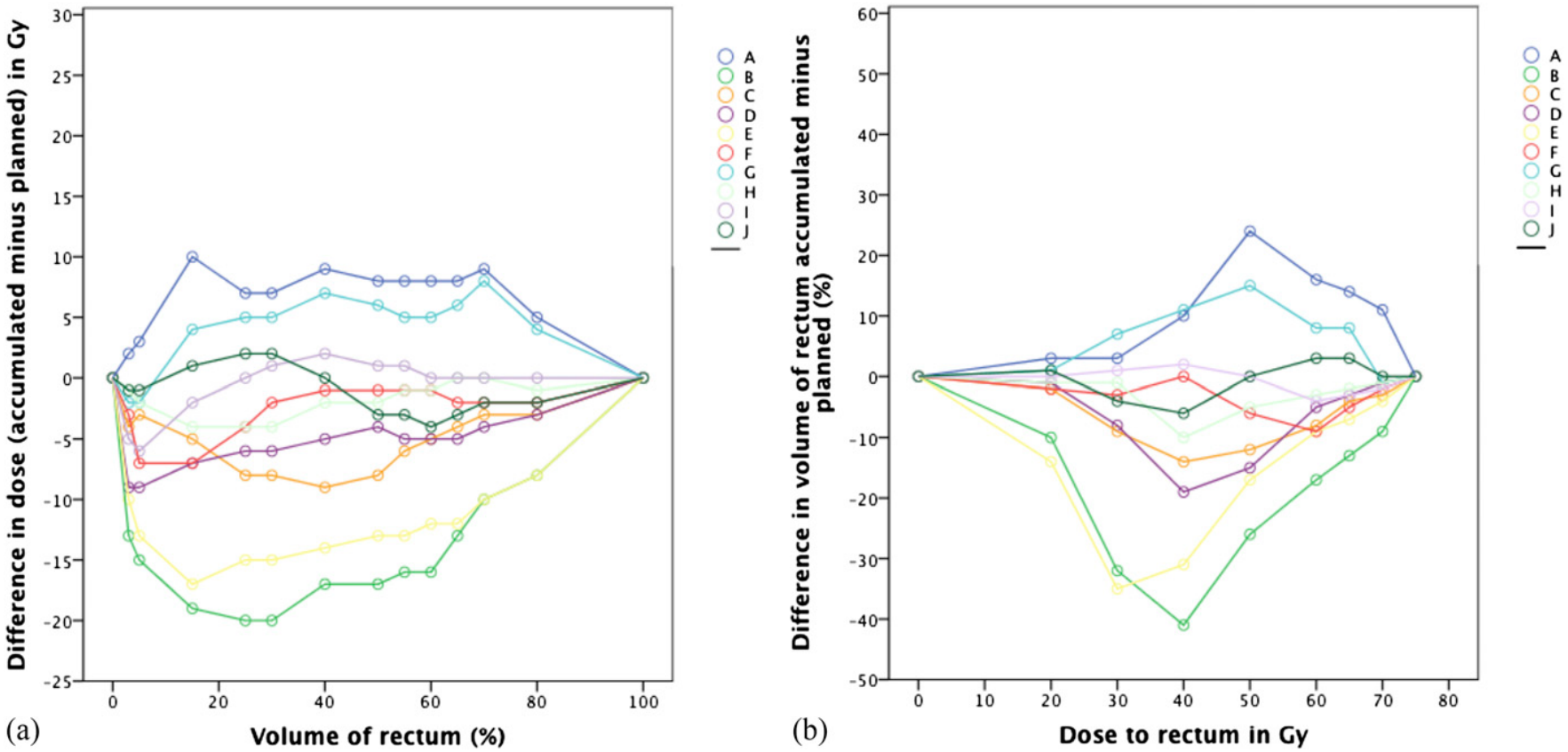


IGRT

In vivo dosimetry (IVD)

VoxTox Study (2015):
How to assess dose deliverd to rectum without loosing spatial information

10 prostate patients



Scaife JE, Thomas SJ, Harrison K, Romanchikova M, Sutcliffe MPF, Forman JR, et al. Br J Radiol 2015; 88: 20150243

How do OAR change on a daily basis (2010)

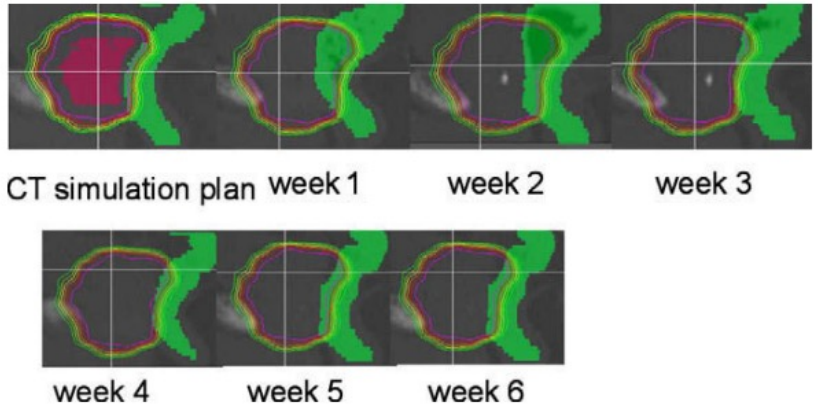


Fig. 1. CT-on-rails images, the variation of rectal volume during the treatment course for patient #6.

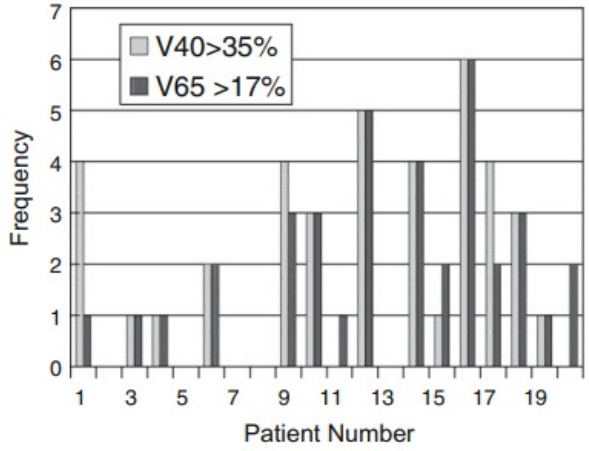


Fig. 4. The number of times the rectal DVH criteria were violated based on the daily treatment CT-on-rails images.

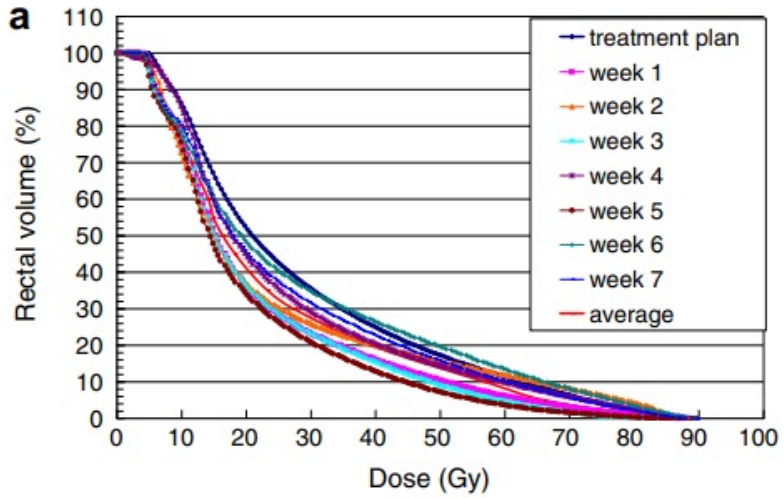
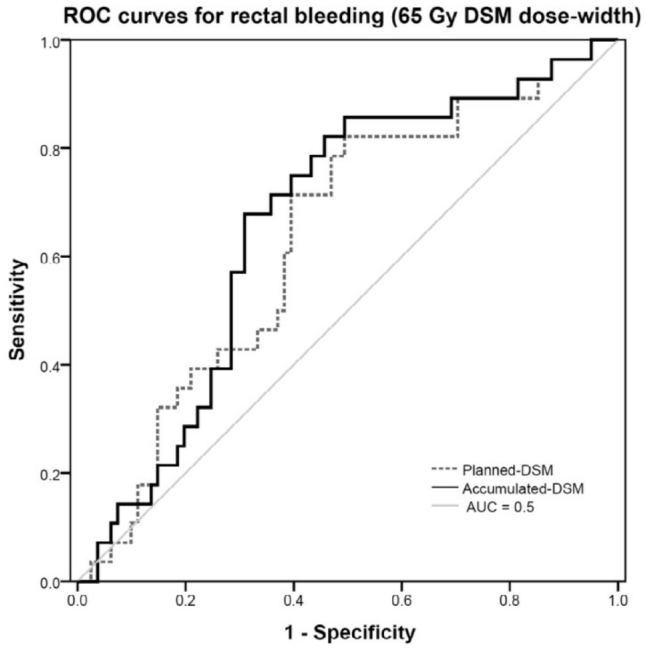
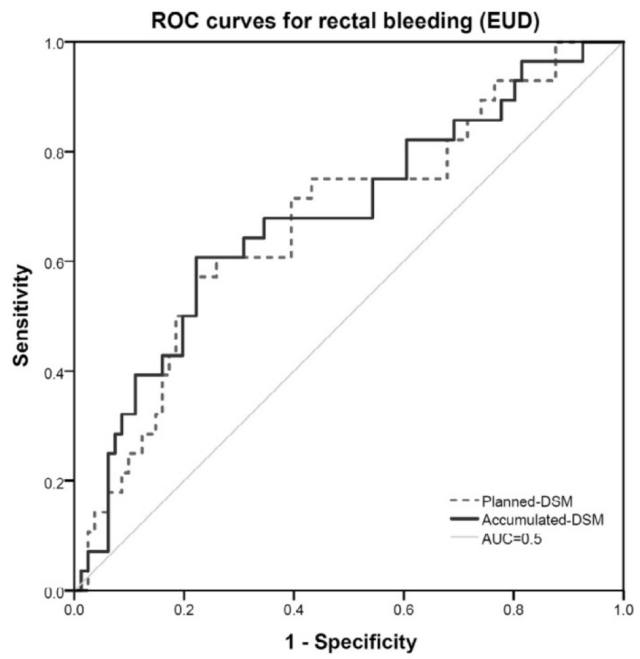


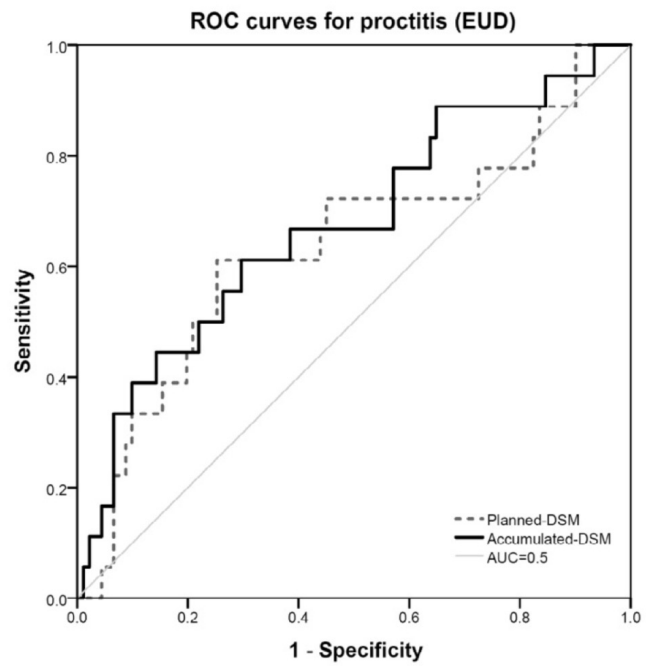
Fig. 3. Rectal DVHs for individual fractions during the treatment course for patient #8 (a) and for patient #16 (b). The average DVHs after combining doses from all

Lili Chen et al. Radiotherapy and Oncology 95 (2010) 198–202

Stronger correlations with rectal bleeding and proctitis are achieved with delivered dose to the rectal wall than for planned dose







Spatial considerations could complement current DVH-based approaches to treatment planning.

L.E.A. Shelley et al. VoxTox Radiother. Oncol 2017

Either we estimate delivered dose metrics

or we try that delivered dose = planned dose

Patient instructions/preparation: Consistency between planning and delivery.

IGRT: Image guidance (CBCT or MR)

Registration surrogates

Adaptation

Tracking

Robust/probabilistic planning

Decrease on accute and late rectal toxicity combining IMRT and IGRT

(CBCT or fiducial markers)

IGRT plays an extremely important role in the reduction of rectal and genitourinary toxicity

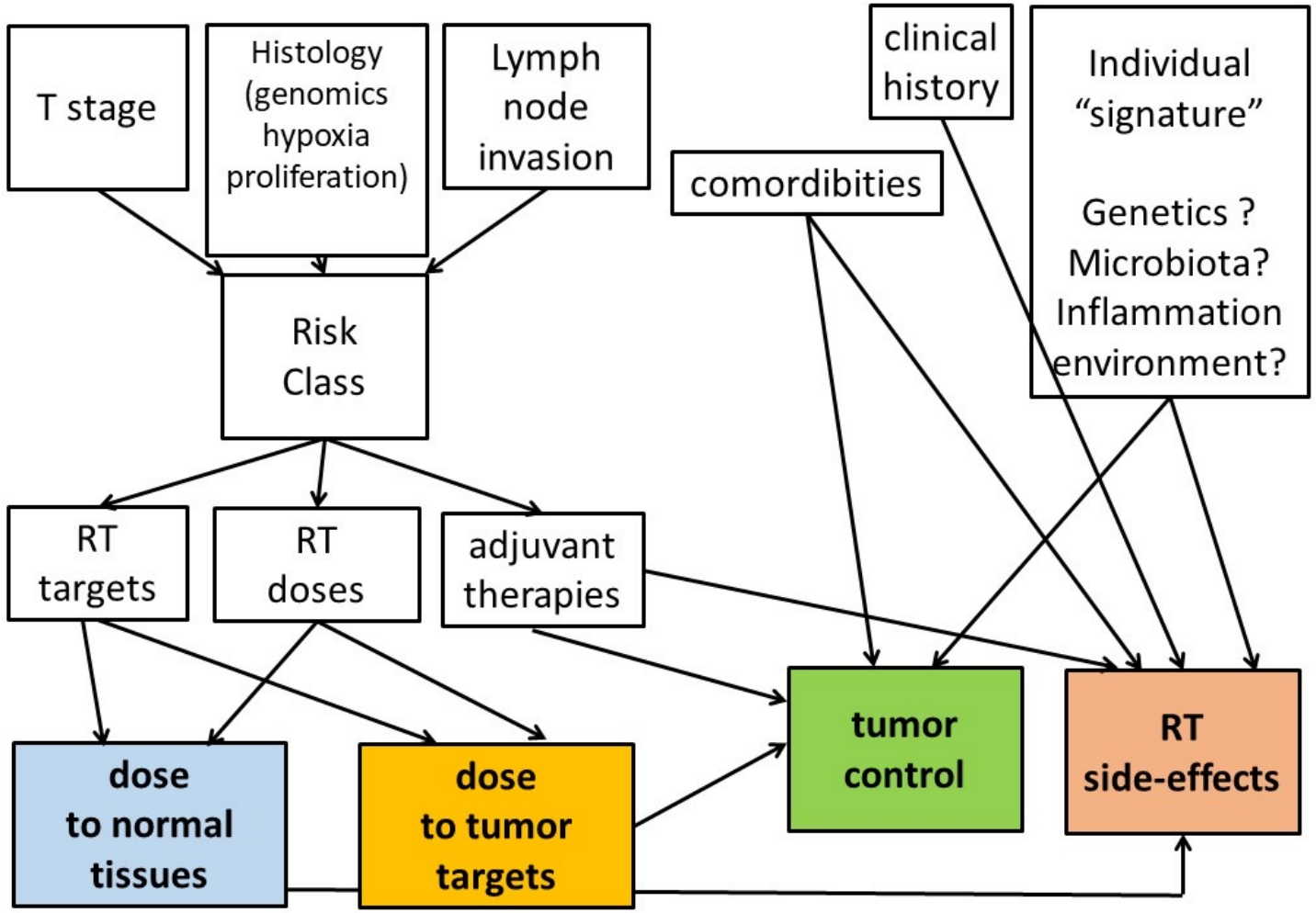
Reference	Image guidance	Conclusions
Valeriani et al. 2013	kV CBCT soft tissue matching	Rectal toxicity grade 2 reduced from 15% (bone matching) to 2%
Kok et al 2013	kV fiducial markers	Rectal toxicity grade 2 reduced when comparing fiducial markers IGRT to bone matching.
Zapatero et al. 2017	kV fiducial markers	Genitourinary grade 2 toxicity reduced when comparing IMRT with IGRT to 3DCRT without IGRT
Deboel et al. 2017	kV fiducial markers or kV CBCT	Decrease of acute and late rectal toxicity Grade 2 rectal toxicity was 19%, 13% and 4% (3DCRT, IMRT and IMRT+IGRT)

What else:

Same dose different toxicity:

Predictive modelling where dose is only one of the variables

Radioinduced toxicity and tumor control are multi-factorial problems



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Previous surgery higher risk of rectal toxicity

Table 3
Summary of the main results of multivariate analysis for the study endpoints (see text for definitions). Bold *p*-values refer to the overall multivariate model fit.

	OR	*p*-Value
Chronic late faecal incontinence (grade ⩾2)		**0.0023**
Surgery (y/n)	3.26	0.09
Use of anti-hypertensives (y/n)	0.31	0.05
Presence of haemorrhoids (y/n)	2.43	0.10
Grade ⩾2 acute faecal incontinence (y/n)	4.34	0.004
V40 Gy (%) (continuous)	1.015	0.30
Actuarial late faecal incontinence (grade ⩾2)		**0.0005**
Presence of haemorrhoids (y/n)	1.6	0.13
Grade 3 acute faecal incontinence (y/n)	6.9	0.001
Mean rectal dose (Gy) (continuous)	1.023	0.12
Rectal bleeding (grade ⩾2)		**0.0059**
Surgery (y/n)	2.24	0.056
Androgen deprivation (y/n)	0.63	0.17
Grade ⩾2 acute LGI toxicity (y/n)	1.80	0.056
V75 Gy (%) (continuous)	1.062	0.0049
Rectal bleeding (G3a lrb)[a]		**0.035**
Surgery (y/n)	3.64	0.0097
Grade ⩾2 acute LGI toxicity (y/n)	2.01	0.12
V75 Gy (%) (continuous)	1.037	0.27
Rectal bleeding (G3b lrb)[b]		**0.035**
Surgery (y/n)	2.94	0.018
Grade ⩾2 acute LGI toxicity (y/n)	1.68	0.19
V75 Gy (%) (continuous)	1.05	0.065

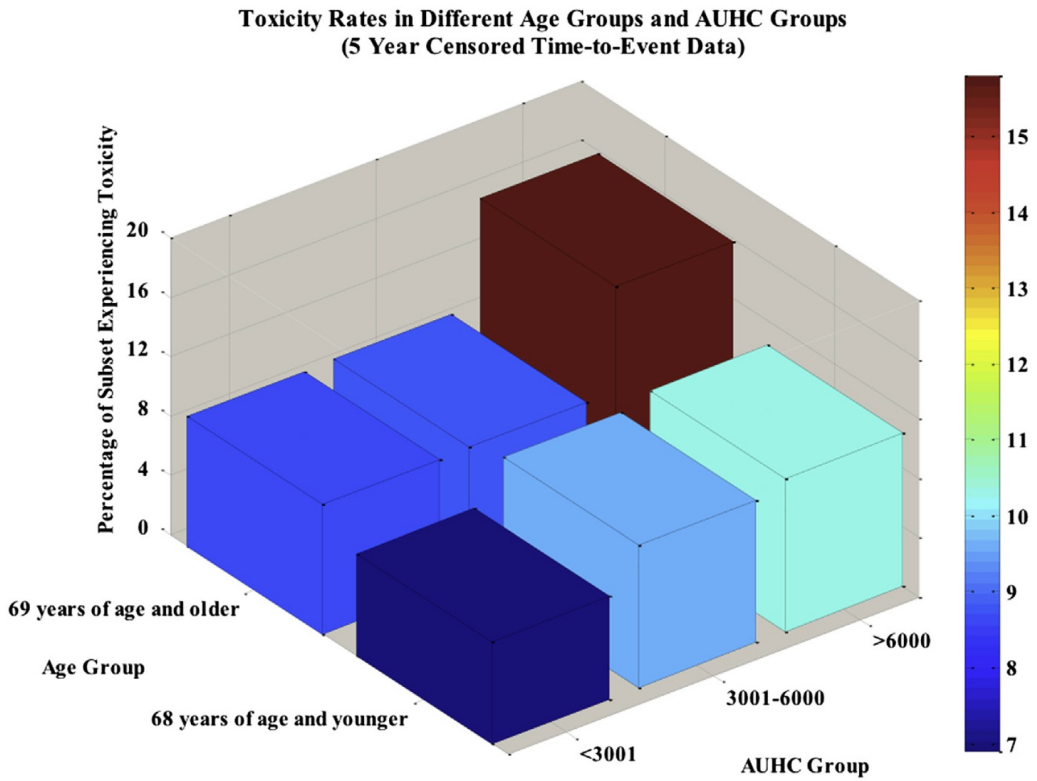
Abbreviations: OR, odds ratio; lrb, late rectal bleeding; y, yes; n, no; G3, grade 3; LGI, lower gastro-intestinal; V40 Gy, volume receiving more than 40 Gy; V75 Gy, volume receiving more than 75 Gy.

[a] More than 2 blood transfusions and/or laser coagulations.

[b] At least one transfusion and/or laser coagulation.

G. Fellin et al. / Radiotherapy and Oncology (2009)

> 69 years old patient higher risk of genitourinary toxicity



Ahmed et al. Int. J. Radiat. Oncol. Biol. Phys (2013)

One thing is clear:

The less ⇨ The better Treatment planning

Patient specific QA improves outcomes. IGRT/IVD

Need to include patient specific characteristics in a predictive toxicity model

New techniques:

What do we know…

SBRT vs conventional and moderate hypofractionnated regimes

What do we know?

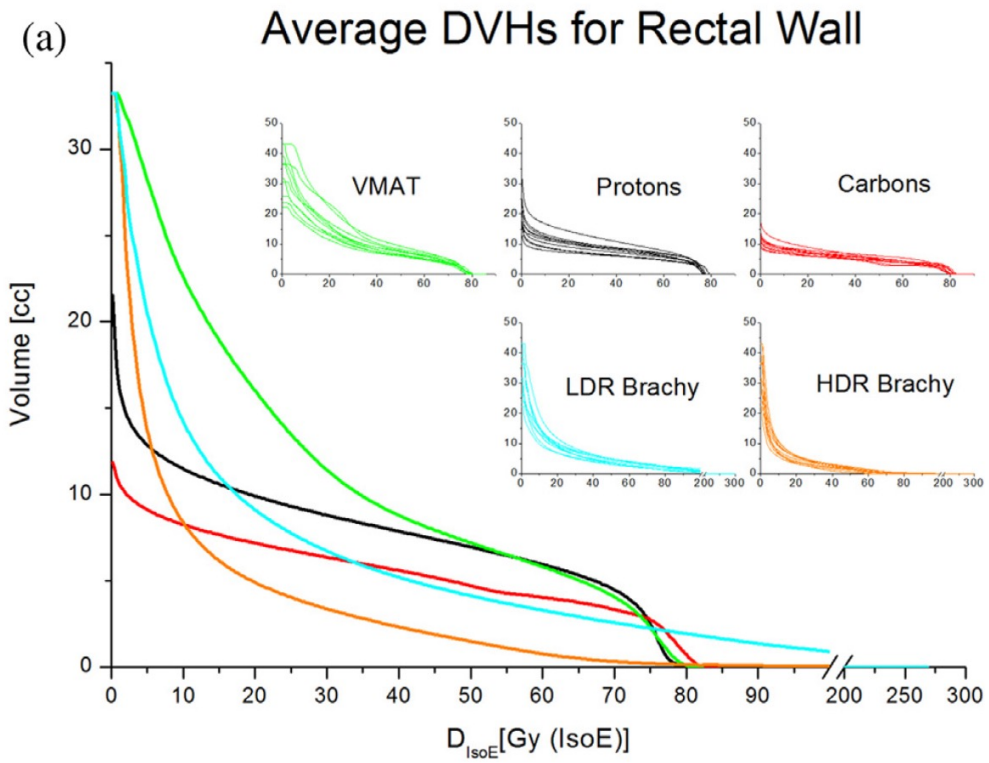
Early toxicity data from PACE-B compared with HYPO-RT-PC suggest that the lower BED in this trial might be preferable.

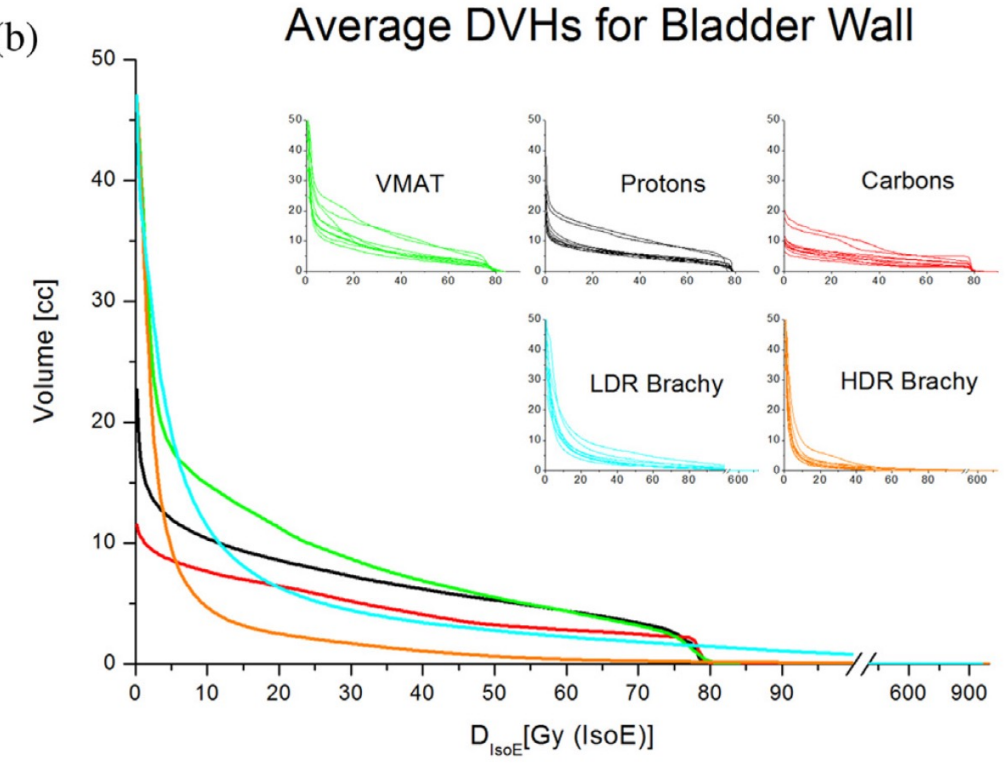
All patients in PACE-B were treated with IMRT/VMAT whereas this proportion was only 20% in HYPO-RT-PC

Trials comparing moderate conventional, hypofractionated and stereotactic body radiotherapy						
PACE-B[19]	2019	874	Low and intermediate risk	78 Gy/39 vs 62 Gy/20 vs 36.25 Gy/5 fractions; no ADT; non-inferiority design	Pending	No difference in acute GI or GU toxicity
HYPO-RT-PC[20]	2019	1,200	Intermediate and high risk	78 Gy/39 vs 42.7 Gy/7 fractions; no ADT; non-inferiority design	5-year RFS was 84% in both arms (HR 1.002, 95% CI 0.758–1.325); SBRT was non-inferior	Worse late GU toxicity in SBRT arm at 1 year using clinician and PRO measures; significantly higher acute GI and GU toxicity in the SBRT arm using PRO measures but not observed in clinician-reported outcomes

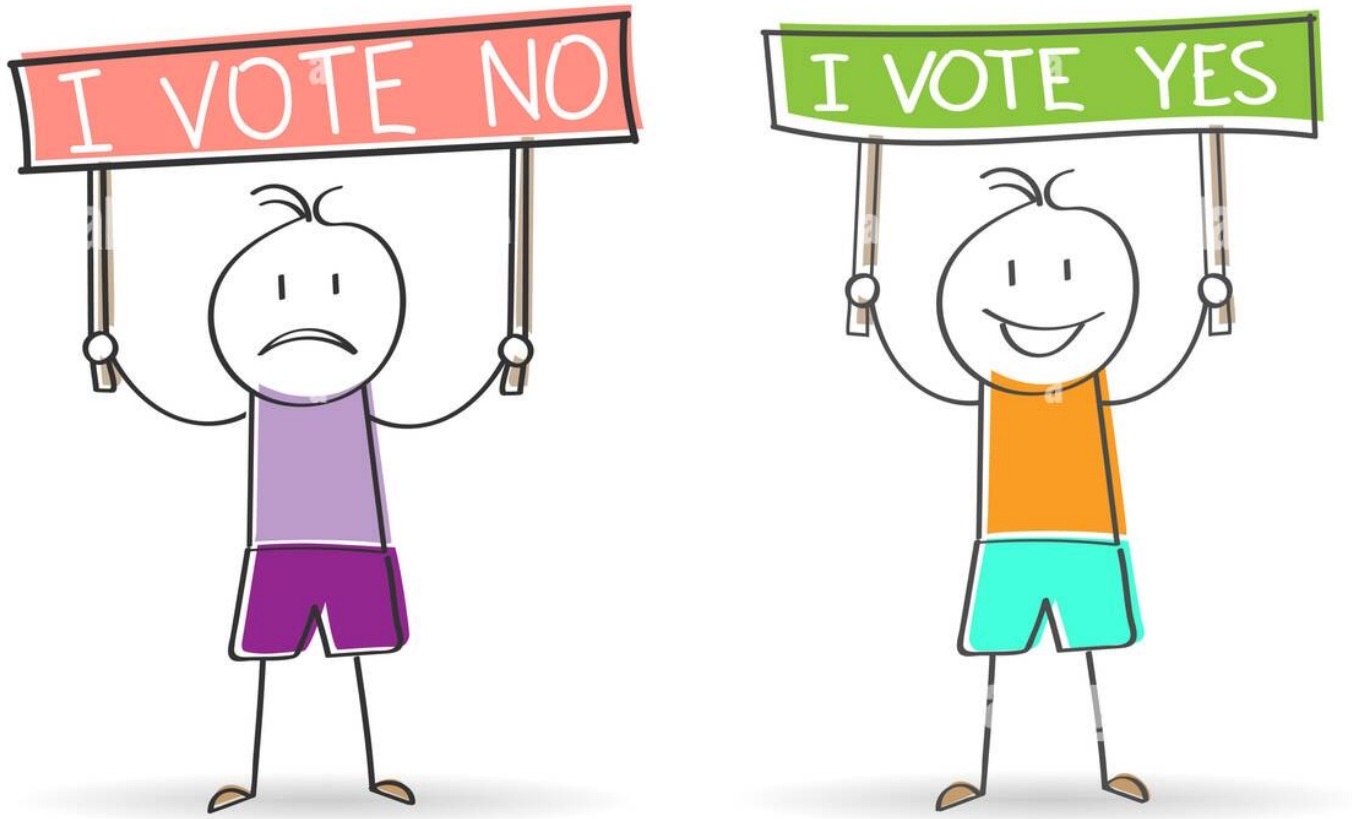
ADT, androgen deprivation therapy; BCDF, biochemical and/or clinical disease failure; BCFS, biochemical recurrence-free survival; DFS, disease-free survival; PRO, patient-reported outcomes; GI, gastrointestinal; GU, genitourinary; RFS, relapse-free survival; SBRT, stereotactic body radiotherapy. [a]Primary outcome for this trial was assessing late toxicity.

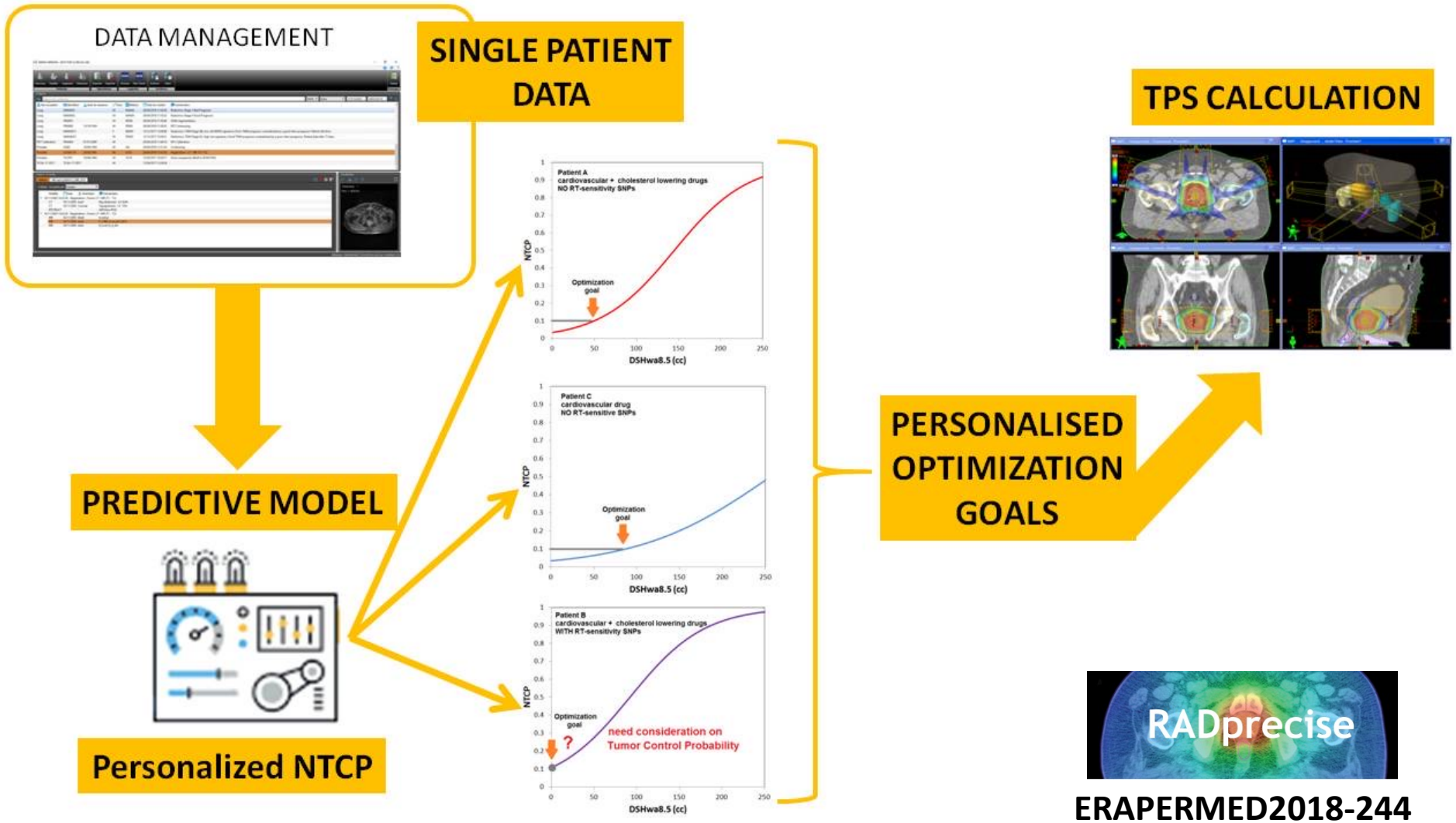
Planning comparison





D. Georg et Al. Int. J. Radiat. Oncol. Biol.Phys. 2015





RADprecise

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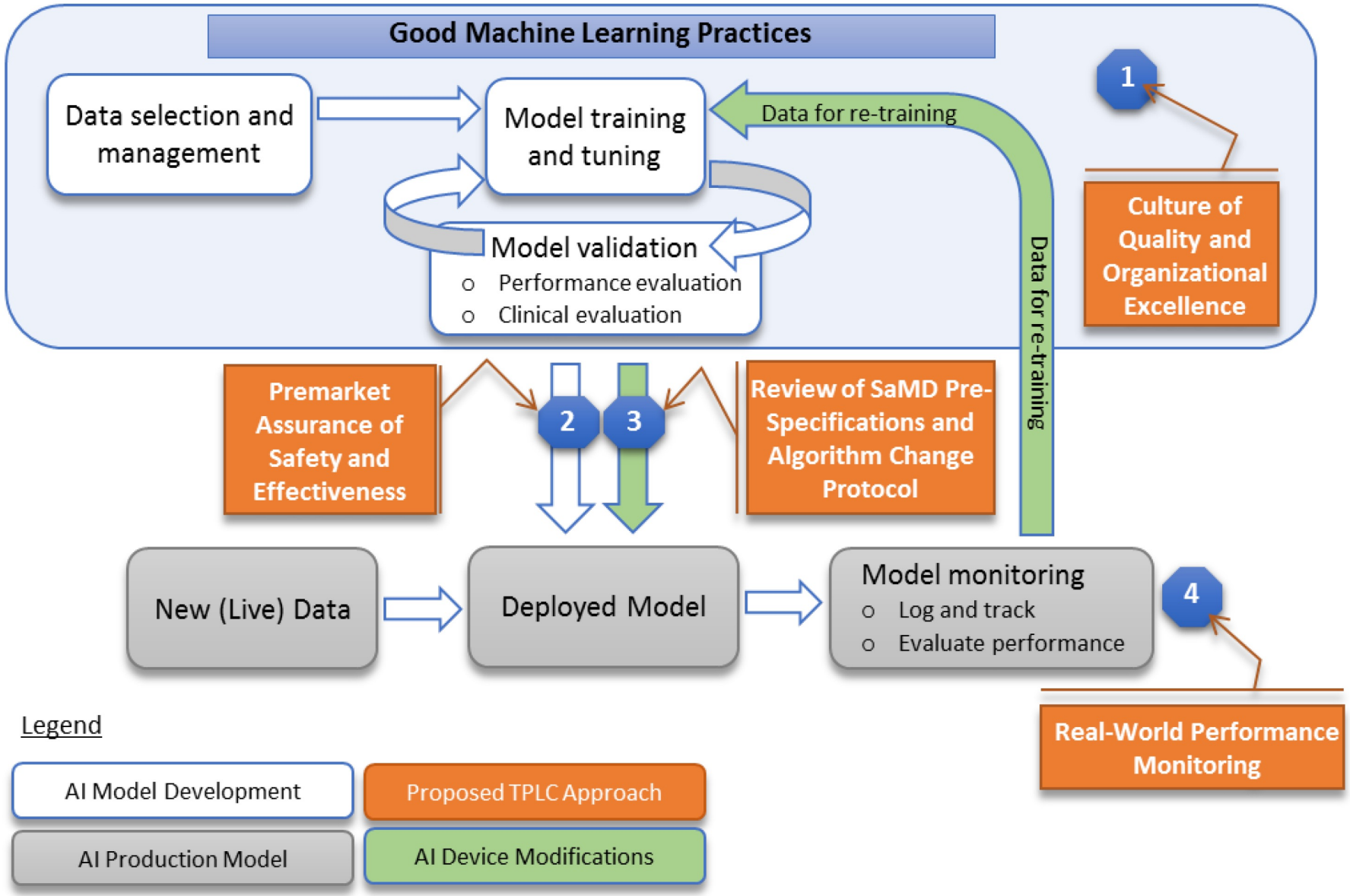

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To wrap up

- Need of including spatial information of dose distribution in the predictive models
- Need to minimize differences between planning and delivery. Or else estimate delivered dose.
- Need to include patient information (genomics, previous treatments, clinical data) in predictive models
- Dose indices ALONE cannot predict toxicity