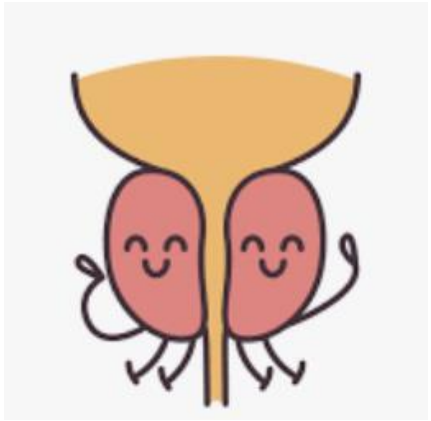
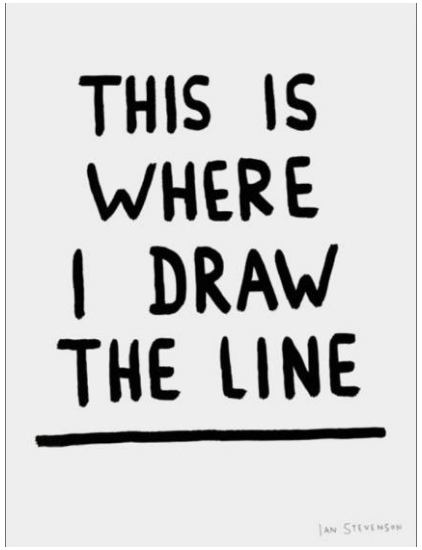
Precision art for prostate radiotherapy





Prof Isabel Syndikus / Dr Julia Murray

Clatterbridge Cancer Centre / Royal Marsden Hospital

NPCA quality improvement workshop

Thursday 21st March

Vincent van Gogh, Sunflowers, 1888

Some factors to consider for prostate radiotherapy

- Patient history
- Clinical parameters
- Anatomy
- Treatment delivery

Prostate gland delineation

- MRI *cf* CT superior in terms of contrast resolution allowing detailed visualization of prostate and peri-prostatic structures
- Currently, CT/MRI is the modality of choice for prostate gland delineation
- Reduced inter-observer delineation variability of up to 3.5 times on CT / MRI compared to CT[1]
- However, fusion uncertainties of the prostate gland

Debois M, Oyen R, Maes F, et al. The contribution of magnetic resonance imaging to the three-dimensional treatment planning of localized prostate cancer. *Int J Radiat Oncol Biol Phys. 1999; 45(4): 857-865*

Prostate gland contouring

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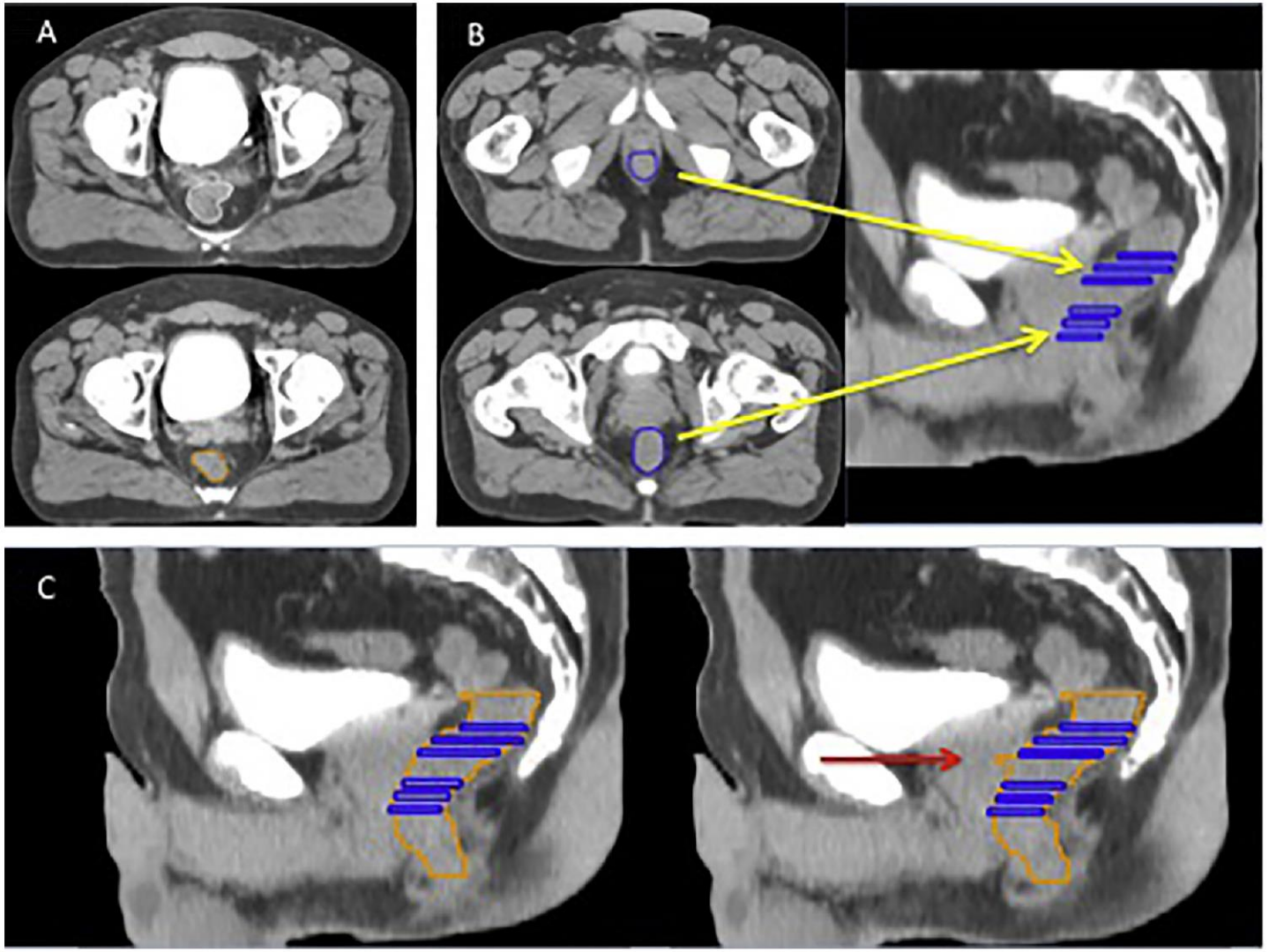
ESTRO ACROP guideline

ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer

Carl Salembier[a], Geert Villeirs[b], Berardino De Bari[c], Peter Hoskin[d], Bradley R. Pieters[e], Marco Van Vulpen[f], Vincent Khoo[g], Ann Henry[h], Alberto Bossi[i], Gert De Meerleer[j], Valérie Fonteyne[k,*]

Guide to delineate the rectum:

Recto-sigmoid junction – where the rectum turns horizontally in the sigmoid colon



In the axial plane: delineate the rectum contour on all slices where you can easily differentiate from the surrounding tissues, use the interpolation tool

Review contours in the sagittal plane to detect inappropriate protrusions

OAR: PENILE BULB

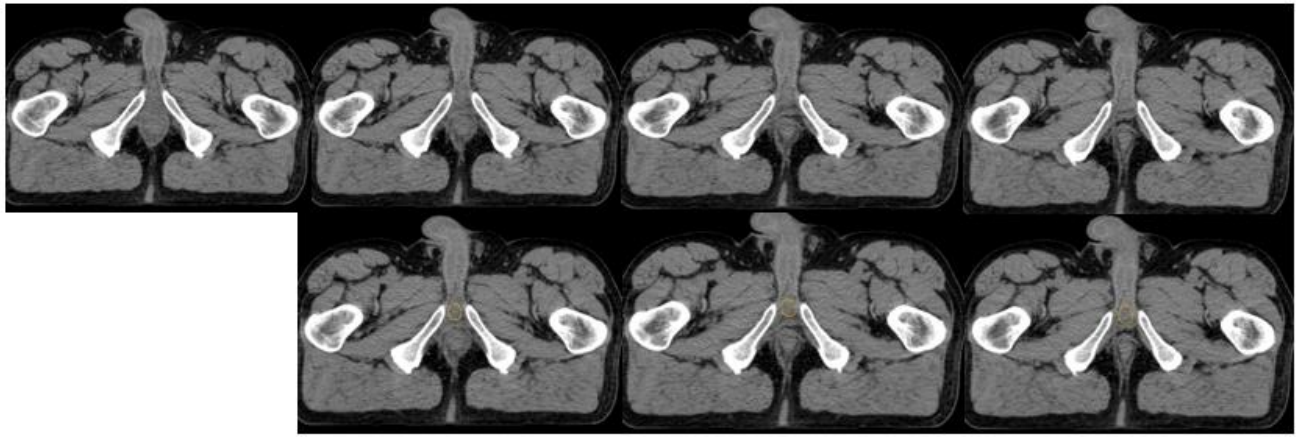
RTOG definition

(Gay et al. IJROBP 2012):

Portion of bulbous spongiosum of the penis immediately inferior to the GU diaphragm.

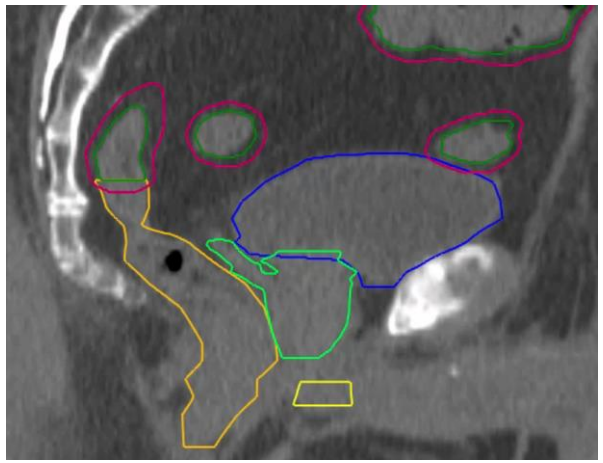
Structure should not be extended anteriorly into the shaft or pendulous portion of the penis.

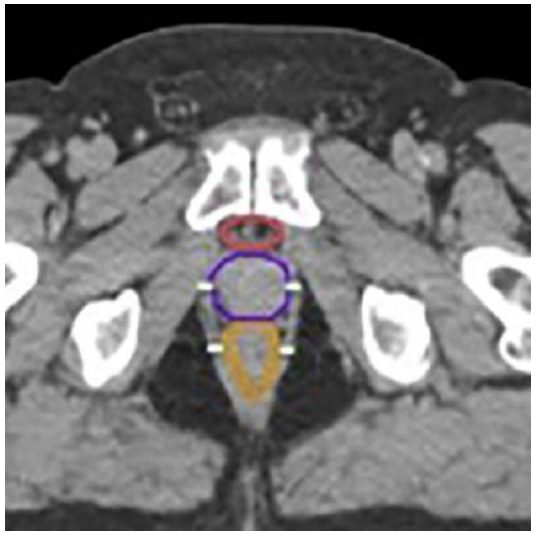
On CT, the penile bulb will be posterior to the urethra and has a round shape

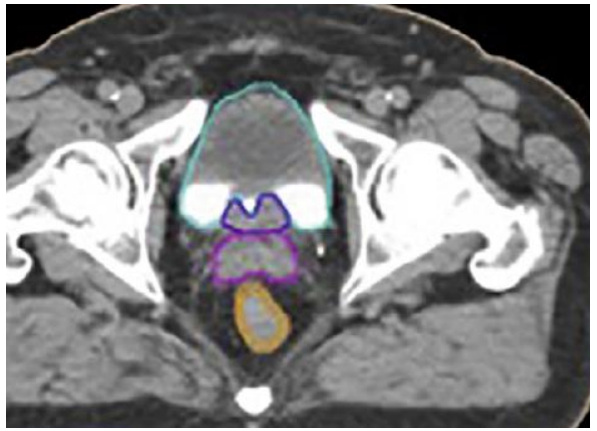


Prostate CTV

- Apex: approx. 1cm above the upper border of the PB
- Mid prostate:
  - lateral border – levator ani
  - anterior border – include the anterior fascia and exclude the fat area in front of the anterior fascia
  - posterior border – anterior border of rectum
- Base: in continuity with the bladder

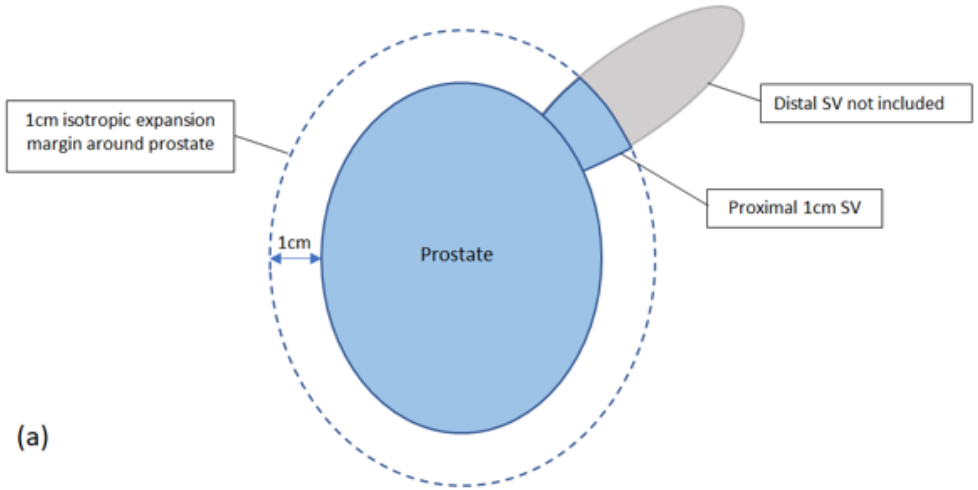


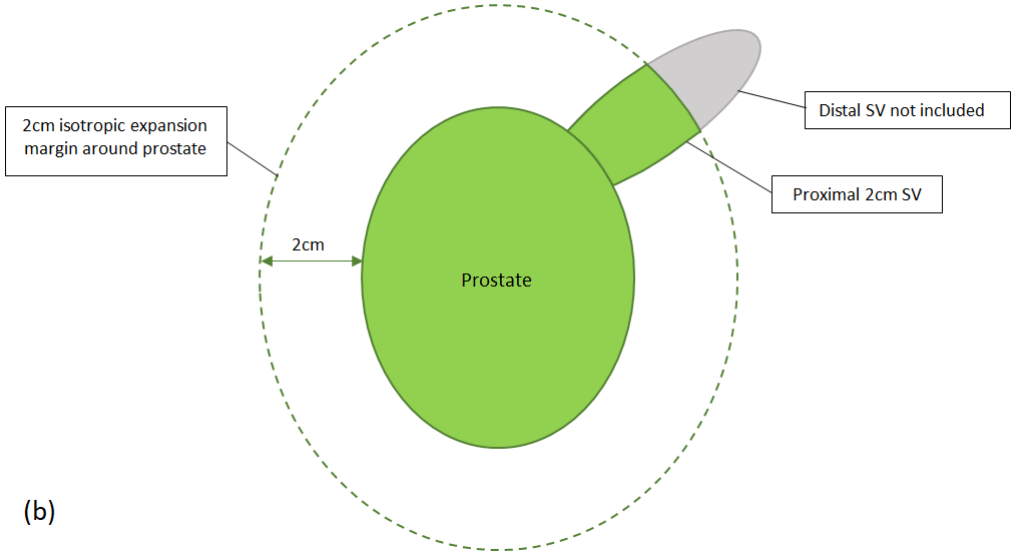




Seminal vesicle contouring

- Contour prostate first
- Expand by 1cm or 2cm, and use these ring structures as a guide for SV contouring
- Include the base SV for tumours at base and T3b disease





Clinical target volume

(adapted from PACE protocol)

- Low risk : T1-T2a, Gleason 6, PSA <10ng/ml
  - CTVp = prostate only

- Intermediate risk: T2b-T2c, Gleason 3+4, PSA 10-20ng/ml
  - CTVpsv = prostate + proximal 1cm of SV

- High risk: T3a, Gleason 8-10, PSA >20ng/ml
  - CTVsv = prostate + proximal 2cm of SV
  - CTVpsv = prostate + proximal 1cm of SV

- Very high risk: T3b
  - CTVsv = prostate + full length of SV
  - CTVpsv = prostate + involved SV length / 1cm if involvement is less

Pelvic lymph node contouring

Clinical trial radiotherapy planning guidelines:

- PIVOTALboost
- PEARLS
- PACE-NODES

NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes for Intact and Postoperative Prostate Cancer (Hall WA et al. IJROBP 2021: 109 (1): 174-185

Inter-observer variability in contouring

- Found in all treatment sites
- Reasonable agreement for prostate contouring, found most variation with the prostatic apex and rectum contours
- Use of imaging (diagnostic / planning) to aid contouring
- Patient preparation
- Peer review
- Role of automated contouring
- Variations in contouring -> impact on dosimetric parameters

Bowel toxicity after prostate radiotherapy

Project report 14/8/2023

Rhiju Chatterjee

Isabel Syndikus

Phil Reynolds

Clatterbridge Canter Centre

Introduction

This audit included patient treated between 2016 and 2017

- 802 patient who had primary prostate radiotherapy.
- 39 patients were recorded to have toxicity (National Prostate Cancer Audit NPCA).

- Exclusion
  - **No-toxicity group**

  - missing radiotherapy data (55),

  - HDR brachytherapy (3), postoperative RT (1), previous procto-colectomy (1).
  - **Toxicity group**

  - 3 patients with a new diagnosis of colo-rectal cancer during the 2 year follow up.
- Evaluation of risk factors for bowel toxicity.
  - Clinical characteristics
  - Treatment volume (prostate only versus prostate and pelvic nodes)
  - Rectum and bowel dose volume histograms

Baseline characteristics

	All (n=802)	GI toxicity (n=39)	No toxicity (n=763)	
Age mean (SD)	70.5 (6.5)	71.4 (6.4)	70.4 (6.4)	p=0.37
IMD5 1 or 2 (%)	348 (43.4)	16 (41.0)	235 (43.5)	p=0.40
Charlson score (%) 0	461 (57.5%)	23 (59.0%)	438 (57.4%)	p=0.96
1	247 (30.8)	12 (30.8%)	235 (30.8%)	
2	94 (11.7)	4 (10.3%)	90 (11.8%)	
Low risk	4 (0.5%)	1 (2.6%)	3 (0.4%)	Low/intermed vs high/mets: RR: 1.47 95% CI: 0.71-3.1 p=0.30
Intermediate	239 (29.8%)	8 (20.5%)	231 (30.3%)	
High risk	530 (66.1%)	29 (74.4%)	501 (65.7%)	
Metastatic	20 (2.5%)	1 (2.6%)	19 (2.5%)	
missing	9 (1.1%)	0 (0%)	9 (1.2%)	

Bowel symptoms in the NCPA cohort

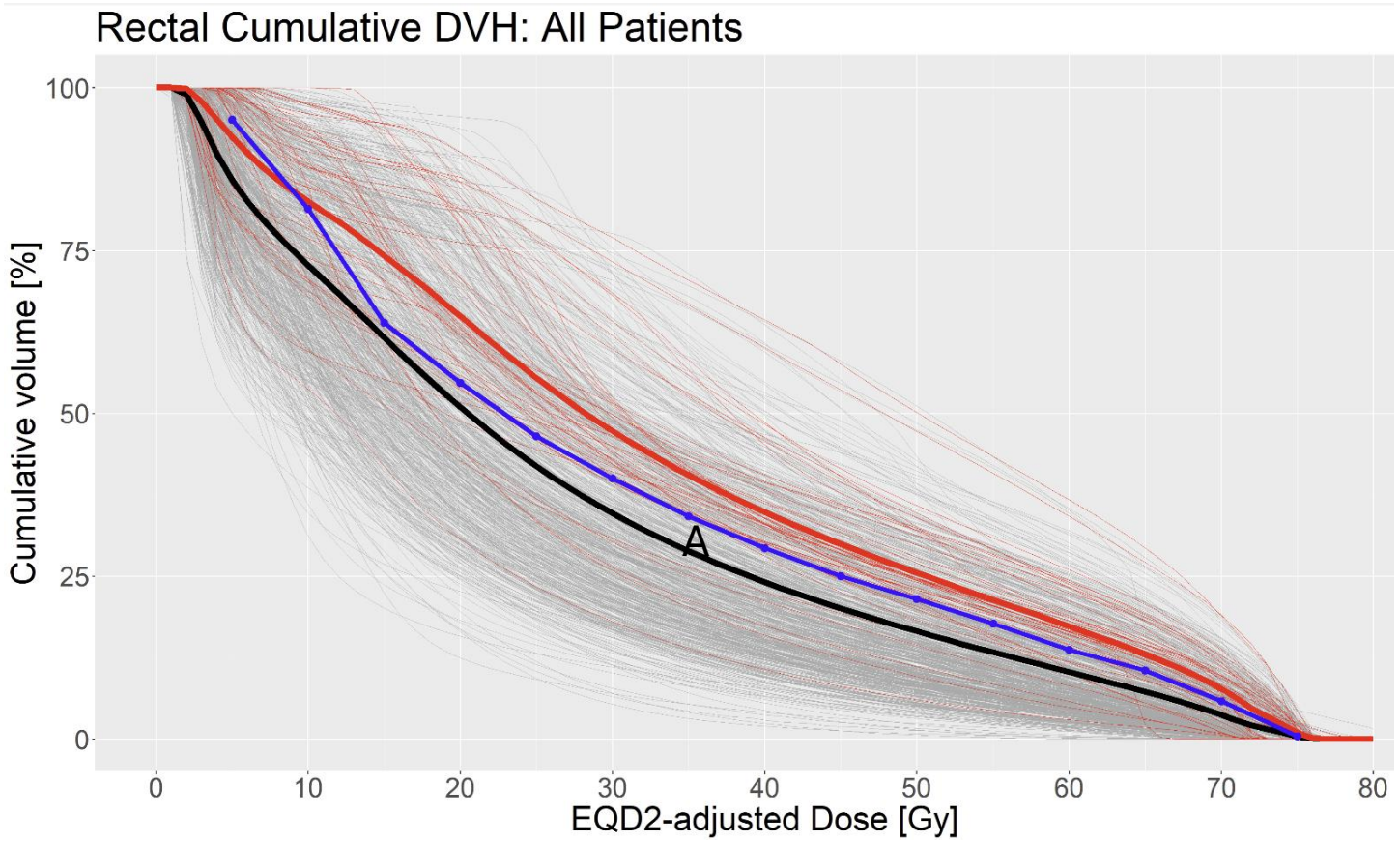
n = 42	number	comment
Second cancer	4	Excluded: 3 patient with colon cancer or rectal cancer Included: 26 months metastatic pancreas cancer
No symptoms	2	
Bleeding	14	
Bleeding diarrhoea	3	
Bleeding proctitis	2	
Diarrhoea	6	
Proctitis	11	
Total	39	

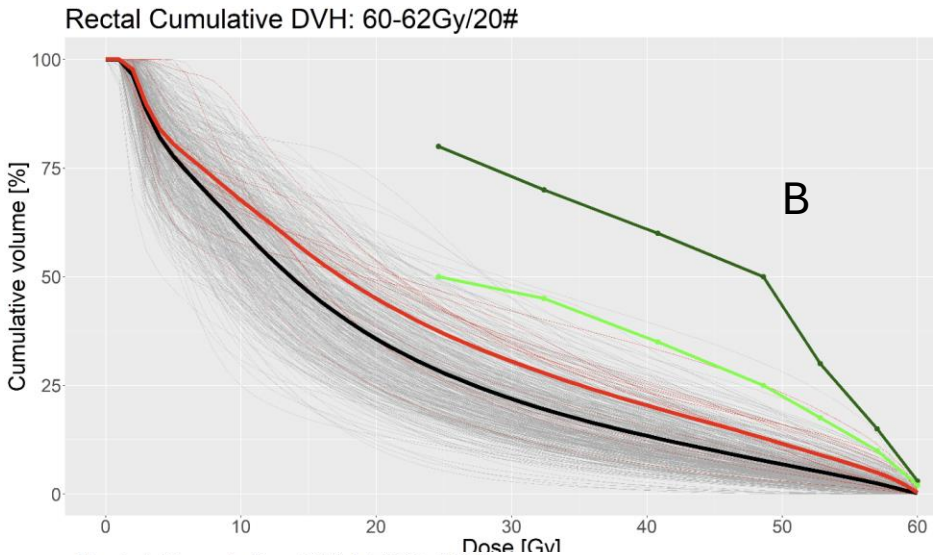
Radiotherapy

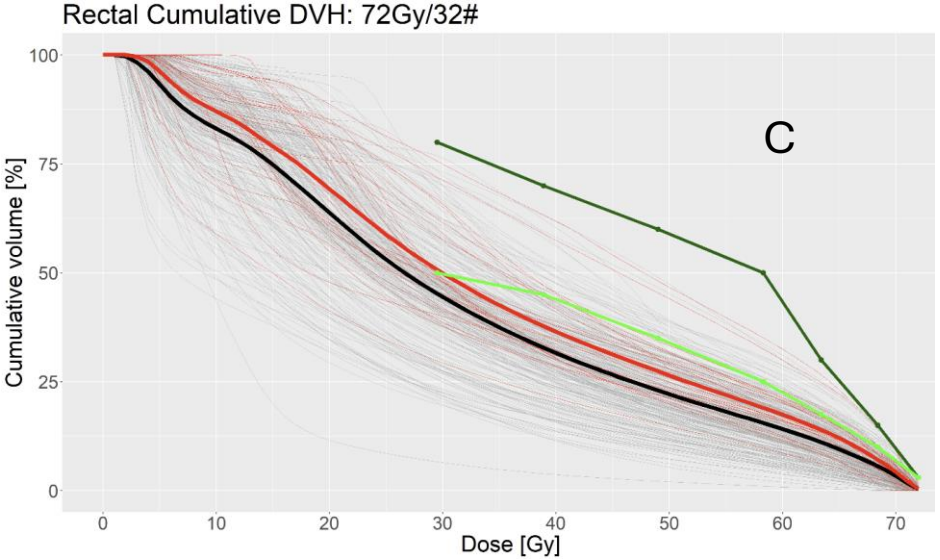
Dose	All n=802	GI toxicity n=39	No toxicity n=763	
PPN (72Gy/32)	300 (37.4%)	25 (64.1%)	275 (36%)	RR: 3.15 (95% CI: 1.58-5.66), p<0.0006 PPN vs PO
Prostate only (60Gy/20, 62Gy/20, PACE)	492 (62.6%)	14 (35.9%)	488 (64%)	
Palliative (36Gy/6, STAMPEDE)	10 (1.2%)	1 (2.6%)	9 (1.2%)	
Prostate PTV, cm^3 (SD)				
Whole cohort (802)	81.8 (35.4)	85.0 (37.2)	81.6 (35.3)	p=0.29 toxicity vs no toxicity
PPN (300)	84.3 (28.8)	85.1 (29.6)	84.2 (28.8)	p=0.0003 PPN vs PO
Prostate only (492)	77.4 (27.5)	73.2 (22.6)	77.5 (27.7)	
Palliative (10)	224.6 (136)	237.3 (N/A)	223.1 (144)	Volume included SV

There was a higher incidence of bowel dose in the prostate pelvic node cohort compared to prostate only

Dose volume histogram (DVH)







Thick line Averaged DVH

Red line Toxicity cohort

Black line No toxicity cohort

Light Green Optimal dose constraints

Dark green Mandatory dose constraints

Blue New optimal dose constraints

Rectum DVH logistic regression (EQD2)

Dose	Toxicity group mean volume* (SD)	Non-toxicity group mean volume* (SD)	OR (99.3% CI)	P value
$V20_{EQD2}$	64.8% (14.4)	51.0% (16.7)	1.04 (1.01-1.08)	p<0.007
$V30_{EQD2}$	47.1% (12.5)	34.8% (13.9)	1.05 (1.01-1.09)	p<0.007
$V40_{EQD2}$	34.6% (10.4)	24.2% (11.3)	1.06 (1.02-1.11)	p<0.007
$V50_{EQD2}$	25.3% (8.6)	16.6% (9.0)	1.08 (1.02-1.14)	p<0.007
$V60_{EQD2}$	17.1% (6.9)	10.3% (6.8)	1.10 (1.03-1.18)	p<0.007
$V65_{EQD2}$	12.6% (6.2)	7.2% (5.6)	1.12 (1.03-1.22)	p<0.007
$V70_{EQD2}$	7.4% (4.7)	3.7% (3.9)	1.18 (1.04-1.33)	p<0.007

Atlas of complications rectum

NPCA data: 72Gy/32# prostate pelvic nodes

Relative Volume (%)	72Gy/32#	5	10	15	20	25	30	35	40	45	50	55	60	65	70
100		19/165	5/35	0/5	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
90		4/70	12/116	9/63	2/13	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
80		2/25	5/69	7/93	9/53	2/15	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
70		0/10	2/30	6/56	4/65	6/32	4/17	1/4	0/0	0/0	0/0	0/0	0/0	0/0	0/0
60		0/2	1/15	2/28	7/84	6/73	3/30	1/13	2/7	0/1	0/0	0/0	0/0	0/0	0/0
50		0/1	0/6	1/18	2/24	8/96	9/93	5/39	2/15	2/8	1/3	0/0	0/0	0/0	0/0
40		0/0	0/2	0/9	1/24	2/27	8/85	15/121	6/75	5/35	1/13	2/4	0/0	0/0	0/0
30		0/0	0/0	0/0	0/8	1/27	1/32	2/60	14/119	13/120	9/83	5/39	2/11	0/0	0/0
20		0/0	0/0	0/1	0/0	0/1	0/14	1/35	1/47	5/84	13/129	17/145	14/107	5/34	0/0
10		0/0	0/0	0/0	0/1	0/1	0/1	0/0	0/9	0/24	1/44	1/82	9/147	19/197	9/65
0		0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/1	0/1	0/3	0/8	1/42	16/208
	Dose (Gy) (Not adjusted)														

60-100%
40-60%
25-40%
15-25%
5-15%
0-5%

NPCA data: 60Gy/20# prostate only

Relative Volume (%)	60Gy/20#	5	10	15	20	25	30	35	40	45	50	55	60
100		2/15	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
90		1/86	1/4	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
80		7/180	1/51	0/2	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
70		1/113	6/116	2/25	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
60		1/43	3/126	5/79	0/18	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
50		0/5	1/105	4/134	8/69	1/19	0/2	0/0	0/0	0/0	0/0	0/0	0/0
40		0/0	0/35	0/123	3/133	7/76	4/30	1/7	0/1	0/0	0/0	0/0	0/0
30		0/0	0/4	1/70	0/152	3/160	4/108	7/54	2/21	1/5	0/1	0/0	0/0
20		0/0	0/1	0/9	1/64	1/164	3/212	2/180	7/131	7/60	4/20	1/3	0/0
10		0/0	0/0	0/0	0/6	0/23	1/87	2/195	3/272	3/322	6/253	5/98	0/0
0		0/0	0/0	0/0	0/0	0/0	0/3	0/6	0/17	1/55	2/168	6/341	12/442
	Dose (Gy) (Not adjusted)												

60-100%
40-60%
25-40%
15-25%
5-15%
0-5%

The pelvic node group had higher risks for all dose levels

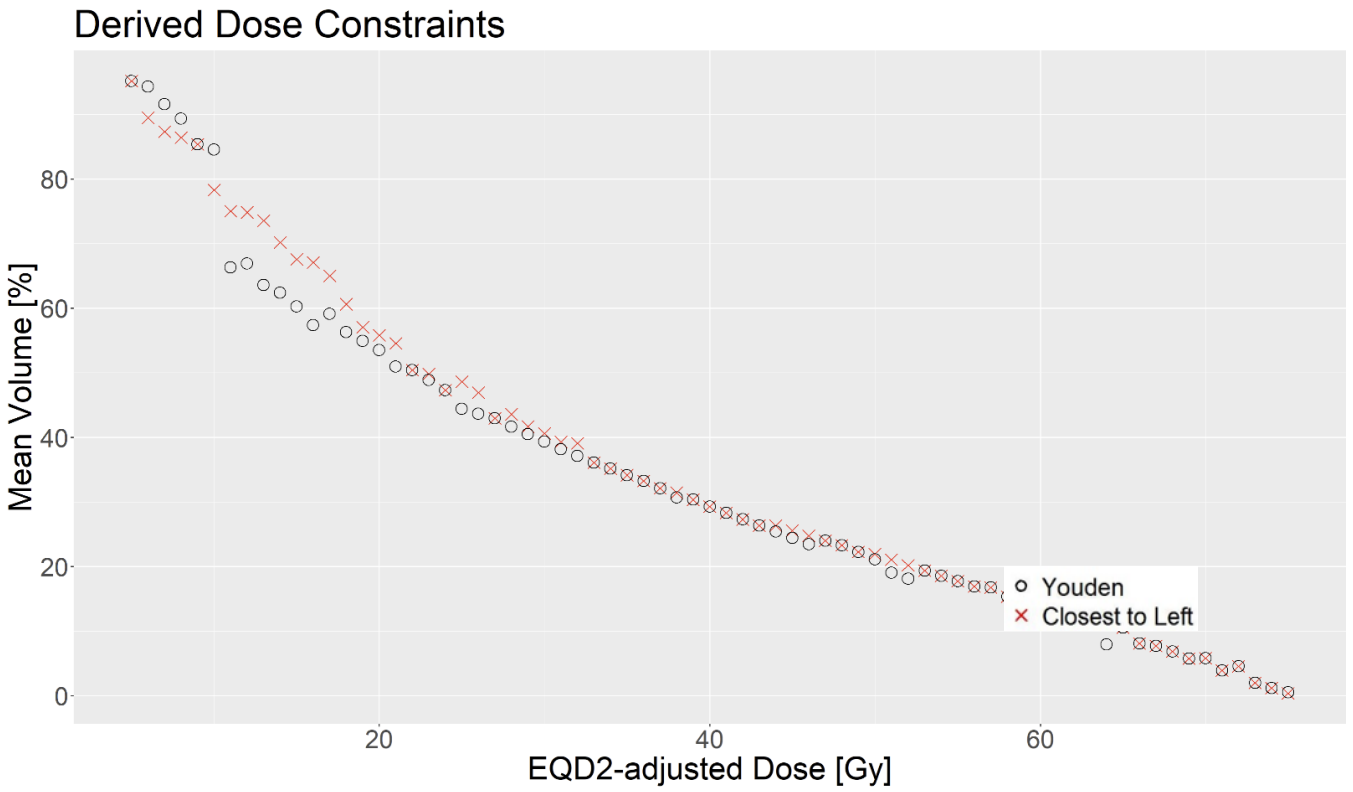
Bowel DVH logistic regression

Dose	Toxicity group mean volume (SD)	Non-toxicity group mean volume (SD)	OR (99.3% CI)	P value
$V20_{EQD2}$	249.1 cm^3 (254.4)	103.4 cm^3 (204.6)	1.00 (1.00-1.01)	p=0.0682
$V30_{EQD2}$	140.4 cm^3 (146.9)	56.2 cm^3 (115.6)	1.00 (1.00-1.01)	p=0.0522
$V40_{EQD2}$	70.9 cm^3 (73.5)	28.9 cm^3 (59.0)	1.00 (1.00-1.01)	p=0.0644
$V50_{EQD2}$	13.2 cm^3 (14.4)	5.4 cm^3 (12.5)	1.02 (0.99-1.04)	p=0.1365
$V60_{EQD2}$	0.7 cm^3 (1.4)	0.2 cm^3 (0.8)	1.21 (0.95-1.49)	p=0.0854
$V65_{EQD2}$	0.1 cm^3 (0.4)	0.0 cm^3 (0.2)	1.92 (0.72-4.33)	p=0.1257

ROC analysis : optimal rectal dose-volume constraints

Dose [Gy]	NPCA	CHiPP Wilkins	CCC 2015 O	CCC 2015 M	CCC 2024 O	CCC 2024 M
5	95.1					
10	81.4					
15	63.9					
20	54.7		80	70	80	70
25	46.5					
30	40.0	49.5	70	45	65	51
35	34.2					
40	29.3	39.3	60	35	50	38
45	25.0					
50	21.5	31.5	50	25	30	30
55	17.7					
60	13.7	17.5	30	17.5	15	15
65	10.5		15	10	3	5
70	5.8	2.3	3	2	0	1
75	0.4		0	0	0	0

EQD2-Adjusted Dose α/β=3
Optimal and mandatory dose constraints



Logistic regression average of Youden and CTL indices
Wilkins et al IJROBP 2020;106:928–38.

Issues with previous models

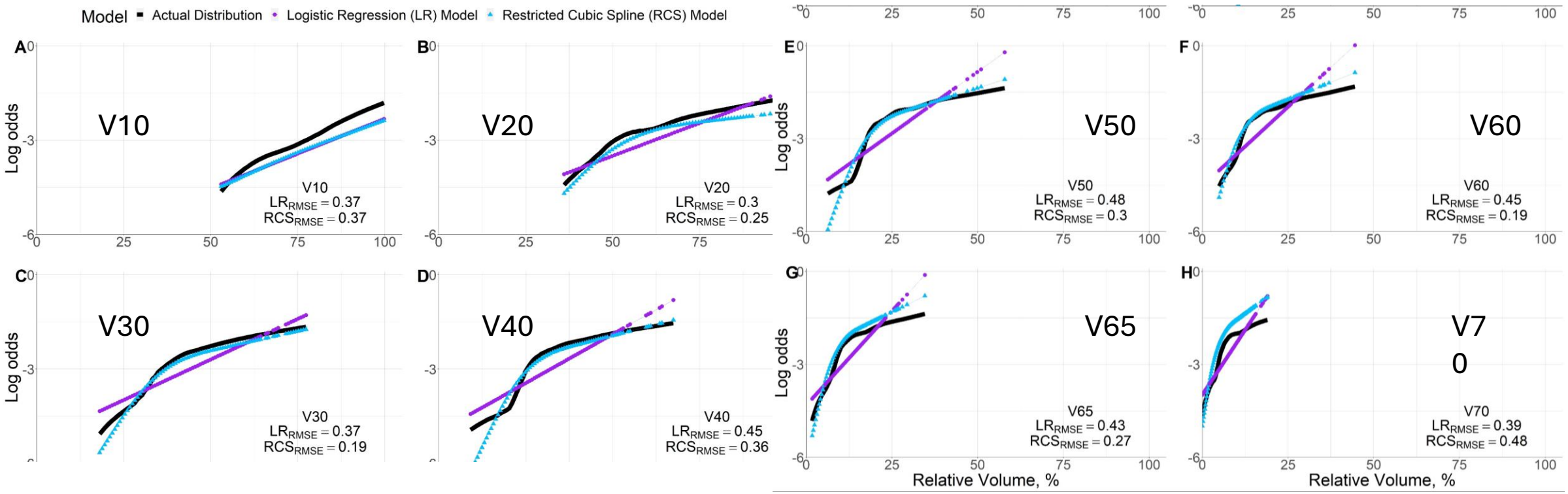
- Independent discrete dose bins (ie: V10, V20…)
  - Loose info by using discrete bins, also neglects lower doses

  →Treat dose as continuous functio
- Linear models on non-linear distributions
  - Toxicity may not increase linearly with volumes irradiated

  → Restricted cubic splines, piecewise polynomial function that captures non-linear relationships
- Single threshold to separate toxicity vs non-toxicity
  - Generated thresholds may be sensitive but are not specific (ie: many false positives)

  → Use forecasting model “x% chance of toxicity”
- No modelling on small bowel doses
  - To what extent does small bowel volume irradiation contribute?

Rectal doses: Restricted cubic spline

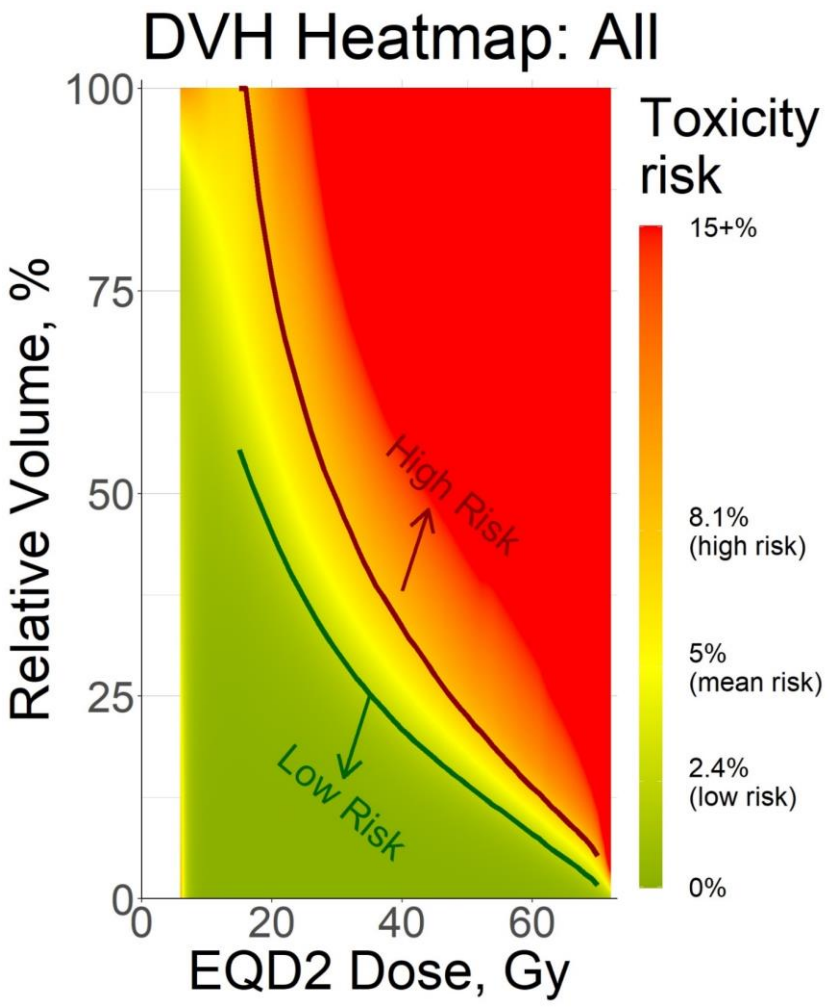


Black actual distribution

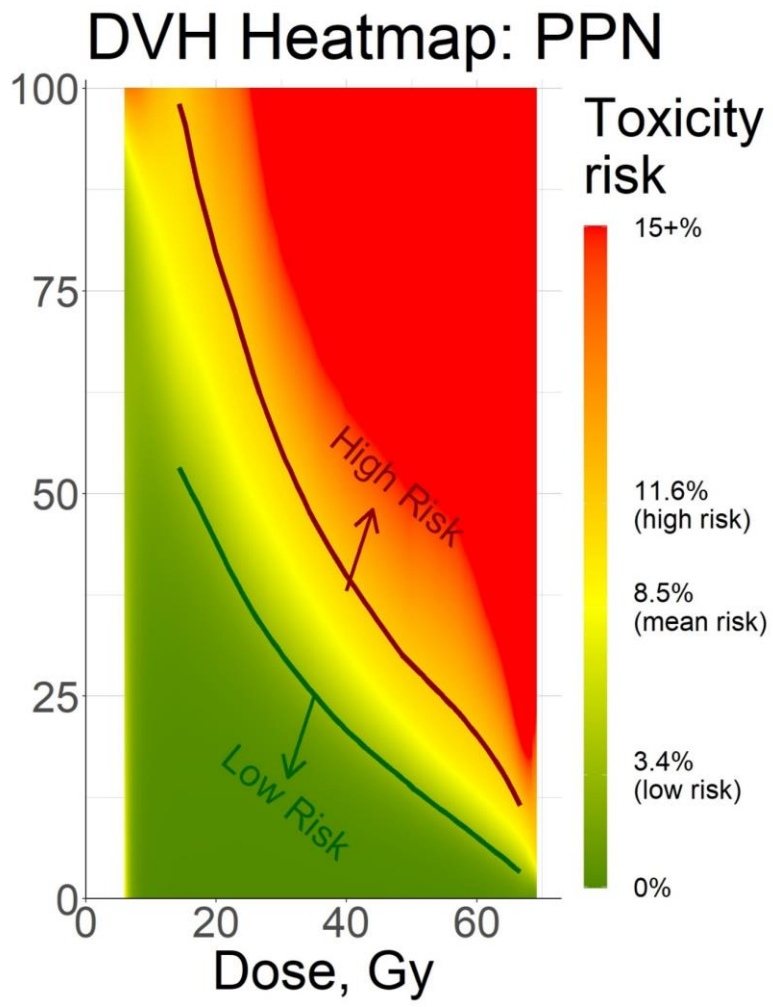
Purple logistic regression

Blue restricted cubic spline

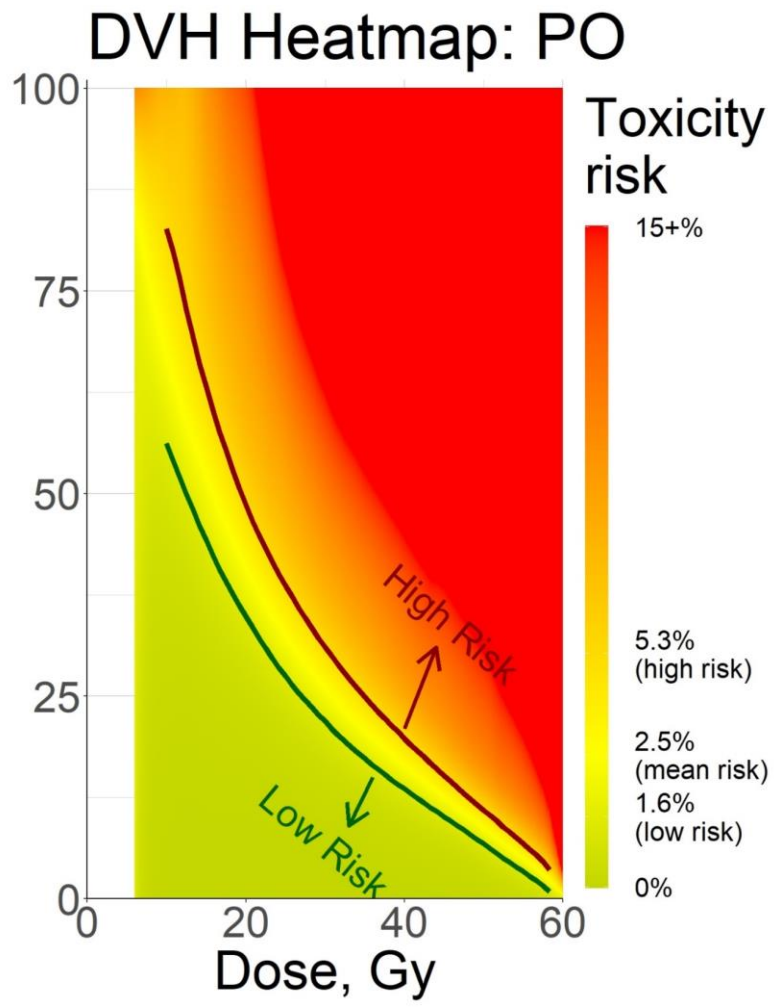
Probability Generating Function with thresholds



Mean risk 5%

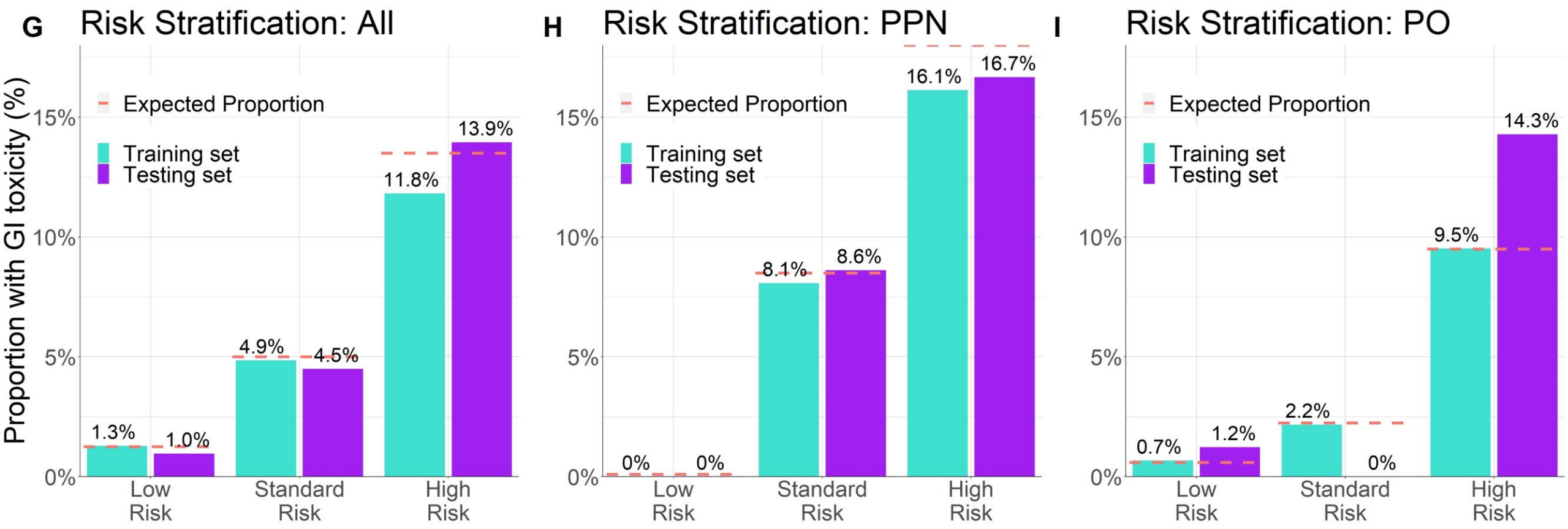


mean risk 8.5%



mean risk 2.5%

Risk stratification



Conclusions

- All patients were planned with the same class solution VMAT plans
- The rectal and bowel dose constraints were effective and realised for all plans.
- We achieved overall a low bowel toxicity level.
- The toxicity reported by NCPA was verified 39/42 patients
- Patients undergoing pelvic node radiotherapy or high-risk localised disease were more likely to experience gastrointestinal complications.
- Differences in PTV margins and IGRT techniques might have contributed to this.
- Higher rectal doses had a higher risk of toxicity from V20 –V70 in logistic regression analysis.
- There was a trend to more bowel toxicity for bowel doses from V20 –V40.

Future

- Explore how the analysis method will perform in the PIVOTALboost trial (prostate pelvic node randomisation)
- How do we explain the higher toxicity in the pelvic node group?
- These effects were not found in PIVOTAL and POP RT trials

Thank you

- NCPA team, Ajay Aggarwal
- Urology team Clatterbridge Cancer Centre