

# Dose-volume constraints and volume effects for rectal toxicity after external RT for prostate cancer

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Despite increasing planning and delivering skills, the high-dose volume inevitably includes some portions of the bladder and the rectum: therefore, the total dose of radiotherapy that can be delivered is still limited by the tolerance of surrounding normal tissues, mainly the rectum and the bladder.

A precise understanding of the tolerance of these two organs is essential because it determines the dose to the target.

# Rectal toxicity: collecting clinical data

- 2 major grading schemes: RTOG and SOMA/LENT

Table 1. RTOG/EORTC late radiation morbidity scoring scheme

	Grade 1	Grade 2	Grade 3	Grade 4
Rectum	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus; intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/perforation fistula

Table 2. LENT/SOMA scales for rectum

	Grade 1	Grade 2	Grade 3	Grade 4
<i>Subjective</i>				
Tenesmus	Occasional urgency	Intermittent urgency	Persistent urgency	Refractory
Mucosal loss	Occasional	Intermittent	Persistent	Refractory
Sphincter control	Occasional	Intermittent	Persistent	Refractory
Stool frequency	2-4/day	4-8/day	> 8/day	Uncontrolled diarrhea
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
<i>Objective</i>				
Bleeding	Occult	Occasionally > 2/ week	Persistent/daily	Gross hemorrhage
Ulceration	Superficial $\leq 1 \text{ cm}^2$	Superficial > 1 $\text{cm}^2$	Deep ulcer	Perforation, fistula
Stricture	> 2/3 normal diameter with dilatation	1/3-2/3 diameter with dilatation	< 1/3 normal diameter	Complete obstruction
<i>Management</i>				
Tenesmus & stool frequency	Occasional, $\leq 2$ antidiarrheals/week	Regular, > 2 antidiarrheals/ week	Multiple, > 2 antidiarrheals/day	Surgical intervention/ permanent colostomy
Pain	Occasional non-narcotic	Regular non- narcotic	Regular narcotic	Surgical intervention/ permanent colostomy
Bleeding	Stool softener, iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention/ permanent colostomy
Ulceration	Diet modification, stool softener	Occasional steroids	Steroids per enema, hyperbaric oxygen	Surgical intervention/ permanent colostomy
Stricture	Diet modification	Occasional dilatation	Regular dilatation	Surgical intervention/ permanent colostomy
Sphincter control	Occasional use of incontinence pads	Intermittent use of incontinence pads	Persistent use of incontinence pads	Surgical intervention/ permanent colostomy
<i>Analytic</i>				
Barium enema	Assessment of lumen and peristalsis			
Proctoscopy	Assessment of lumen and mucosal surface			
CT	Assessment of wall thickness, sinus, and fistula formation			
MRI	Assessment of wall thickness, sinus, and fistula formation			
Anal manometry	Assessment of rectal compliance			
Ultrasound	Assessment of wall thickness, sinus, and fistula formation			

- RTOG and SOMA/LENT: modifications by single institution
- low-grade lrb  $\Rightarrow$  responsive to steroids and usually resolving in few months
- higher grade lrb  $\Rightarrow$  requiring transfusions and/or coagulation procedures, may continue for up 2-3y
- **major difference** between grading schemes concerns number of transfusion/coagulation procedures to define **grade 3 lrb**



**ATTENTION WHEN COMPARING RESULTS  
FROM DIFFERENT INSTITUTIONS**

# Dose-volume constraints: collecting dosimetric data

- DVH=classical dosimetric “tool”
- geometry of rectum raises question about accuracy and relevancy of solid organ DVH
  - ⇒ novel ways of describing dose distributions in the rectal wall  
(DWH, DSH, NDSH, NDVH, DCH, zDVH)
- using DVH as surrogate of real DWH  
(empty rectum to reduces deviations between the two,  
*Fiorino et al., PMB 2003*)

## Volume definition:

The rectum was drawn on CT slices starting just above the anal verge and continuing to the point at which it turns into the sigmoid colon. The definition of the cranial-caudal

## ... organ definition ...

large rectal volumes introduce non-negligible systematic shift between planning and treatment DVH



effort to empty rectum before simulation and planning CT

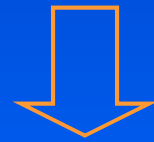


More reliable DVH  
and  
most important  
no geographic missing of target

## “Confounding” factors

Factors specific to individual patients will affect the response to radiation:

previous disease related to rectum, hypertension, cardiovascular history, diabetes, use of drugs, type and duration of hormonal therapy

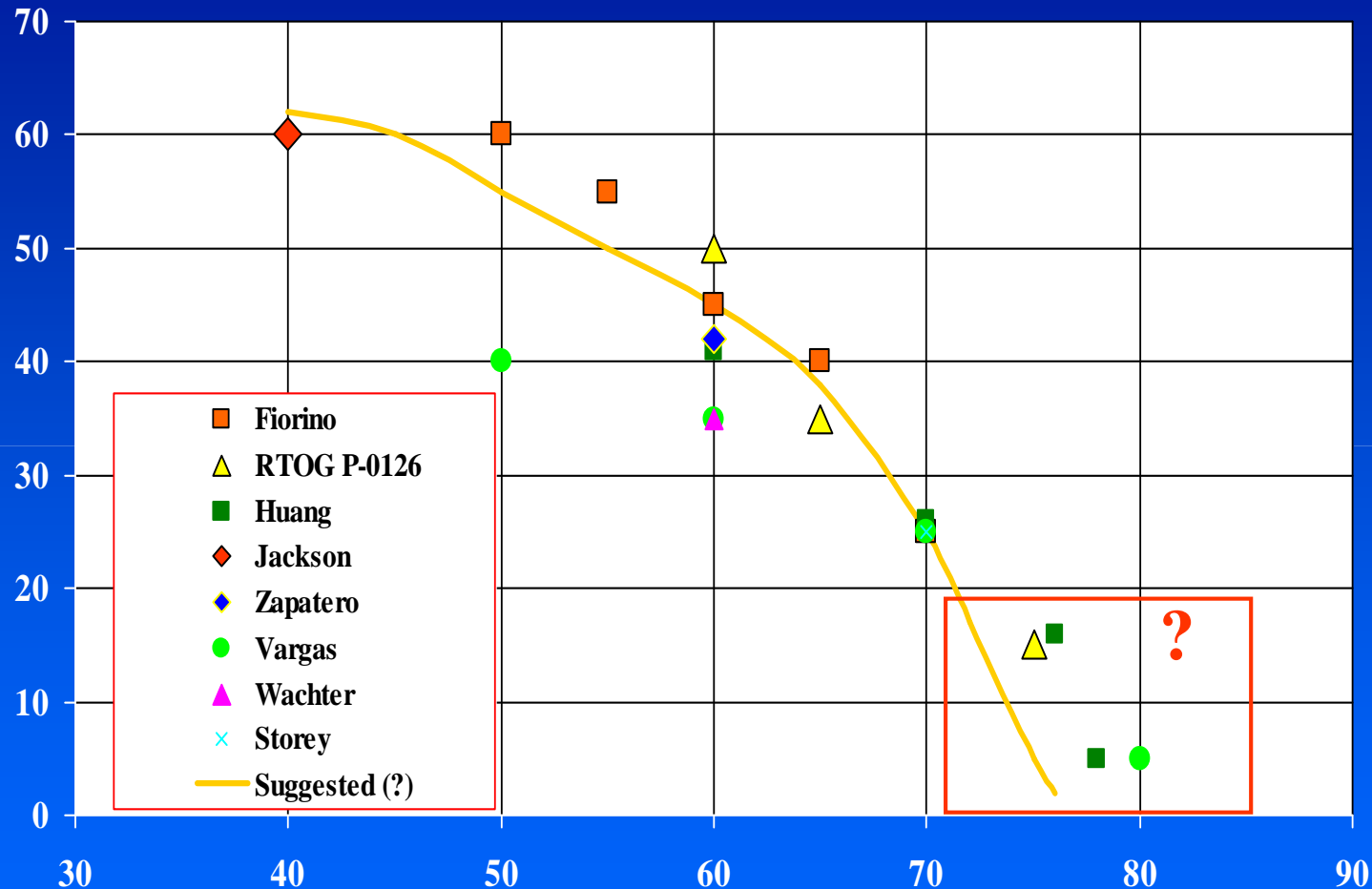


**LARGE ENOUGH DATABASE**  
to discriminate between different patient groups  
and to analyze data meaningfully

## Dose-volume constraints: published results (..large populations)

- ✦ NKI (Amsterdam, 130 pts) Boersma *et al.* IJROBP 98
- ✦ MSKCC (New York, 171 pts) Skwarchuk *et al.* IJROBP 00  
Jackson *et al.* IJROBP 01
- ✦ MD Anderson CC (Houston, 91 pts) Storey *et al.* IJROBP 00
- ✦ Univ Hosp of Vienna (109 pts) Wachter *et al.* RO 01
- ✦ AIRO-PROS0101 (Italy, 324 pts) Fiorino *et al.* RO 02  
Fiorino *et al.* IJROBP 03  
Cozzarini *et al.* IJROBP 03
- ✦ MD Anderson CC (Houston, 163 pts) Huang *et al.* IJROBP 02
- ✦ Hosp Univ Princesa (Madrid, 107 pts) Zapatero *et al.* IJROBP 04
- ✦ Dutch trial (643 pts) Peeters *et al.* IJROBP 05
- ✦ W Beaumont Hosp (Royal Oak, 331 pts) Vargas *et al.* IJROBP 05

# Keeping Grade 2/3 below 10-15 % and grade 3 below 5% DVH CONSTRAINTS



The suggested cut-off DVH is not intended to express the probability of late rectal bleeding. It is a tool that can be used in order to prospectively assess the risk of bleeding starting from the shape of the DVH and to discriminate between low-risk and high-risk patients.

*Applying DVH constraints:  
the experience of three Italian centres*

Analyses of the data coming from three Italian centres which participated in both the AIROPROS01-01 retrospective study and in the AIROPROS01-02 prospective investigation.

two dosimetric variables were chosen: V50 and V70

DVH of low-risk patients

$V50 \leq 45\%$

$V70 \leq 20\%$

DVH of high-risk patients

$V50 > 60\%$

$V70 > 20\%$

	pts	median V50	III q V50	median V70	III q V70	low risk %	high risk %	gr>=2 lrb %	gr 3 lrb %
<b>Hospital A</b>									
retrospective	43	57	68.6	15	22	11.6	23.3	11.6	0
prospective	116	48.2	54.5	21	24	28.4	5.2	8.6	4.3
<b>Hospital B</b>									
retrospective	73	62.1	71.6	19	29.3	17.8	34.2	6.8	1.4
prospective	25	36.5	45	8.9	13.3	76	8	0	0
<b>Hospital C</b>									
retrospective	76	46.5	57.6	26.7	34.4	23.7	21.1	10.5	5.3
prospective	66	40.3	44.8	16.8	19.4	66.7	0	6.1	0

a reduction of the fraction of rectum receiving intermediate-high doses produces a substantial reduction of moderate/severe bleeding and attention to V70 values is effective in lowering the probability of grade 3 injury

## Fitting late rectal bleeding data using different NTCP models: results from an Italian multi-centric study (AIROPROS0101)

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RO 2004

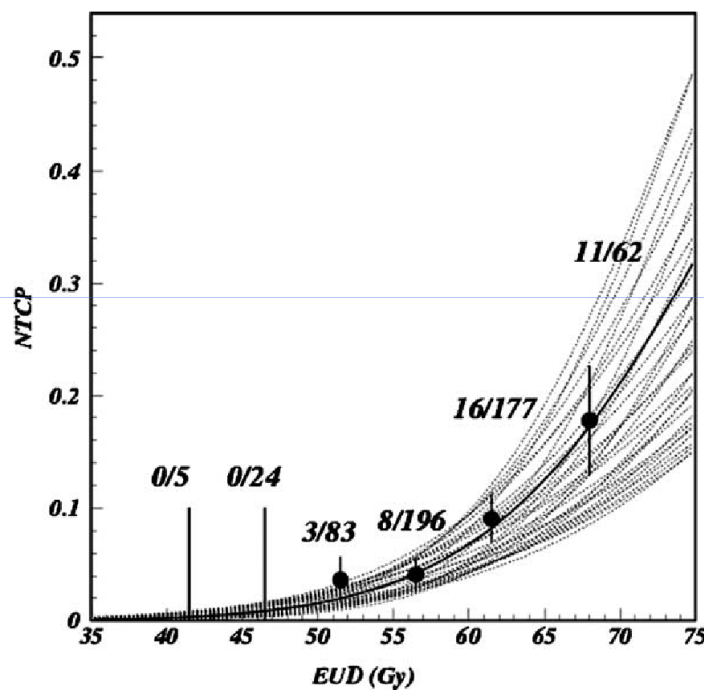


Fig. 2. Incidence of late rectal bleeding as a function of EUD for the LEUD model: observed complication rates (solid circles) and predicted NTCP curve (continuous line, curve obtained using best estimated parameters). The dotted lines depict the 3D-68% CI (see the text) for the NTCP curve.

Model	D50 (Gy)	$m/k/\gamma$	$n/s$
LEUD	81.9	$m=0.19$	$n=0.23$
1D-68%CI	$\pm 1.8$	$\pm 0.01$	$\pm 0.05$
3D-68%CI	-5.1, +9.3	-0.04, +0.06	-0.09, +0.19

Lrb grade  $\geq 2$

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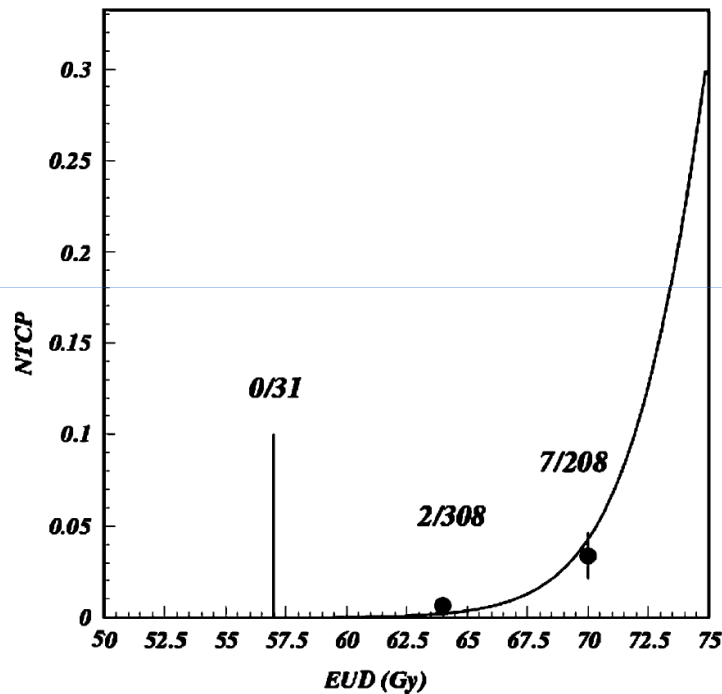


Fig. 4. Dose-volume-response curve obtained with the best estimated parameters for the LEUD model for grade 3 bleeding. Solid circles represent the observed complication rates.

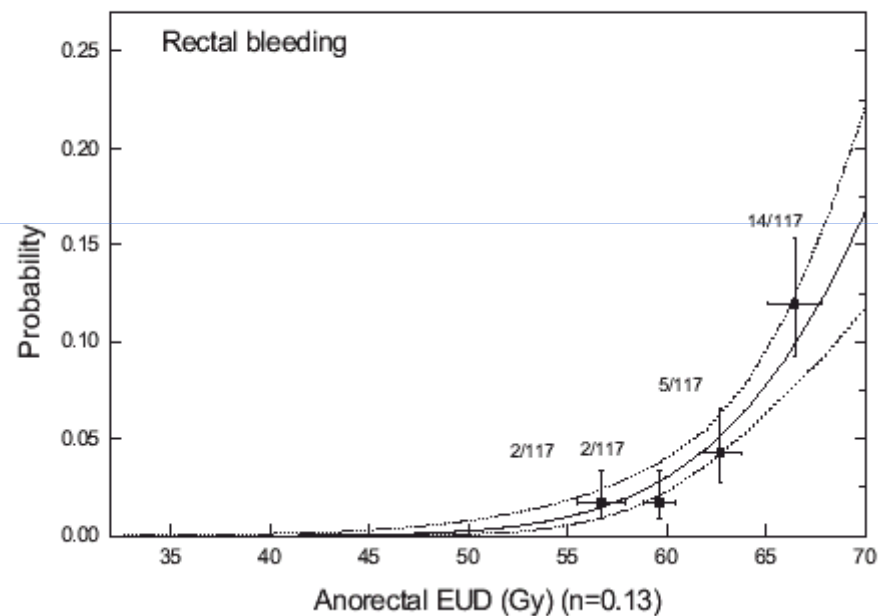
Model	$D50$ (Gy)	$m/k/\gamma$	$n/s$
LEUD	78.6	$m=0.06$	$n=0.06$
1D-68%CI	$\pm 3.7$	$\pm 0.005$	$\pm 0.01$

Lrb grade  $\geq 3$

**RECTAL BLEEDING, FECAL INCONTINENCE, AND HIGH STOOL  
FREQUENCY AFTER CONFORMAL RADIOTHERAPY FOR PROSTATE  
CANCER: NORMAL TISSUE COMPLICATION PROBABILITY MODELING**

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*IJROBP 2006*

Gr 3 lrb

*NTCP modeling: rectal bleeding (and anorectal wall)*

For rectal bleeding, the best fit with the original LKB model was found with  $n = 0.13$ ,  $TD50 = 81$  Gy, and  $m = 0.14$

## Focal points (1/3)

- ✓ Dosimetric variables correlating to lrb do not describe injury biology, BUT can be used as SURROGATE in planning and evaluation

- ✓ Percent volume of rectal wall exposed to doses  $\geq 70$  Gy: crucial role in determining the rectal morbidity of prostate treatment

- ✓ Percent volume of rectal wall exposed to  $40\text{Gy} \leq D \leq 50\text{-}60\text{Gy}$  and a reserve of unexposed tissue play a role in bleeding

## Focal points (2/3)

- ✓ Dose-based surrogates can be powerful, better if multiple constraints are used
- ✓ NTCP models describe the data quite well, prospective validation needed/arriving (*Fiorino, Prostate II Tue 10, 15:15*)
- ✓ changes in tolerance doses for different grades of complications:
  - ⇒ volume parameter  $n$  (0.23-0.25) should be used when considering moderate-severe toxicity
  - ⇒ volume parameter  $n$  (0.06; 0.12) should be used when considering severe toxicity

## Focal points (3/3)

- ✓ EUD is substantially equivalent to multiple DVH constraints
- ✓ use of EUD has the advantage of evaluating the dose given to the whole organ with just one volume parameter and NTCP can be estimated using EUD together with any convenient dose-response function

## Work in progress...

- Efforts to more systematically collect and archive 3D dosimetric data and corresponding clinical outcome data
- Efforts to study other endpoints impacting the patient QOL (including acute effects)

## ENDPOINTS (SOMA/LENT scoring system)

analysing dose–volume effects not only for rectal bleeding, but also for other symptoms of the so called rectal syndrome

toxicity is scored through a self-assessment questionnaire in order to avoid the risk of underestimating toxicity rates and to enhance the sensitivity to detect onset, grade and change of toxicity

first results of these studies, which could give important additional planning indications to clinicians.

stool frequency

tenesmus

soiling

pain

bleeding

drug prescription

## LOCALIZED VOLUME EFFECTS FOR LATE RECTAL AND ANAL TOXICITY AFTER RADIOTHERAPY FOR PROSTATE CANCER

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*IJROBP 2006*

Stool frequency ( $\geq 6$  times a day) was related to the intermediate-dose region of the anorectum (around V40) and to the mean dose to the anorectum. However, these

of incontinence requiring pads was 9.4% at 4 years. We found that incontinence was strongly related to all anal wall dosimetric parameters. For the mean dose to the anal wall, for instance, the hazard ratio was 1.039. This means that for an increase of  $D_{\text{mean}}$  with 33 Gy (from 19 Gy to 52 Gy), we would expect an increased incidence of incontinence by factor of 3.5 (i.e., 1.039 to the power 33). This concurs with

# AIROPROS01-02 preliminary results

*(Fiorino, Prostate II Tue 10, 15:15)*

## **INCONTINENCE, GRADE $\geq 2$ 9/509 (1.8%)**

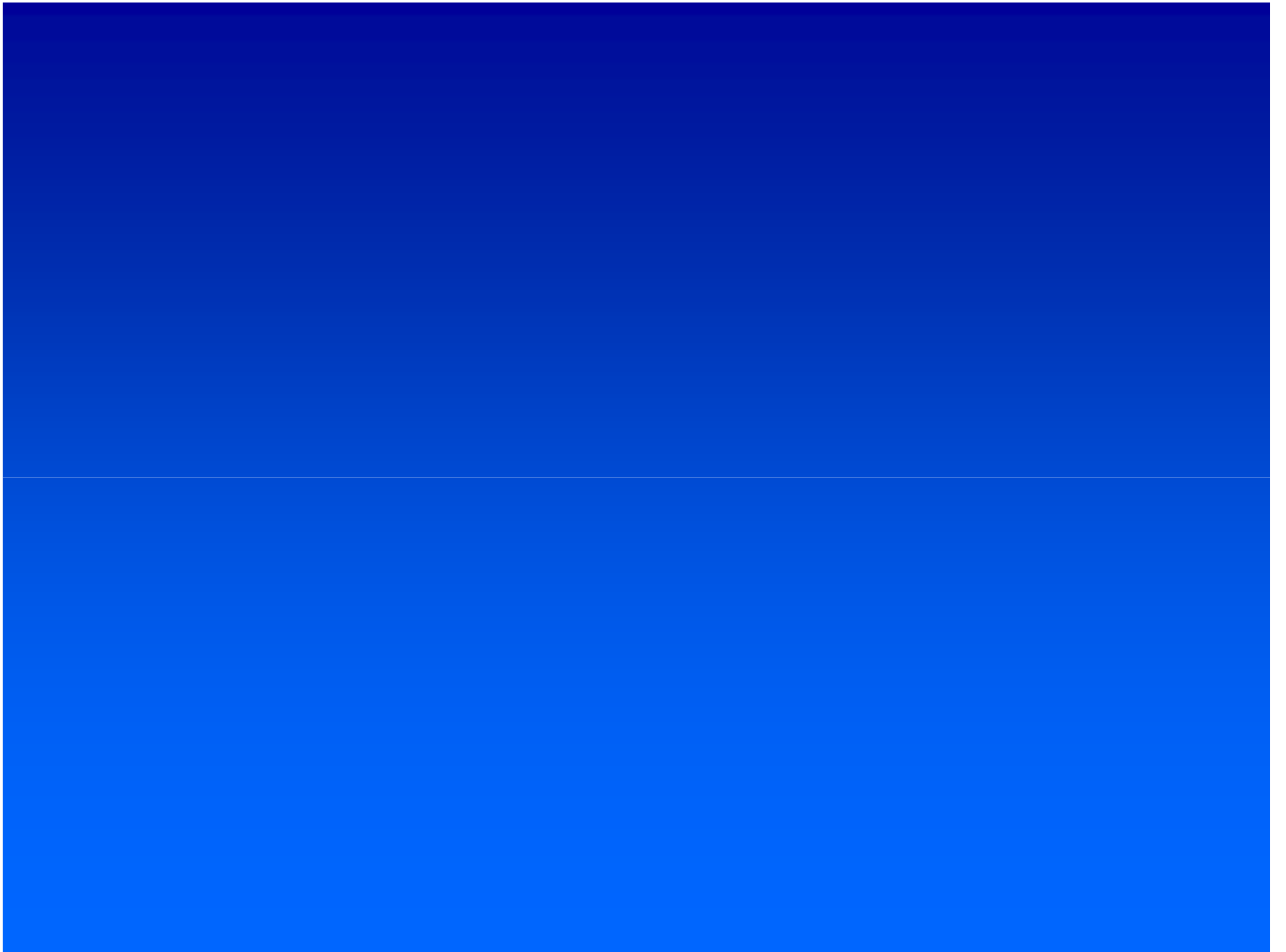
No correlation between toxicity and clinical variables

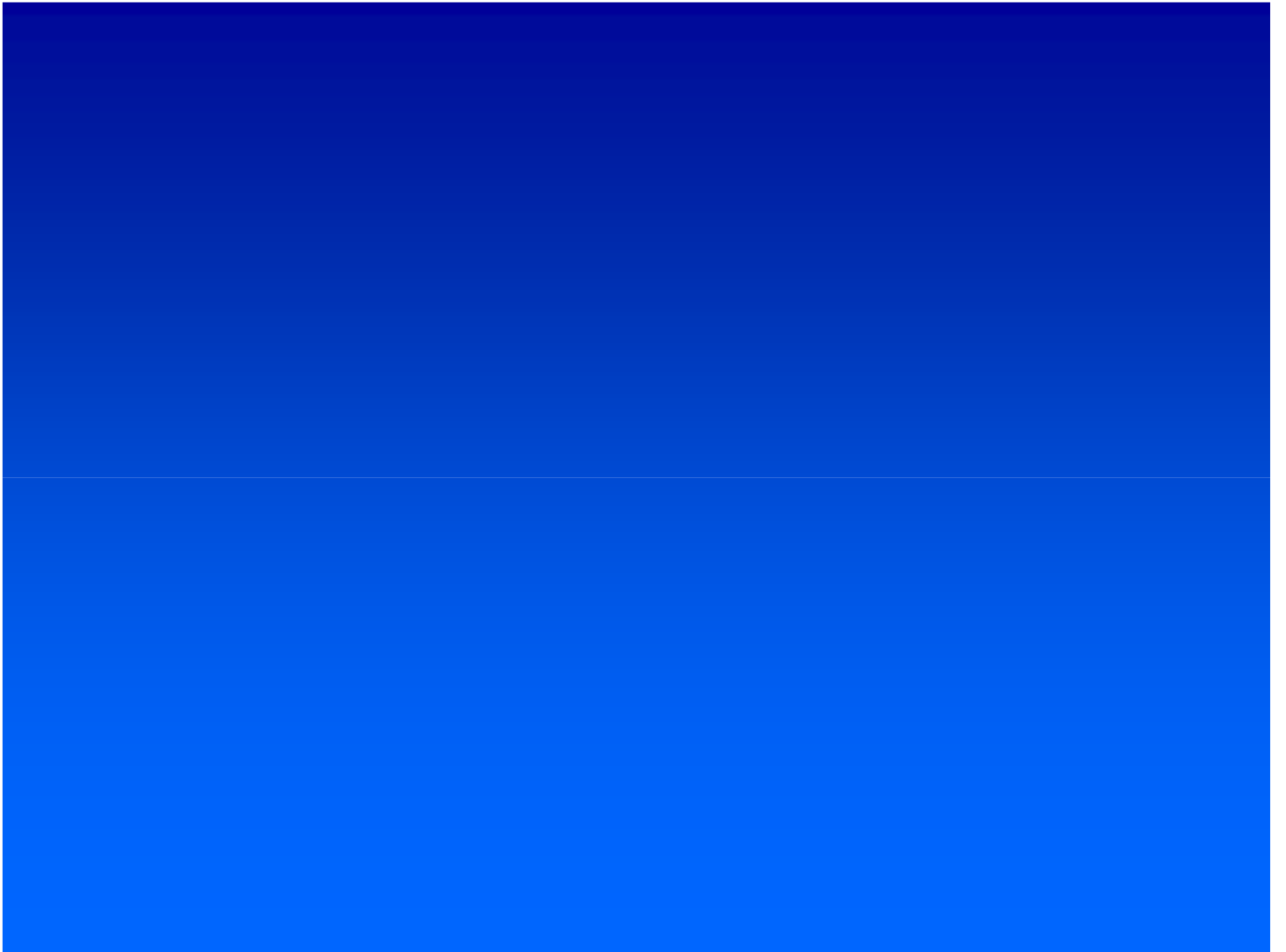
Mean rectal dose                      p=0.001                      OR=1.12

V40Gy                                      p=0.0088                      OR=1.15

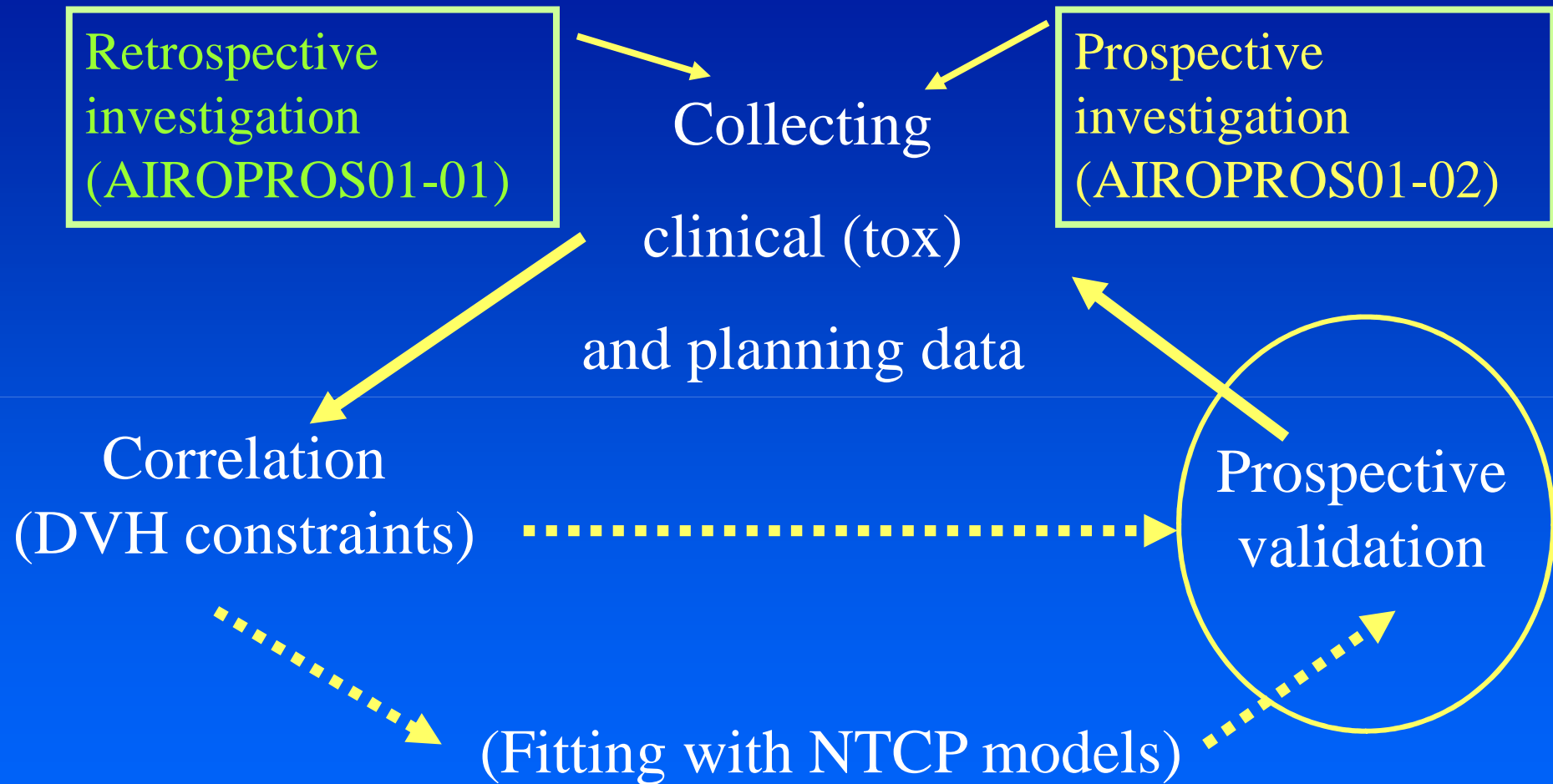
V50Gy                                      p=0.008                      OR=1.05

All tox in pts  
with V40Gy > 70%





# SELF-ADVERTISING... THE ITALIAN TRIALS



SELF-ADVERTISING again...

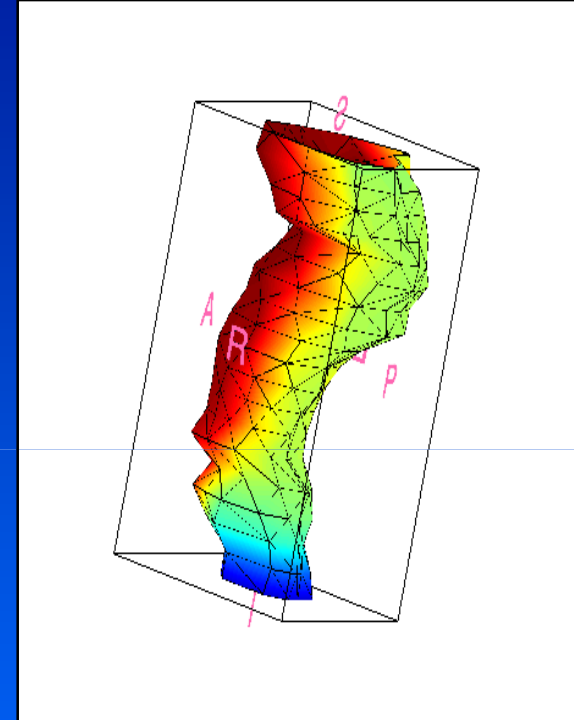
## AIROPROS01-02: Questionnaire-based analysis of acute tox during treatment

- RTOG/EORTC prospective assessment of rectal tox
- 11 end points; scoring prospectively assessed through a validated questionnaire
- Correlation with a number of clinical and dosimetical variables: Hypertension, diabetes, Ormonal therapy, emorroids, previous use of a number of drugs, Total dose, Pelvis irradiation, Tumor volume, Rectal volume, Treetment duration, Mean and maximum dose to the rectum (Dmean, Dmax)
- correlation with DVHs; best fit analysis with EUD and NTCP

DETAILS... later on this morning

# SELF-ADVERTISING... last time!

- Prospective trial
- 1140 patients enrolled
- Questionnaire based assessment of late toxicity
- Analyses including NDVH/NDSH-dose maps (RMH software, *Gianolini et al. ESTRO 2002*)



da qui RISERVA

# Keeping $G \geq 2$ lrb < 10-15% $\Rightarrow$ DVH constraints (1/2)

$V_{40}$  = 60 % *Jackson*

$V_{50}$  = 60-65% *Fiorino*  
= 40% *Vargas*

$V_{60}$  = 57% *Wachter*  
= 50-55% *Fiorino*  
= 41% *Huang*  
= 42% *Zapatero*  
= 35% *Vargas*

# Keeping severe lrb < 5% ⇒ DVH constraints

$V_{65}$	= 40 %	<i>Boersma</i>
$V_{70}$	= 30 %	<i>Boersma</i>
	= 30 %	<i>Storey</i>
	= 30 %	<i>Fiorino</i>
$V_{75}$	= 5 %	<i>Boersma</i>

Keeping  $G \geq 2$  lrb  $< 10-15\%$   
 $\Rightarrow$  DVH constraints (2/2)

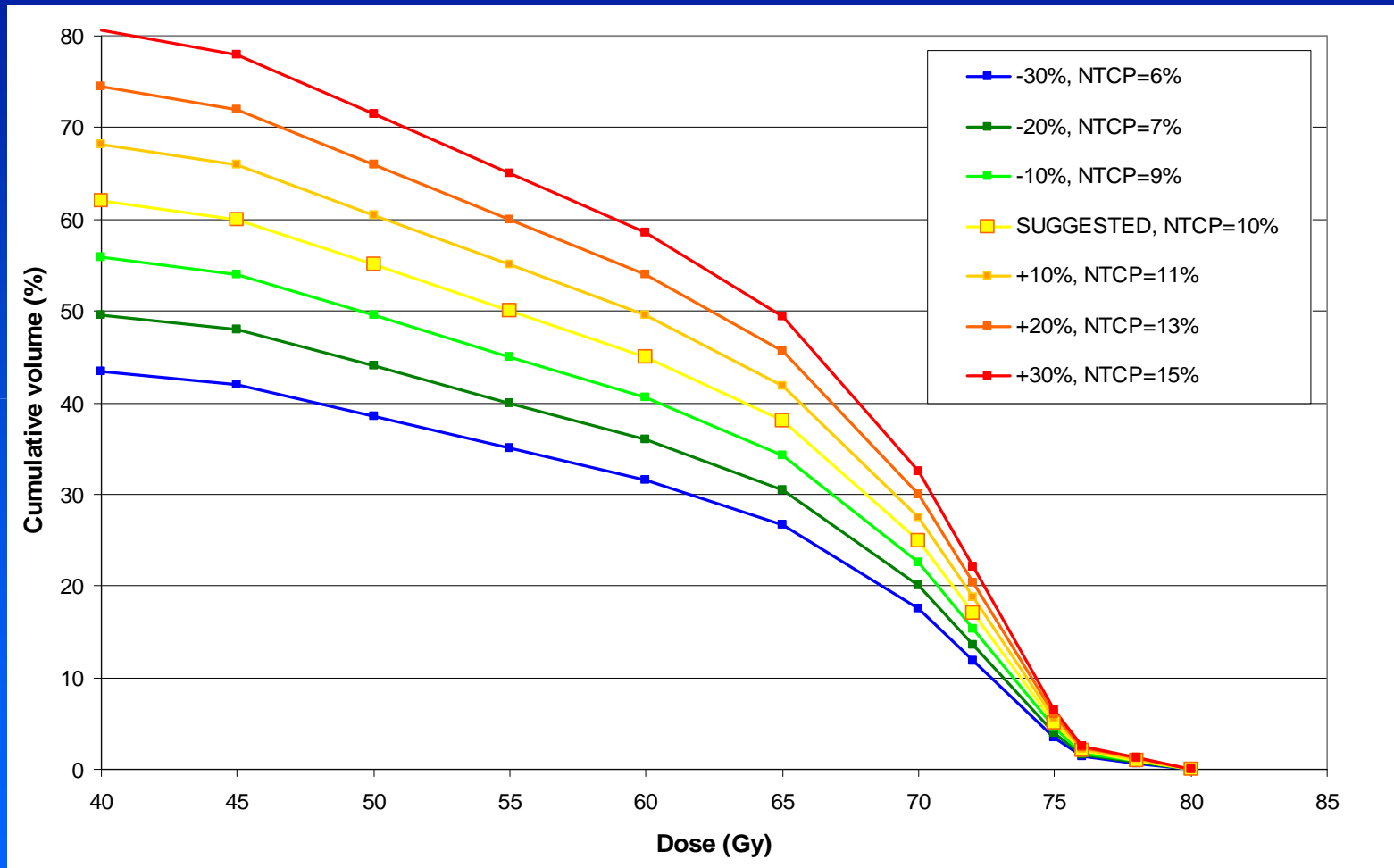
$V_{70}$	= 25%	<i>Storey</i>
	= 30%	<i>Fiorino</i>
	= 26%	<i>Huang</i>
	= 25%	<i>Vargas</i>

$V_{76}$  = 16% *Huang*

$V_{78}$  = 5% *Huang*

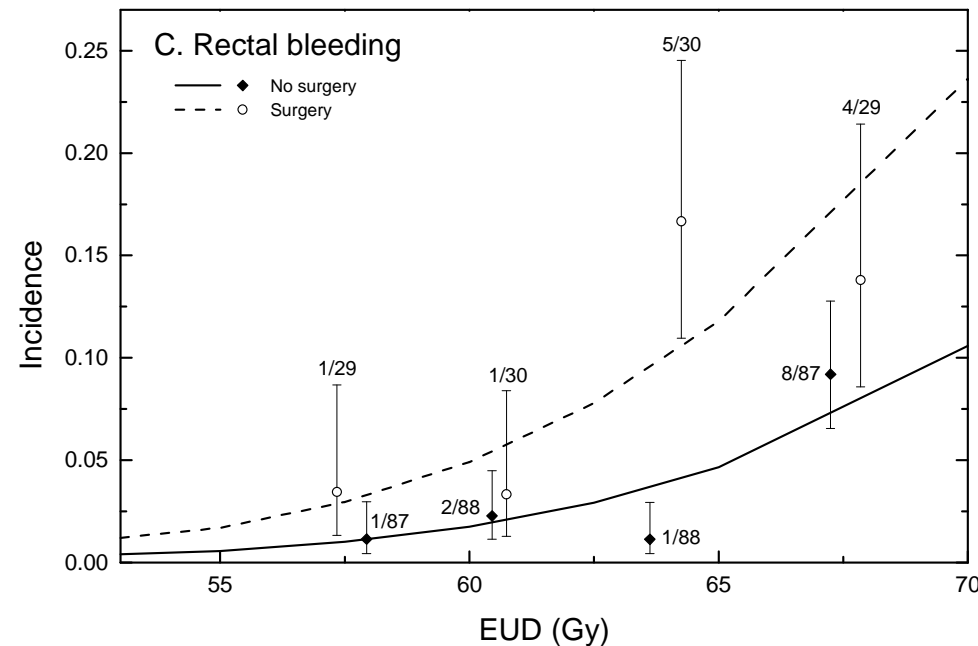
$V_{80}$  = 5% (? , p=0.08) *Vargas*

# Hardening and softening DVH constraints... what happens to estimated NTCP ?



# Rectal bleeding (grade 3) vs anorectum DVHs (wall), incl. clin.variable (abd. surgery); at 3 year: 23 / 468

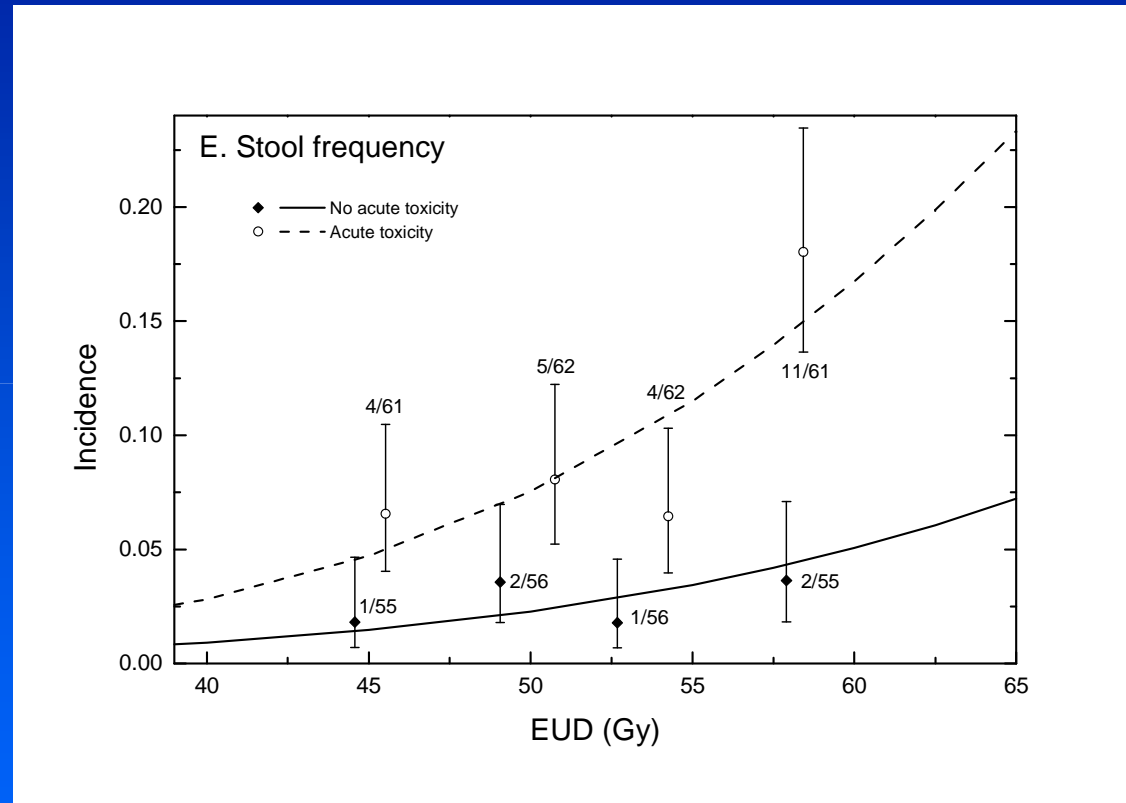
$n = 0.11$ ,  $m = 0.14$ ,  
TD50 = 85 Gy,  
TD50<sub>surg</sub> = 78 Gy



Stephanie Peeters *et al*, Dutch Trial

# Stool freq. (grade $\geq 2$ ) vs anorectum DVHs (wall), incl. clin. variable (ac. tox.); at 3 year: 30 / 468

$n = 0.44$ ,  $m = 0.26$ ,  
TD50 = 106 Gy,  
TD50<sub>acute</sub> = 80 Gy



Stephanie Peeters *et al*, Dutch Trial

**CHARACTERIZATION OF RECTAL NORMAL TISSUE COMPLICATION  
PROBABILITY AFTER HIGH-DOSE EXTERNAL BEAM RADIOTHERAPY  
FOR PROSTATE CANCER**

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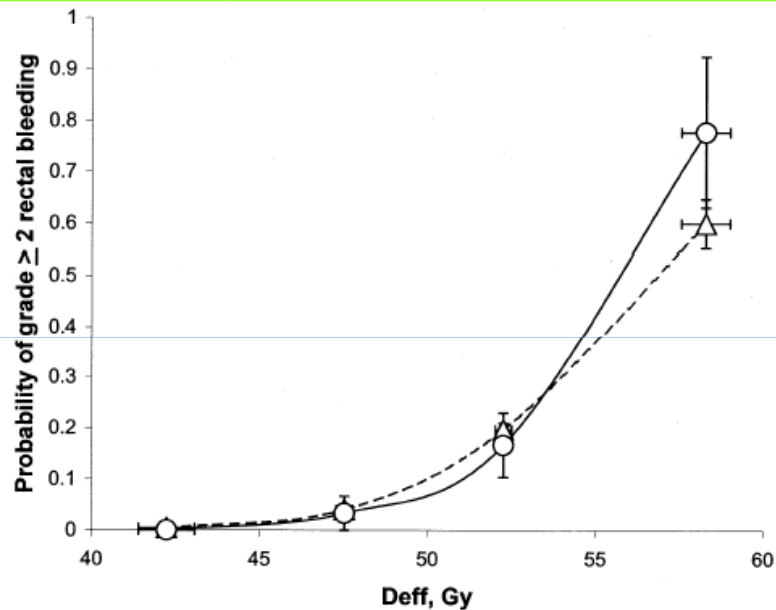


Fig. 3. Observed vs. fitted incidence of Grade 2 or worse rectal bleeding after RT. Cohort of 84 patients without hemorrhoids was used for this fit. Open circles and triangles represent, respectively, observed and predicted rates of rectal bleeding.  $D_{eff}$  = effective dose calculated from DVH reduction scheme. Error bars indicate standard errors.

Patients without hemorrhoids		
Parameter	Estimate	95% Confidence Interval
TD50	56.7 Gy	49.9 Gy to 75.2 Gy
m	0.092 Gy <sup>-1</sup>	0.019 Gy <sup>-1</sup> to 0.189 Gy <sup>-1</sup>
n	0.746	0.026 to ∞

Unrealistic result probably due to  
**LARGE RECTAL VOLUMES**  
(range 57.5-335.1 cc; median 117.9cc)  
which introduce systematic shift  
between planning and treatment DVH