



# Pelvic tumor irradiation New tools to reduce toxicity: from technology to drugs

Karin Haustermans – Ines Joye

# Overview

- Definitions
- Risk factors
- Dose effect relationship
  - Small bowel
  - Bladder
  - Penile bulb
  - Rectum
  - Sacrum
- Technology to reduce side effects
- Drugs to reduce side effects

# Overview

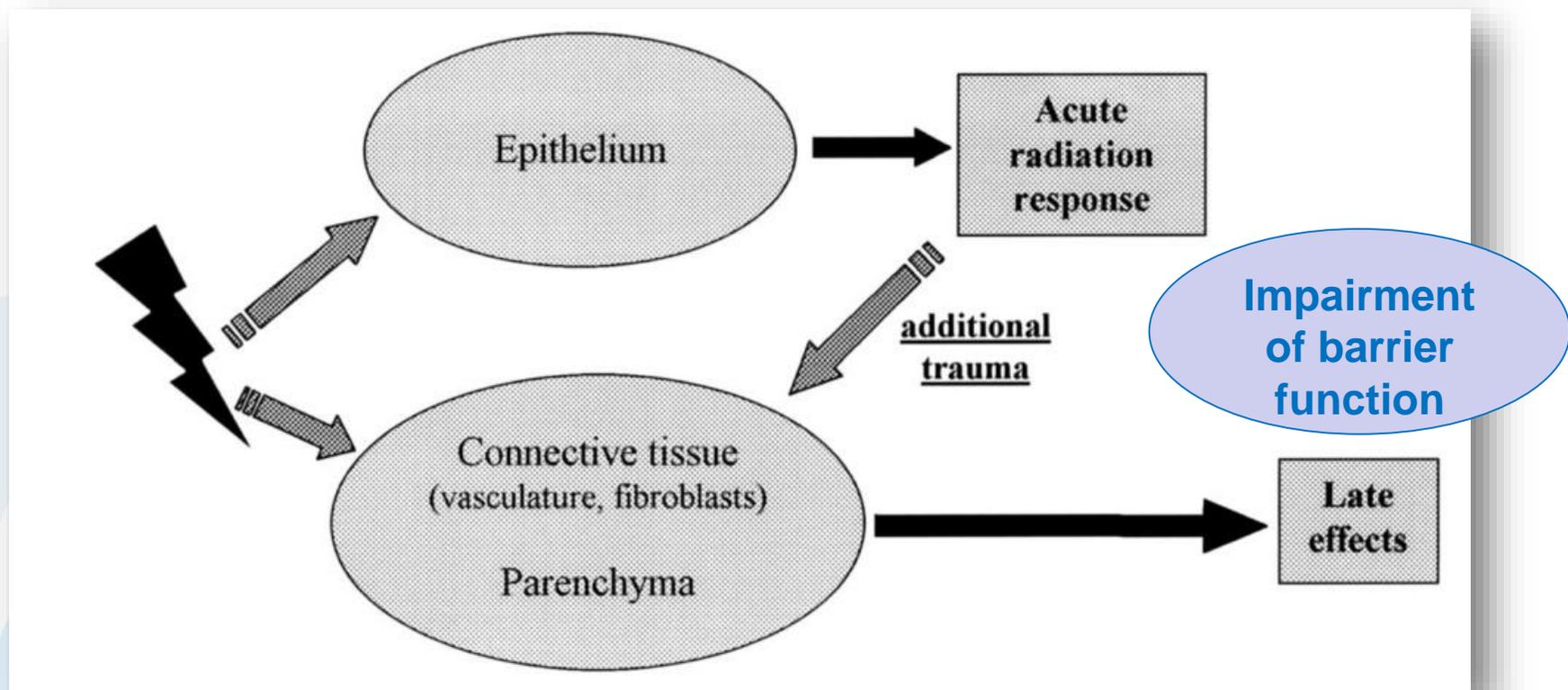
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# Early vs. late toxicity

	Early	Late
Timing	During or shortly after treatment (<3m)	>90 days after onset of treatment (>3m)
Pathophysiology	Progressive cell depletion and inflammation	Vascular sclerosis and fibrosis
Symptoms	<ul style="list-style-type: none"><li>• Diarrhea</li><li>• Cramps</li><li>• Cystitis</li><li>• Perineal dermatitis</li></ul>	<ul style="list-style-type: none"><li>• Bowel dysfunction</li><li>• Faecal incontinence</li><li>• Bleeding and perforation</li><li>• Genitourinary dysfunction</li><li>• Pelvic fractures</li></ul>

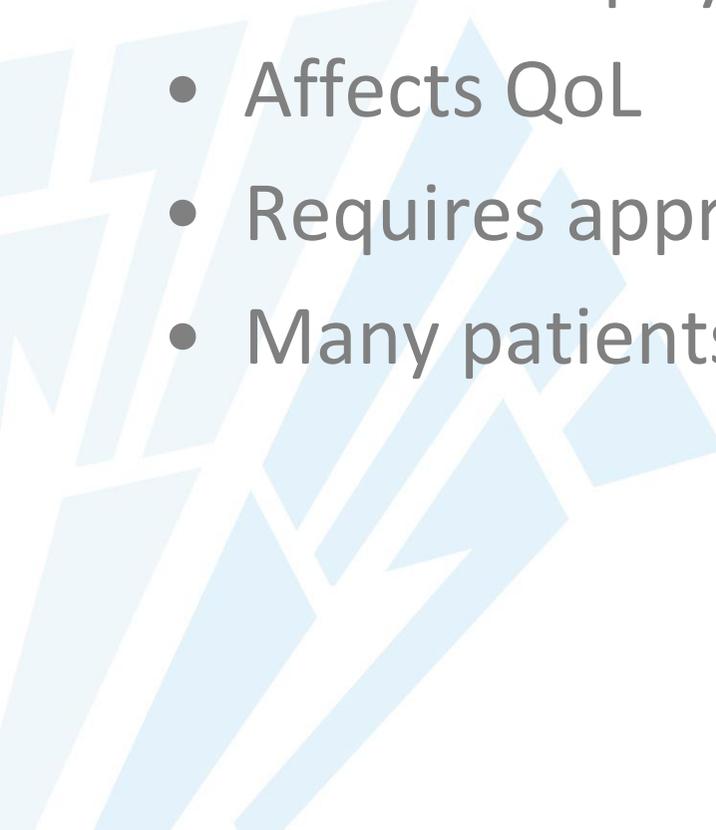
# Consequential late effects

## Mucosa of GU and GI tract



Dörr, Radiother Oncol 2001

# Treatment-related toxicity

- Underreported, vague symptoms ...
  - Different scoring systems used
  - Prospective vs retrospective data
  - Patient vs physician
  - Affects QoL
  - Requires appropriate treatment
  - Many patients have become long-term survivors
- 

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# Patient-related factors

- General condition
- Obesity
- Previous surgery
  - Risk of fistula after laparotomy: 5.2% vs 2.9%
  - Risk of small bowel obstruction: 14.5% vs 3.7%
- Diverticulosis
- Diabetes
- Hypertension
- Inflammatory bowel disease
- Collagen vascular disease

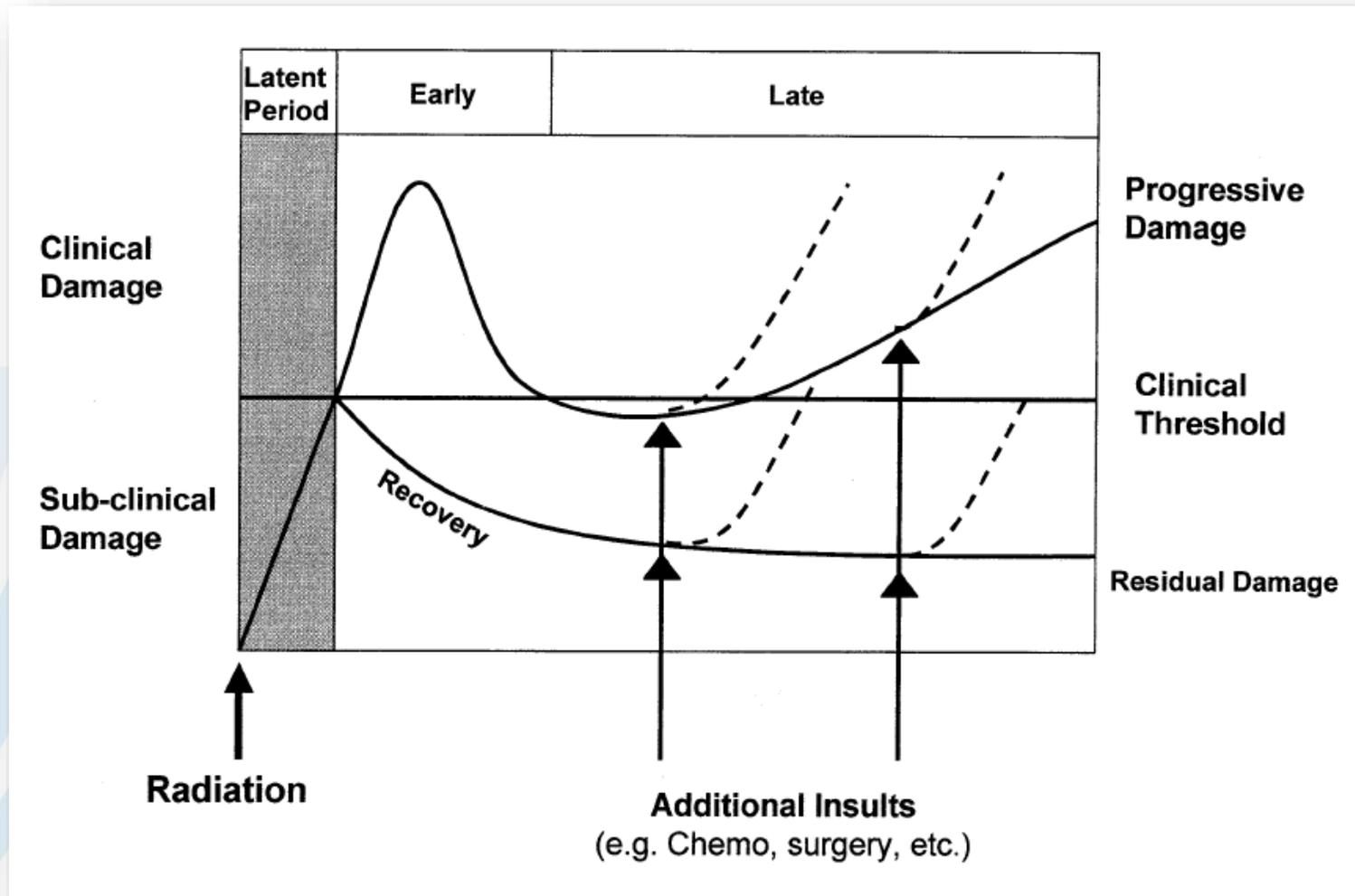
# Tumor-related factors

- Stage of disease
- Volume of the tumor
- Lymphatic spread

# Tumor-related factors

- Radiation dose
- Volume of normal tissue irradiated
- Fractionation schedule
- Use of concomitant chemotherapy
- Co-morbidities
- Observation time

# Combined modality treatment

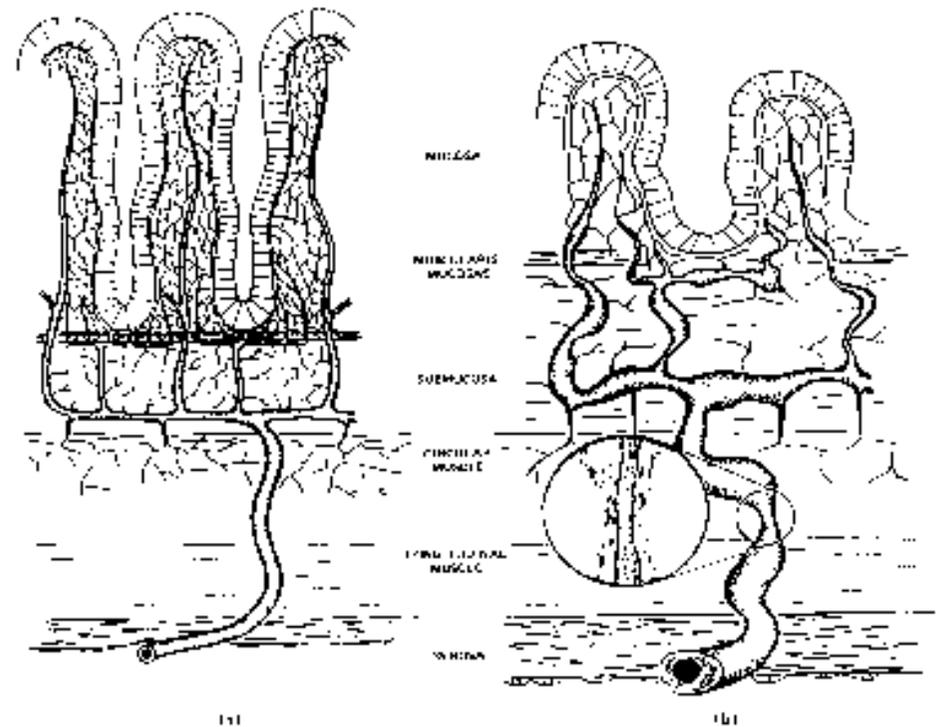


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# Small bowel toxicity

- Acute toxicity
  - Results of cell death in proliferative compartment
  - Failure to replace the villus epithelium
  - Shortening of the villus
  - Endothelial cell swelling and loss with increased vascular permeability
  - Breakdown of the mucosal barrier
  - Mucositis



# Small bowel toxicity

- Late toxicity
  - Mucosal atrophy
  - Vascular sclerosis
  - Focal ischemia, fibrosis, edema, serosal thickening
  - Malabsorption, dysmotility
  - Intestinal obstruction, fistula
  - Presents clinically 6 months to 3 years after radiation
  - May lead to:
    - Complications requiring surgery
    - Parenteral nutrition
  - Prognosis is poor

# Small bowel toxicity

- Radiation enteritis

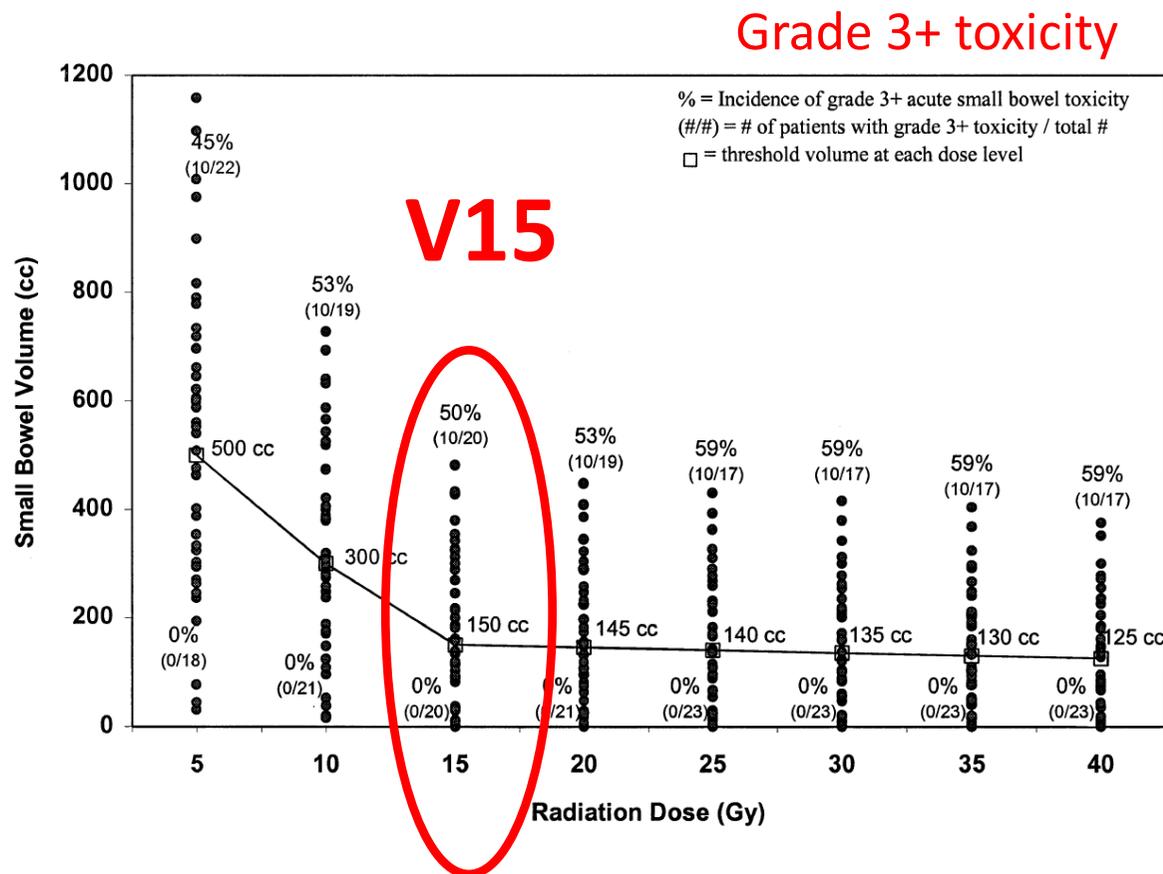


# Small bowel toxicity

- Acute small bowel toxicity depends on irradiated volume

Table 3. Volume of irradiated small bowel at each 5-Gy dose level between 5 and 40 Gy vs. the degree of acute small bowel toxicity (mean  $\pm$  SE, cm<sup>3</sup>)

RT dose level (Gy)	Grade 0–2 toxicity	Grade 3+ toxicity	<i>p</i> value
5	439 $\pm$ 43	798 $\pm$ 76	<0.001
10	246 $\pm$ 30	524 $\pm$ 45	<0.001
15	127 $\pm$ 21	319 $\pm$ 29	<0.001
20	108 $\pm$ 20	286 $\pm$ 27	<0.001
25	99 $\pm$ 19	267 $\pm$ 26	<0.001
30	92 $\pm$ 19	251 $\pm$ 26	<0.001
35	86 $\pm$ 18	237 $\pm$ 25	<0.001
40	78 $\pm$ 17	216 $\pm$ 25	<0.001

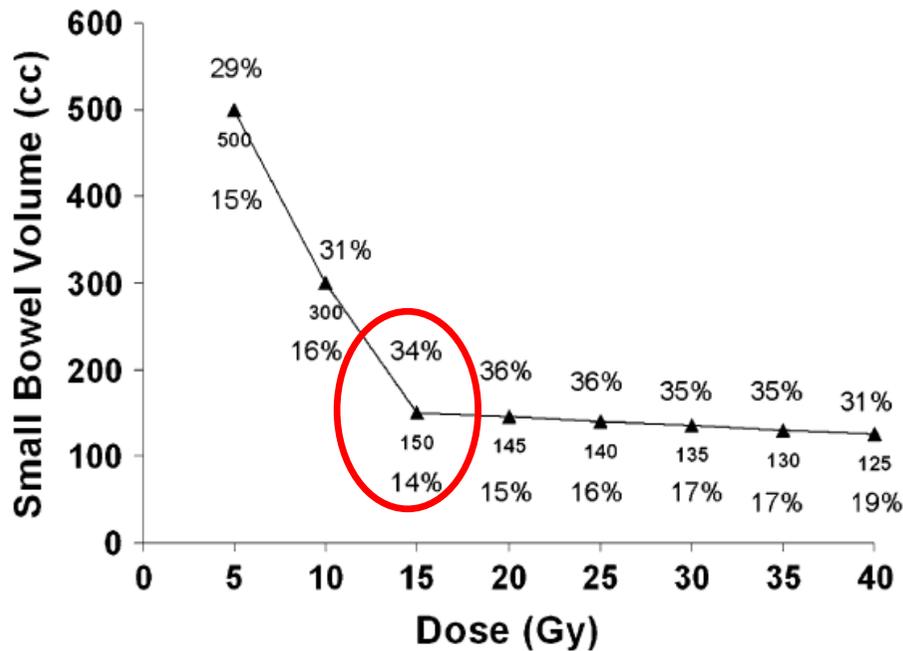


# Small bowel toxicity

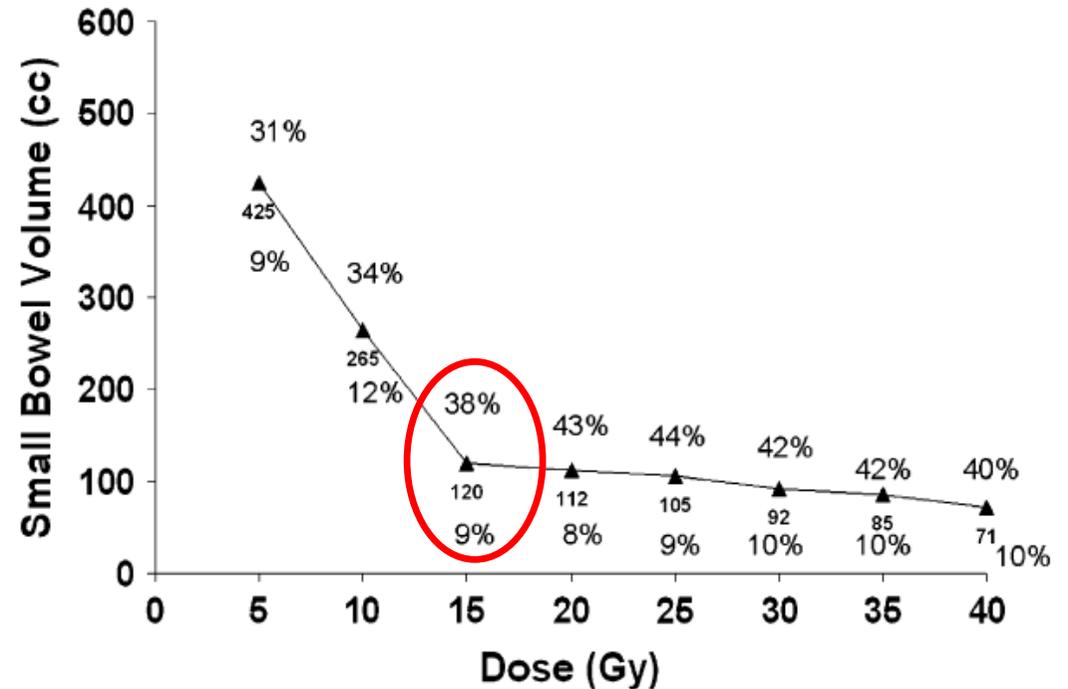
- Acute small bowel toxicity depends on irradiated volume

## Better modeling of preoperative patients

Previous parameters



Revised parameters



# Radiation proctitis

- Inflammation and damage to lower parts of colon (sigmoid colon, rectum) after exposure to ionising radiation
- Acute radiation proctitis
  - Due to direct damage of lining of colon
  - Symptoms: diarrhea, painful defecation, tenesmus
- Chronic radiation proctitis
  - Due to damage to blood vessels
  - Symptoms: diarrhea, rectal bleeding, painful defecation, intestinal blockage, fistulae



# Radiation cystitis

**TABLE 1.** Potential long-term consequences of radiation on the urinary system

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## Radiation damaging effects on the urinary tract

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### Bladder (radiation cystitis)

- Lower urinary tract symptoms
- Hemorrhagic cystitis
- Impaired bladder compliance
- Bladder cancer
- Fistulas

### Urethra

- Stricture disease
- Stress urinary incontinence
- Fibrosis
- Fistula

### Ureter

- Stricture
  - Vesicoureteral reflux
  - Fistulas
    - Ureteroenteric
    - Ureterovascular
    - Ureterovaginal
- 



cystoscopy

# QUANTEC toxicity

- Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated) <sup>†</sup>	Endpoint	Dose (Gy), or dose/volume parameters <sup>†</sup>	Rate (%)
Rectum	Whole organ	3D-CRT	Grade $\geq$ 2 late rectal toxicity, Grade $\geq$ 3 late rectal toxicity	V50 <50%	<15 <10
	Whole organ	3D-CRT	Grade $\geq$ 2 late rectal toxicity, Grade $\geq$ 3 late rectal toxicity	V60 <35%	<15 <10
	Whole organ	3D-CRT	Grade $\geq$ 2 late rectal toxicity, Grade $\geq$ 3 late rectal toxicity	V65 <25%	<15 <10
	Whole organ	3D-CRT	Grade $\geq$ 2 late rectal toxicity, Grade $\geq$ 3 late rectal toxicity	V70 <20%	<15 <10
	Whole organ	3D-CRT	Grade $\geq$ 2 late rectal toxicity, Grade $\geq$ 3 late rectal toxicity	V75 <15%	<15 <10
Small bowel	Individual small bowel loops	3D-CRT	Grade $\geq$ 3 acute toxicity <sup>§</sup>	V15 <120 cc	<10
	Entire potential space within peritoneal cavity	3D-CRT	Grade $\geq$ 3 acute toxicity <sup>§</sup>	V45 <195 cc	<10

# QUANTEC toxicity

- Quantitative Analysis of Normal Tissue Effects in the Clinic

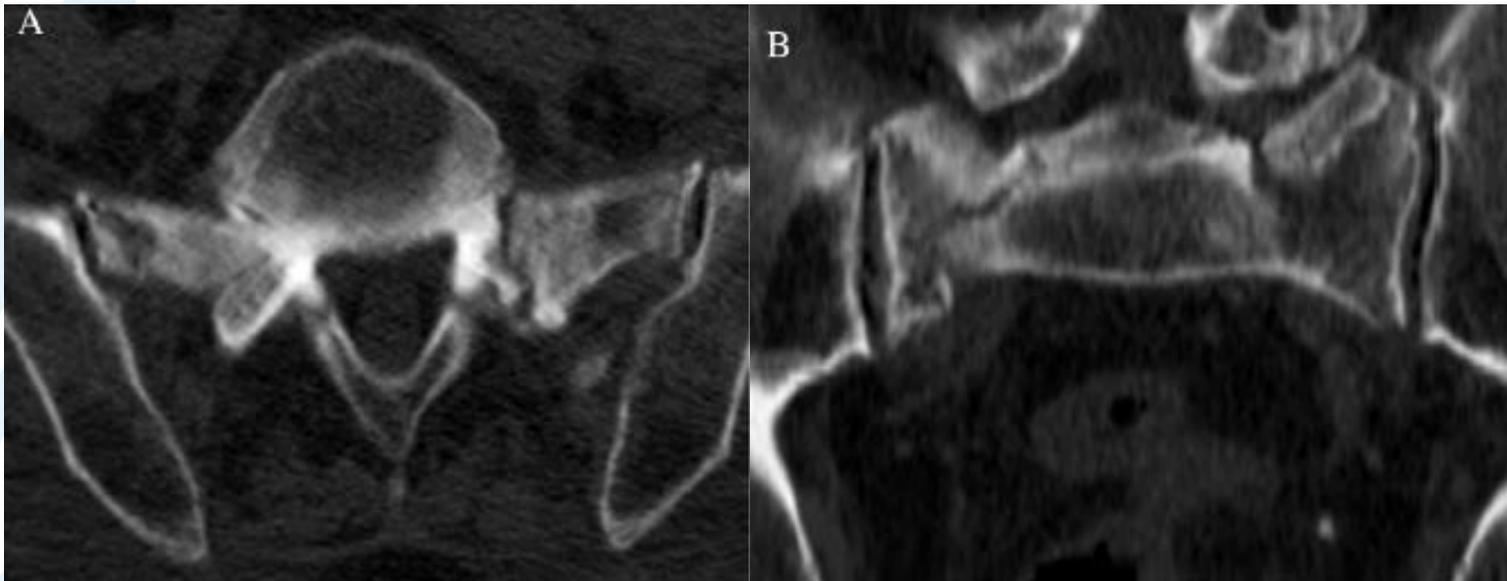
Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated) <sup>†</sup>	Endpoint	Dose (Gy), or dose/volume parameters <sup>†</sup>	Rate (%)
Bladder	Whole organ	3D-CRT	Grade $\geq$ 3 late RTOG	Dmax <65	<6
	Whole organ	3D-CRT	Grade $\geq$ 3 late RTOG	V65 $\leq$ 50 % V70 $\leq$ 35 % V75 $\leq$ 25 % V80 $\leq$ 15 %	
Penile bulb	Whole organ	3D-CRT	Severe erectile dysfunction	Mean dose to 95% of gland <50	<35
	Whole organ	3D-CRT	Severe erectile dysfunction	D90 <sup>  </sup> <50	<35
	Whole organ	3D-CRT	Severe erectile dysfunction	D60-70 <70	<55

# Sacral fractures

- 492 RC patients
- Median follow-up = 3,5 years
- Incidence: 7,1% (35/492)
- 4-year sacral-free rate: 0,91

Underdiagnosed!

Kim et al., IJROBP 2012



Lapina et al. Medicina 2014

# Sacral fractures

- Risk factors

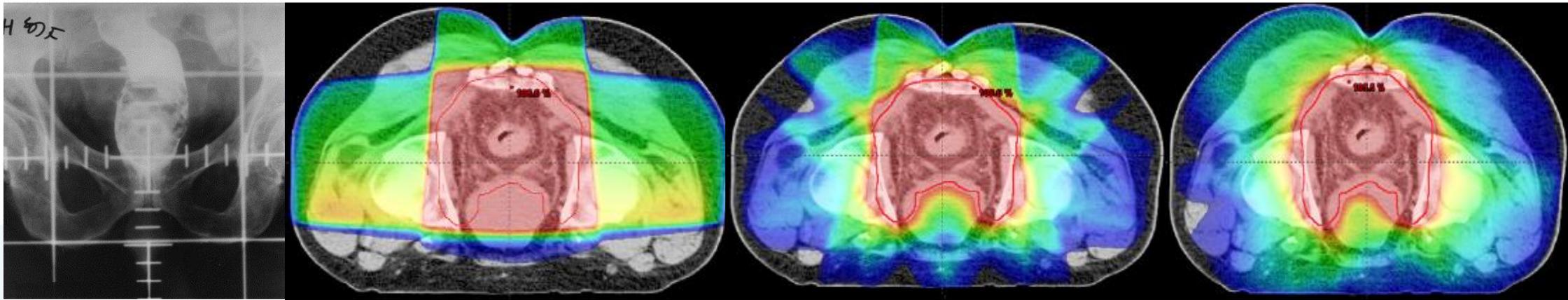
Characteristic	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	Unadjusted <i>P</i> value	Adjusted HR (95% CI)	Adjusted <i>P</i> value
Age at radiotherapy, y				
≤60 (reference)	1	.01	1	
>60	2.48 (1.22-5.07)		2.50 (1.22-5.13)	.01
Sex				
Male (reference)	1		1	
Female	2.81 (1.40-5.65)	.004	2.64 (1.29-5.38)	.008
AJCC stage		.57 (global)		
I/II (reference)	1			
III/IV	0.60 (0.28-1.27)			
Recurrence	0.86 (0.20-3.73)			
NA	0.96 (0.36-2.61)			
Radiotherapy dose, cGy		.87 (global)		
5040 (reference)	1			
<5040	0.61 (0.08-4.46)			
≥5040	1.07 (0.15-7.83)			
Chemotherapy regimen*		.90 (global)		
5-FU based (reference)	1			
FOLFOX based	1.21 (0.52-2.79)			
Irinotecan based/other	0.90 (0.21-3.81)			
History of osteoporosis				
No (reference)	1		1	.02
Yes	4.84 (1.88-12.49)	.001	3.23 (1.23-8.50)	

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# Tools to reduce toxicity

## ADVANCES IN RT



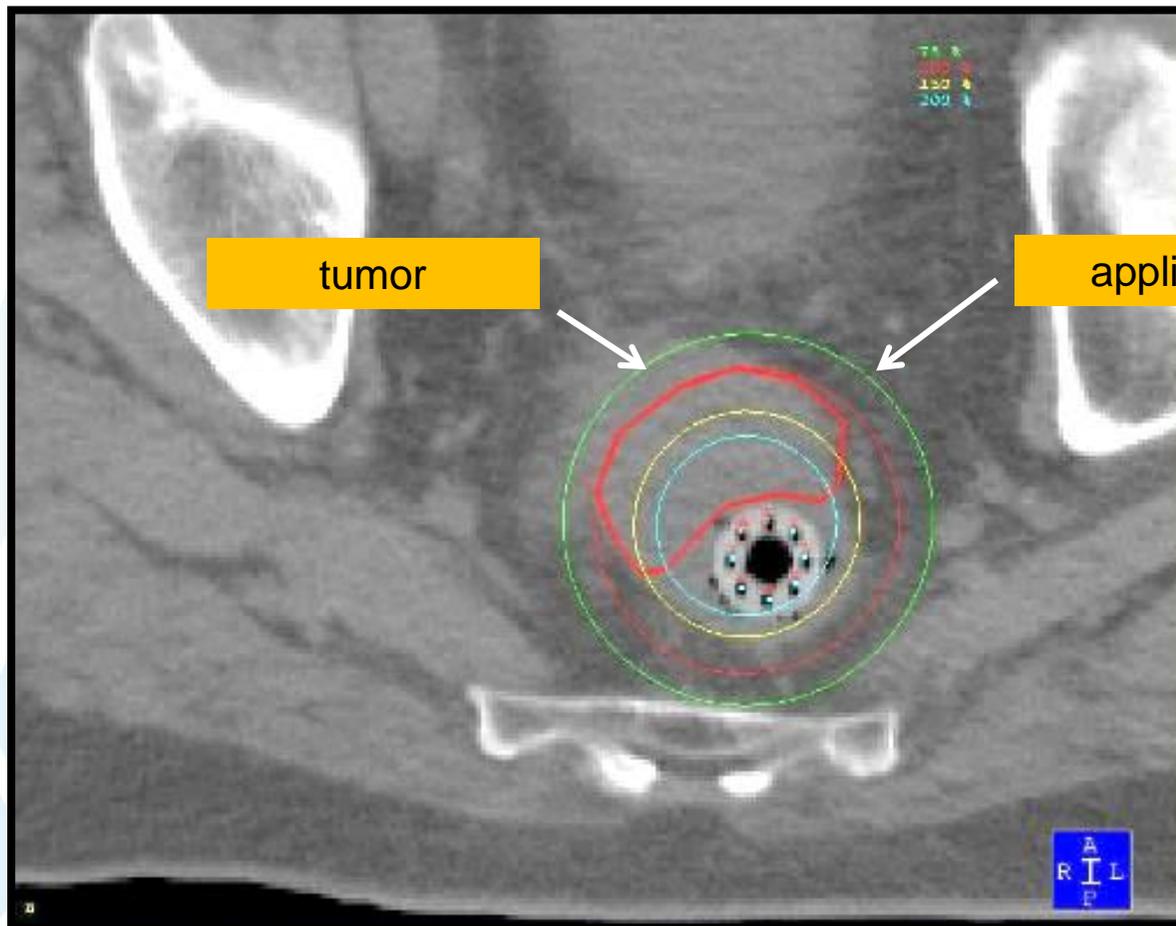
Better dose distribution  
Conforming radiation beams to the tumor  
Avoiding high-dose irradiation of normal tissue

Therapeutic ratio

# Target volume delineation

CTV subregion	Previous guidelines (Roels S, IJROBP 2006)	Updated guidelines (Joye I, IJROBP 2015)
<b>Cranial border</b>	Bifurcation of the common iliac arteries (promontorium)	Branching of superior rectal artery in multiple smaller vessels (S1-S2 interspace) for tumors without MRF involvement and without pathological lymph nodes on staging MRI.
<b>Caudal border and ischiorectal fossa</b>	<ul style="list-style-type: none"> <li>• Inclusion of the ischiorectal fossa and anal sphincter when (1) a sphincter-saving procedure is planned and the tumor is located within <math>\pm 6</math> cm from the anal margin or (2) when the tumor invades the anal sphincter and an APR is necessary.</li> <li>• Delineation of the entire ischiorectal fossa is recommended in all cases.</li> </ul>	<ul style="list-style-type: none"> <li>• Exclusion of the anal sphincter and ischiorectal fossa in patients who undergo sphincter-saving surgery. The anal sphincter should be included if there is sphincter invasion and/or when an APR is planned.</li> <li>• Delineation of the entire ischiorectal fossa is only recommended when there is massive tumoral infiltration.</li> </ul>

# Brachytherapy



- 75 %
- 100 %
- 150 %
- 200 %



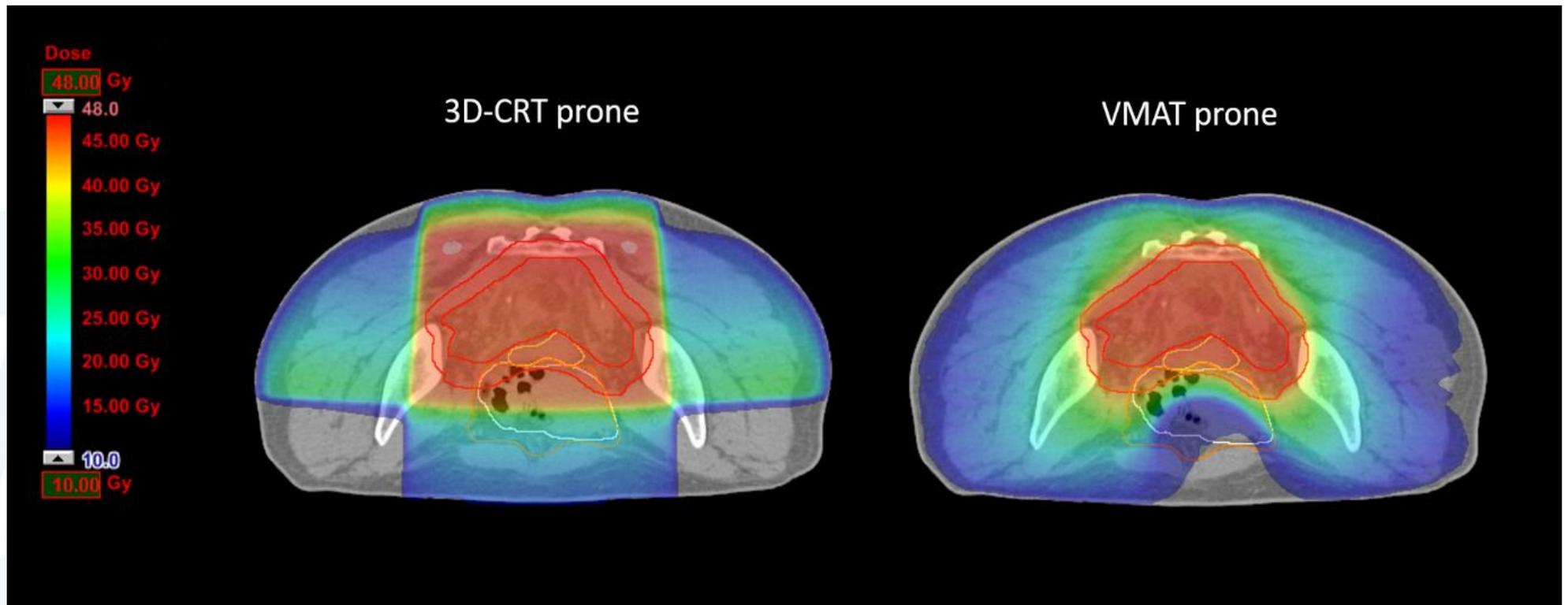
# Bellyboard

- Advantages:
  - Anterior displacement of small bowel loops away from high-dose region
- Disadvantages:
  - Less reproducible treatment position
  - Patient discomfort (i.e. old, frail patients; stoma; central venous catheter)



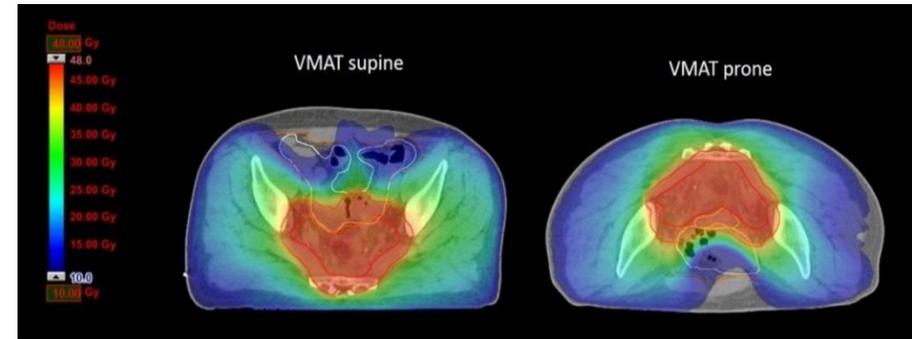
# RT technique: 3D-CRT vs. VMAT

Precise irradiation of the target volume while sparing the organs at risk

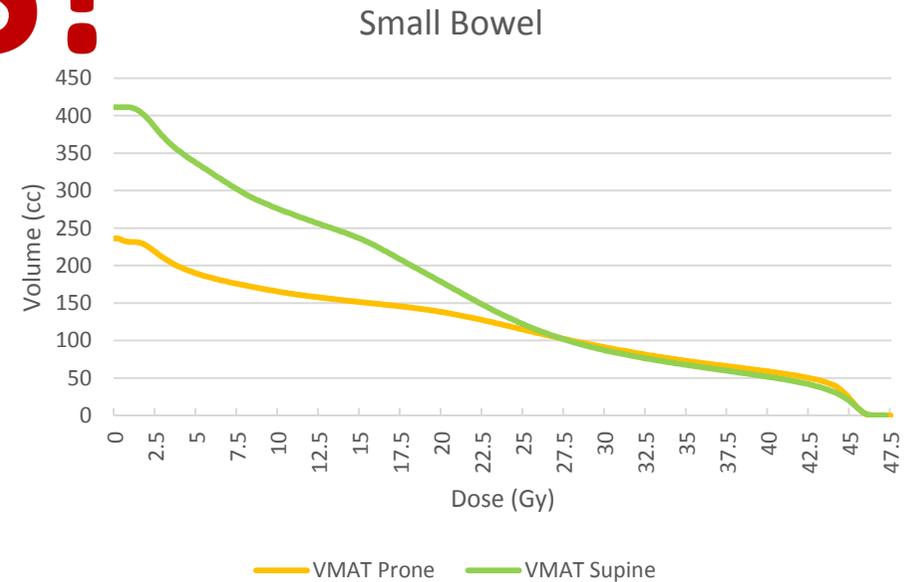
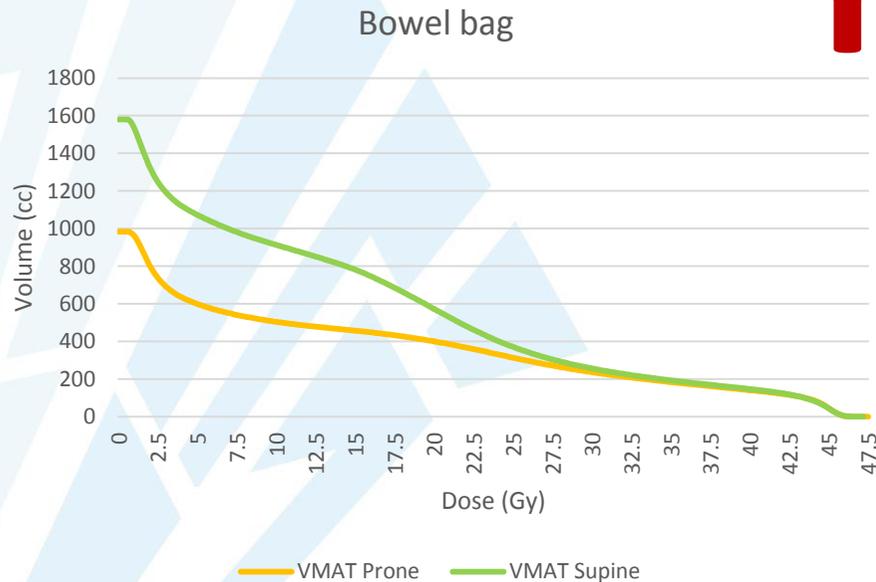


# Benefit of bellyboard?

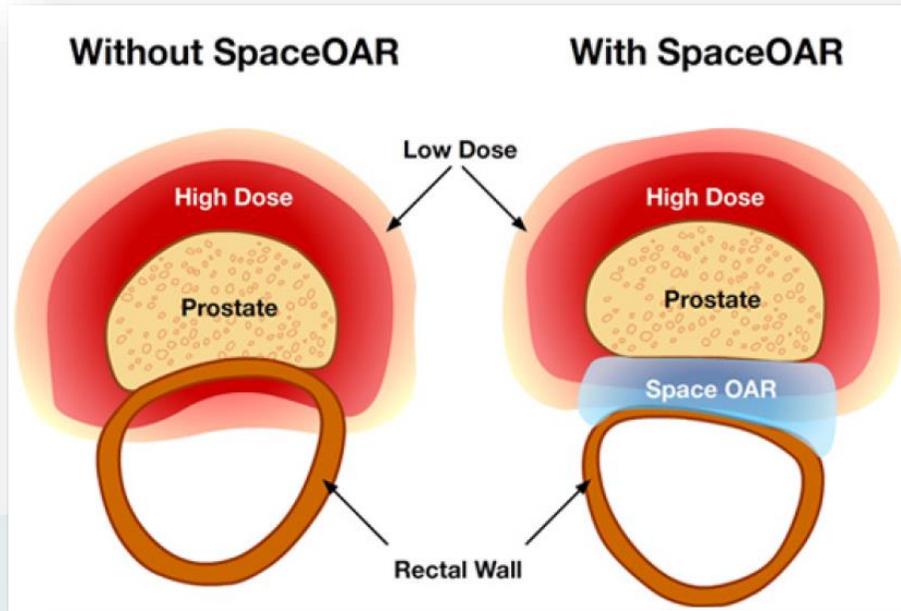
- Dosimetrical study
  - 11 patients
  - prone + bellyboard vs. supine
  - VMAT plans



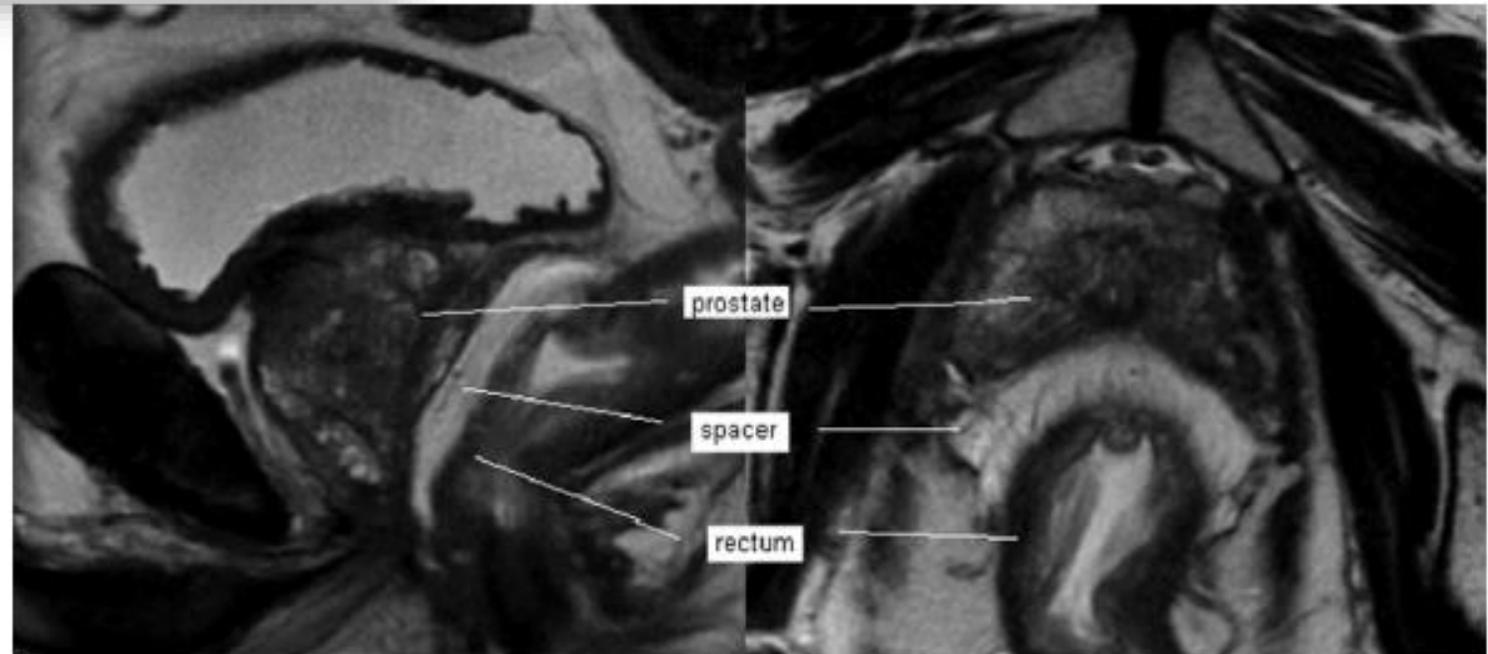
# YES!



# Endorectal spacer gel

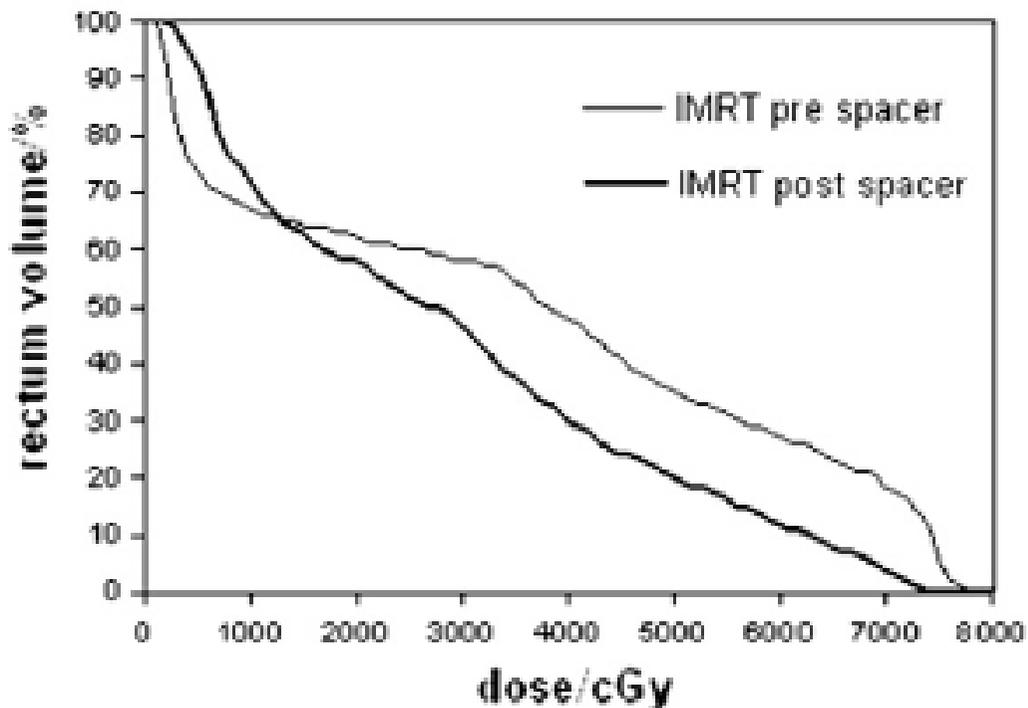
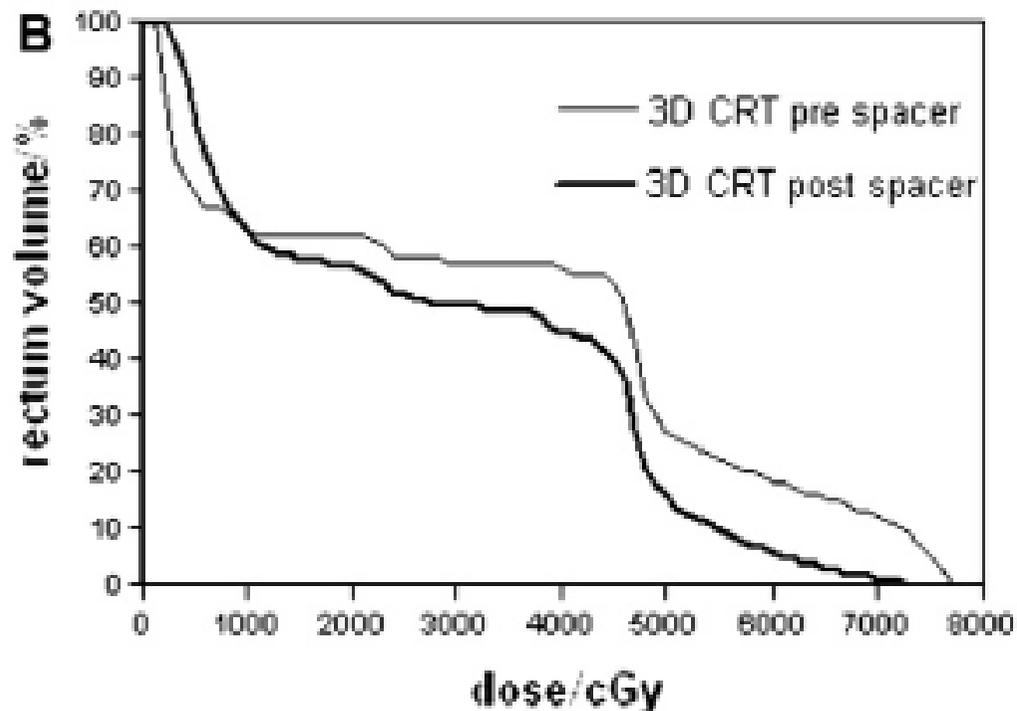


Pinkawa et al., Radiother Oncol 2011

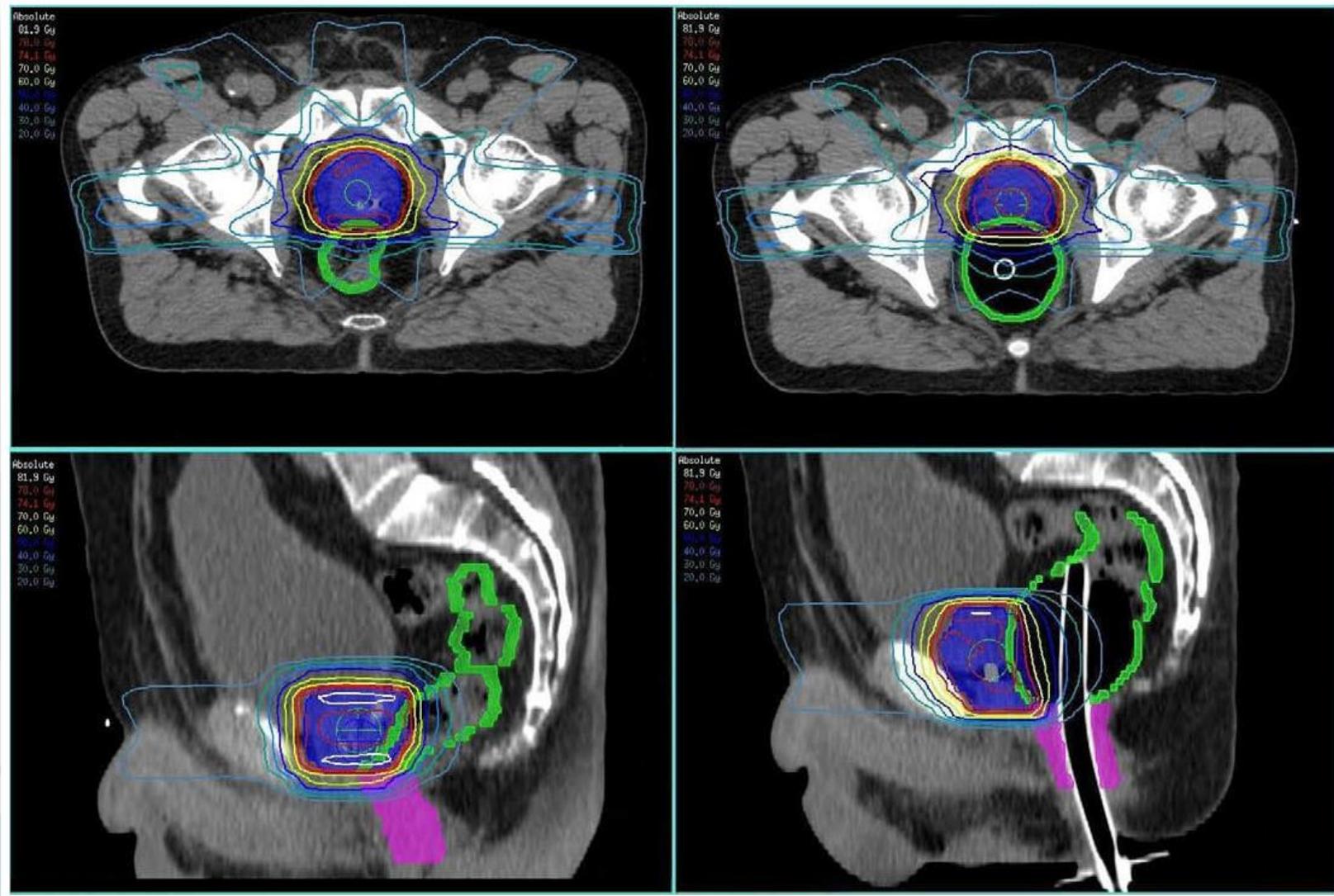


# Endorectal spacer gel

Pinkawa et al., Radiother Oncol 2011



# Endorectal balloon



Smeenk et al., Radiother Oncol 2011

Does a **dosimetrical benefit** also translate  
into a **clinical benefit**?



# Clinical benefit of IMRT

92 rectal cancer patients  
treated with chemoradiotherapy

61 3D-CRT  
31 IMRT

Toxicity scoring CTCAE v 3.0

Decrease in  $\geq$  G2 GI toxicity

No difference in  $\geq$  G2 non-GI toxicity

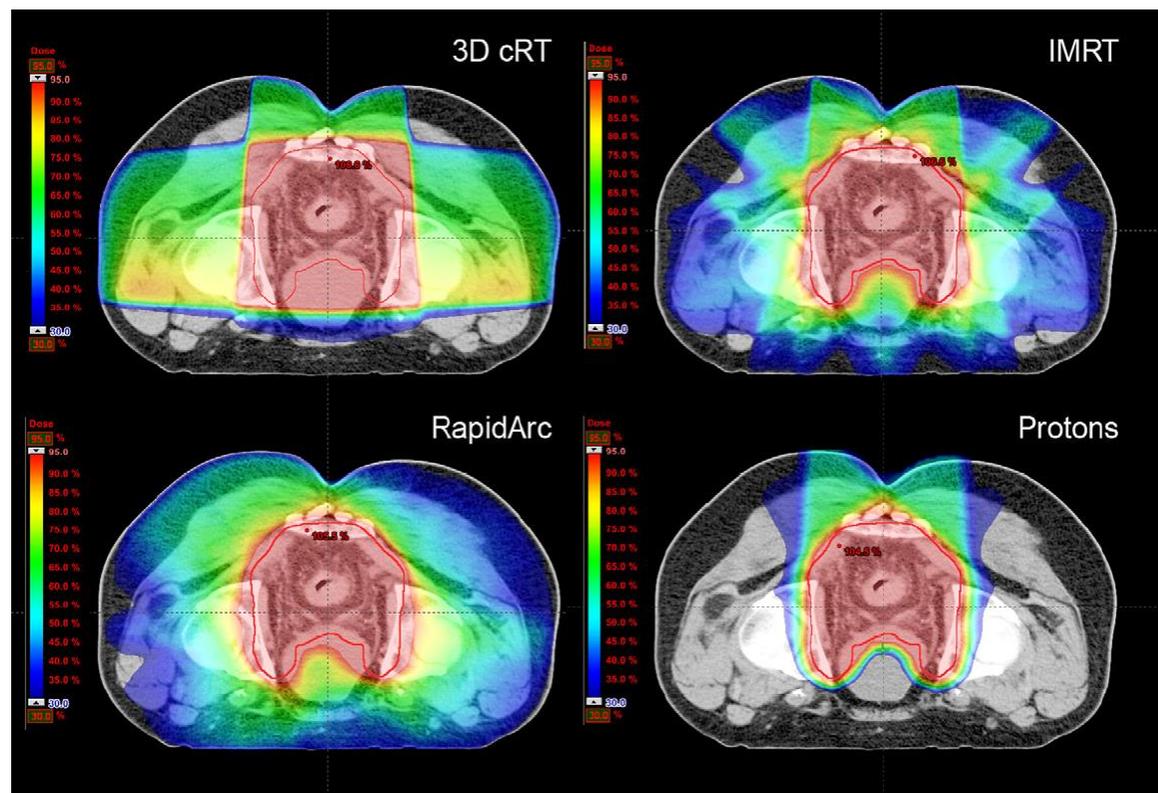
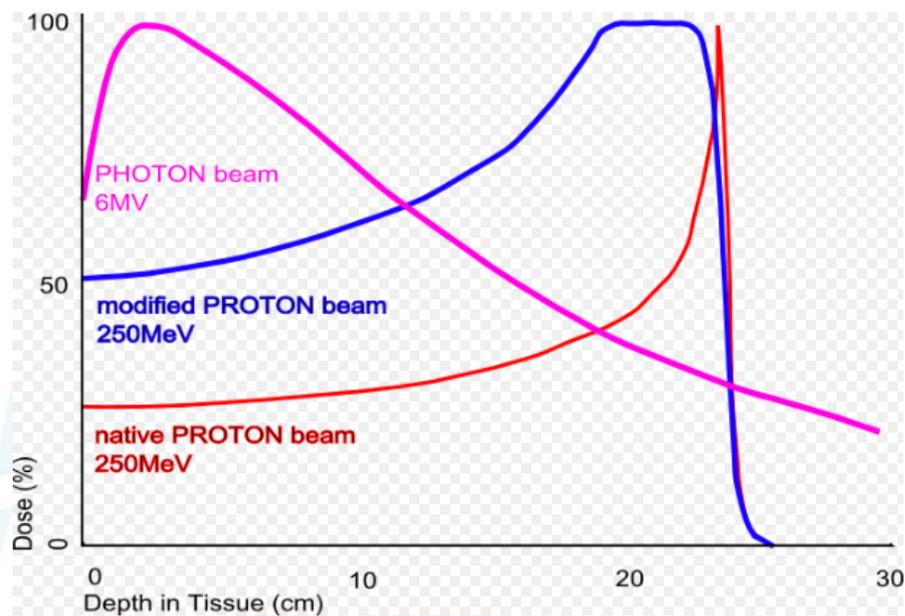
Late toxicity?

Toxicity	IMRT <i>n</i> = 31 (%)	CRT <i>n</i> = 61 (%)	<i>p</i>
Nausea	0 (0)	5 (8)	0.16
Vomiting	0 (0)	1 (2)	1.0
Diarrhea	7 (23)	29 (48)	0.02
Enteritis	2 (6)	18 (30)	0.015
Proctitis	3 (10)	11 (18)	0.37
Dehydration	0 (0)	6 (10)	0.093
Any GI toxicity	10 (32)	38 (62)	0.006

Toxicity	IMRT <i>n</i> = 31 (%)	CRT <i>n</i> = 61 (%)	<i>p</i>
Hematologic			
WBC	3 (10)	13 (21)	0.25
ANC	0 (0)	4 (7)	0.30
Hemoglobin	13 (42)	16 (26)	0.13
Platelets	0 (0)	2 (3)	0.55
Any hematologic	14 (45)	27 (44)	0.93
Any urinary	5 (16)	13 (21)	0.78
Skin	3 (10)	2 (3)	0.33

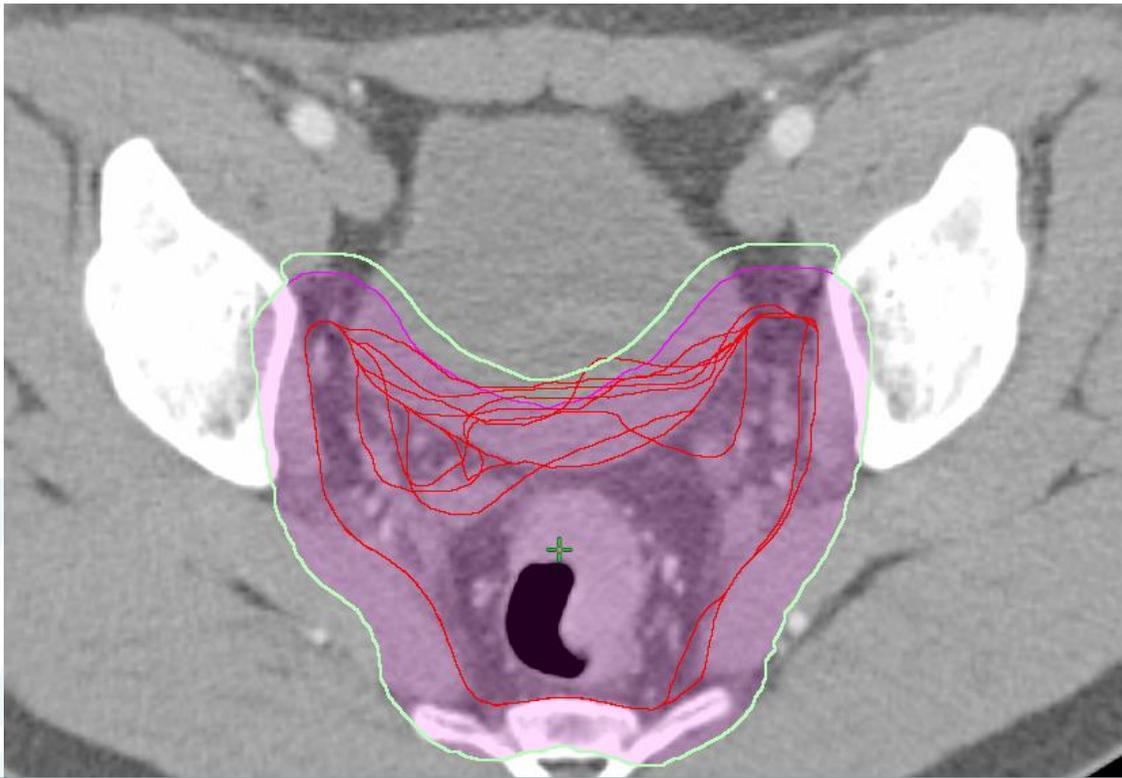
# Proton therapy

- Superior dosimetric properties

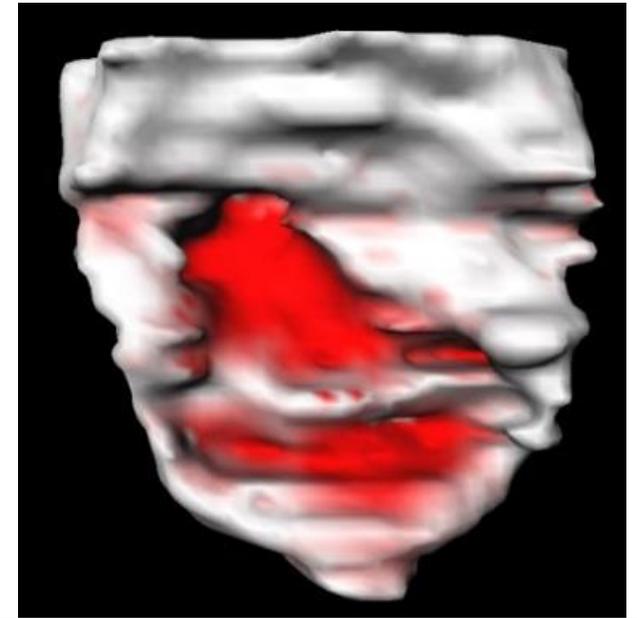


# Image guided RT

Margin reduction



daily image guidance with CBCT



-10.00

10.00

# Fiducial markers

- Indication?
  - All PCa patients scheduled for EBRT to prostate and SV as a primary treatment
  - Contra-indication
    - + pelvic RT (-> bony anatomy matching)
    - Patients on coumarine-anticoagulantia
    - Prior TURP and not enough prostatic tissue left to assure stable and reliable FM position



# Fiducial markers

Varian Medical Systems

Marker Match

Lok Re - 5/8/2008 08:37 - 270 deg - Lok Re

Lok Ant - 5/8/2008 08:38 - 0 deg - Lok Ant

Couch Shift (VAR\_IEC Scale)

	TARGET	ACTUAL	SHIFT		TARGET	ACTUAL	SHIFT	Residual error:
Couch Vrt	11.2	11.2	0.0	<input checked="" type="checkbox"/> Include	Couch Lat	0.0	0.0	0.00
Couch Lng	144.5	144.5	0.0	<input checked="" type="checkbox"/> Include	Couch Rtn	0.00	0.0	0.00

All units in cm and degrees

Perform the marker match

1. Acquire 2. Detect 3. Analyze Cancel

start Varian Medical Systems 8:39 AM

# Fiducial markers

Varian Medical Systems

Marker Match

Lok Re - 5/8/2008 08:37 - 270 deg - Lok Re

Lok Ant - 5/8/2008 08:38 - 0 deg - Lok Ant

Couch Shift (VAR\_IEC Scale)

	TARGET	ACTUAL	SHIFT		TARGET	ACTUAL	SHIFT	Residual error:	
Couch Vrt	11.1	11.2	-0.1	<input checked="" type="checkbox"/> Include	Couch Lat	999.8	0.0	-0.2 <input checked="" type="checkbox"/> Include	0.02
Couch Lng	145.0	144.5	0.5	<input checked="" type="checkbox"/> Include	Couch Rtn	359.9	0.0	-0.1 <input checked="" type="checkbox"/> Include	<input type="button" value="Apply Shift"/>

All units in cm and degrees

Perform the marker match

1. Acquire 2. Detect 3. Analyze

start | Varian Medical Systems | 8:40 AM

# Fiducial markers

Varian Medical Systems

Marker Match

Lok Re - 5/8/2008 08:37 - 270 deg - Lok Re

Lok Ant - 5/8/2008 08:38 - 0 deg - Lok Ant

Couch Shift (VAR\_IEC Scale)

	TARGET	ACTUAL	SHIFT		TARGET	ACTUAL	SHIFT	Residual error:	
Couch Vrt	11.1	11.2	-0.1	<input checked="" type="checkbox"/> Include	Couch Lat	999.9	0.0	-0.1 <input checked="" type="checkbox"/> Include	2.21
Couch Lng	144.9	144.5	0.4	<input checked="" type="checkbox"/> Include	Couch Rtn	359.0	0.0	-1.0 <input checked="" type="checkbox"/> Include	<input type="button" value="Apply Shift"/>

All units in cm and degrees

Perform the marker match

1. Acquire 2. Detect 3. Analyze Cancel

start Varian Medical Systems 8:41 AM

# Image guided RT

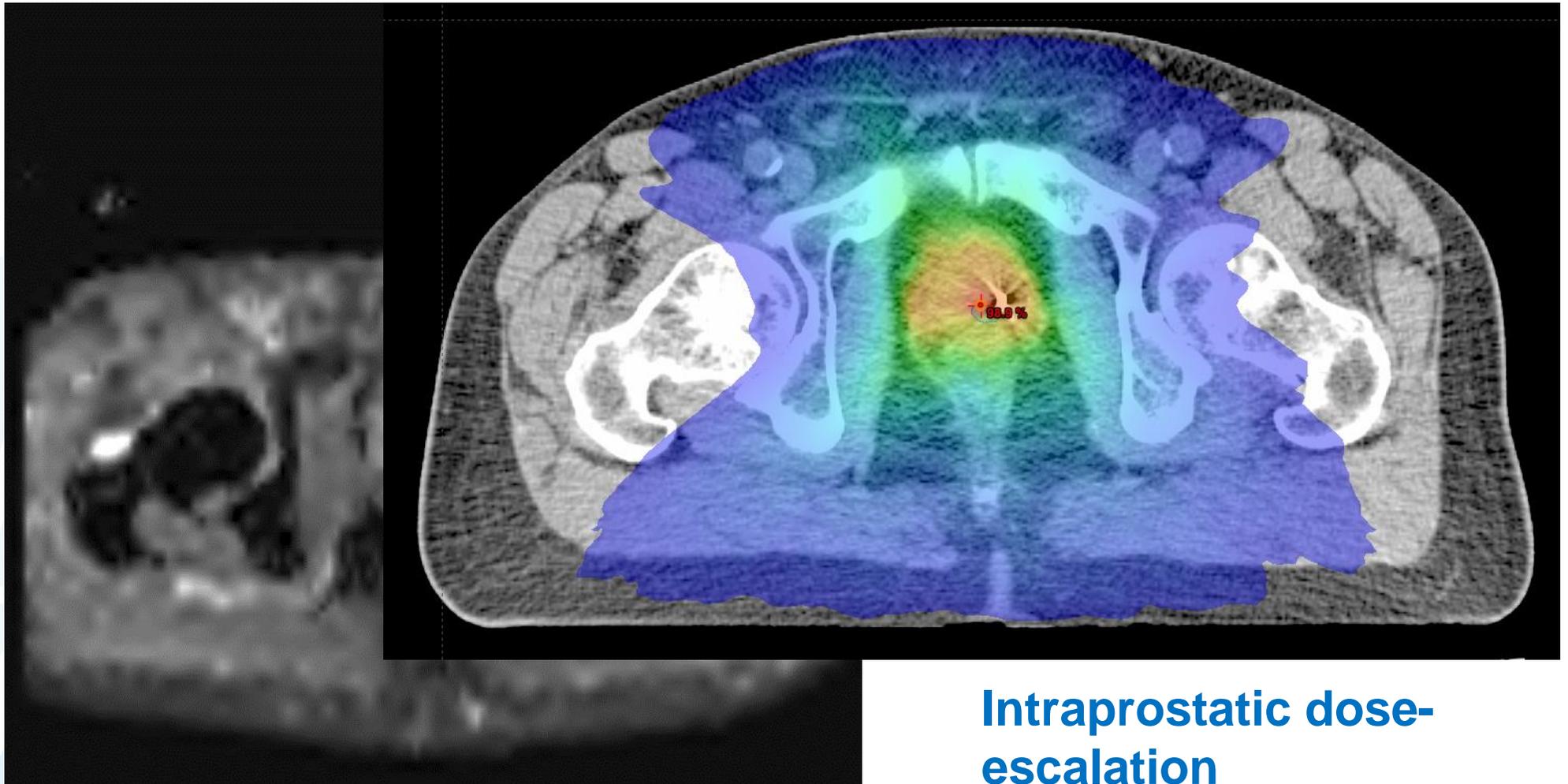
## FLAME trial

- Aim
  - Single Blind Randomized Phase III Trial to Investigate the Benefit of a Focal Lesion Ablative Microboost in Prostate Cancer
  - Addition of an ablative microboost to the macroscopic tumor within the prostate
    - Increase 5-year biochemical control?
    - Change in treatment related toxicity, quality of life or disease free survival?



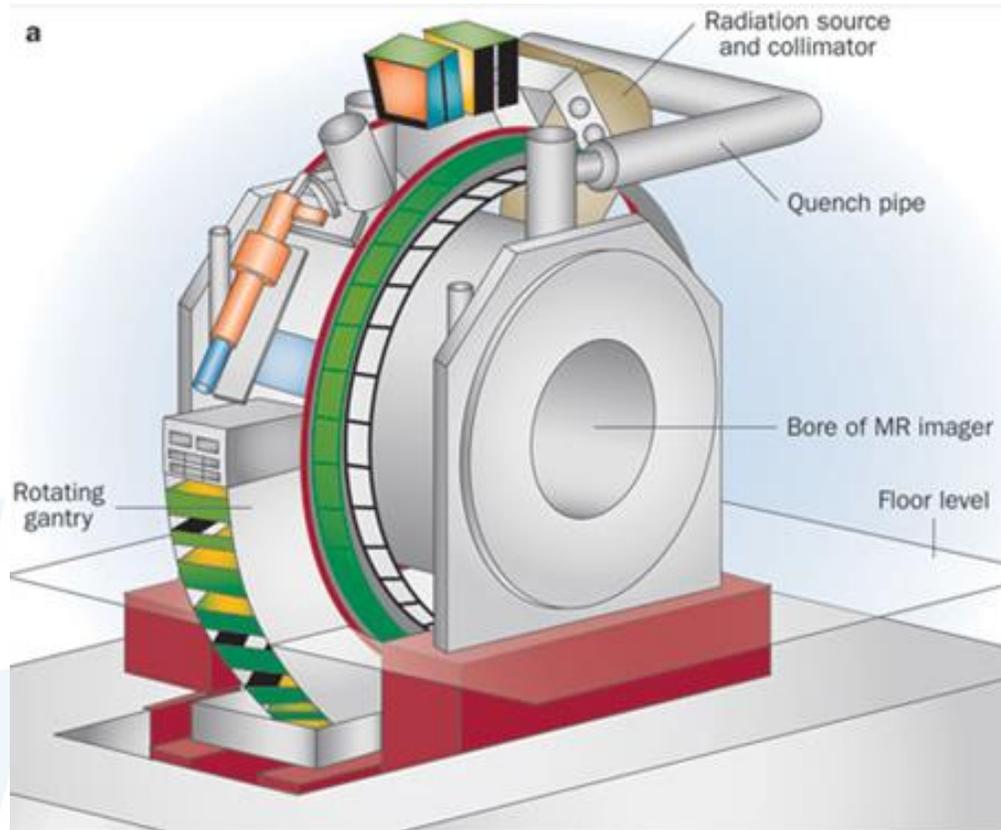
# Image guided RT

FLAME trial

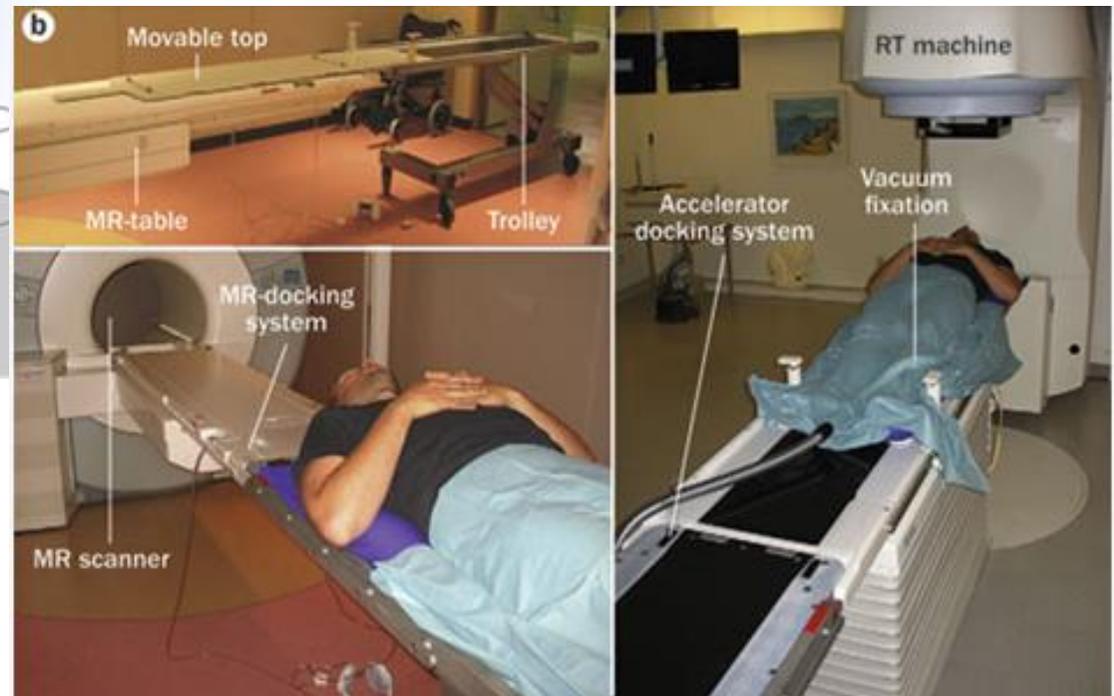


**Intraprostatic dose-escalation**

# Image guided RT



## MRI-guided radiotherapy

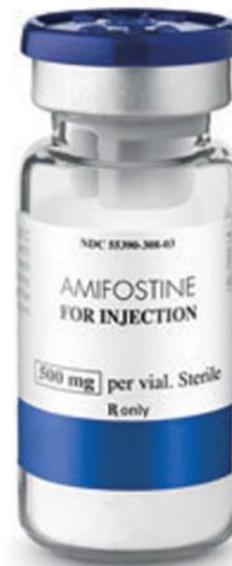
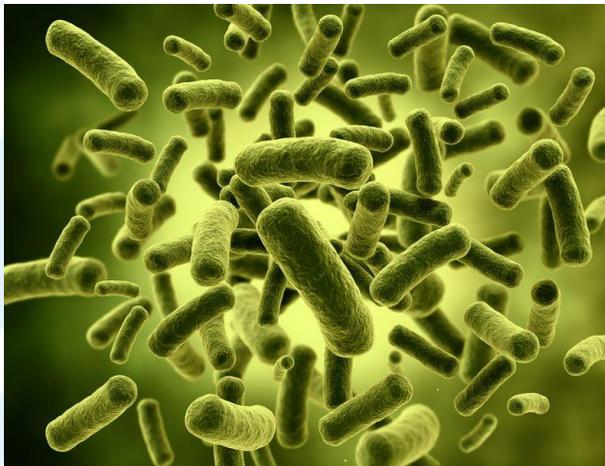
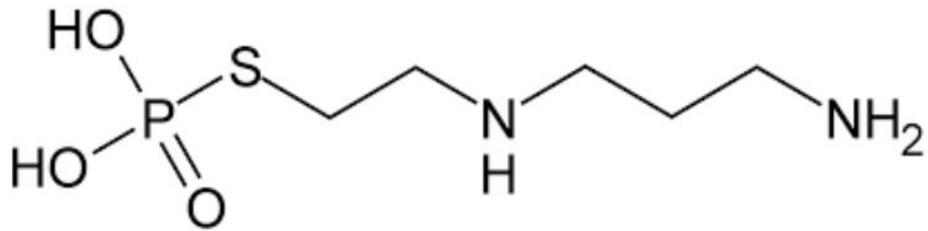


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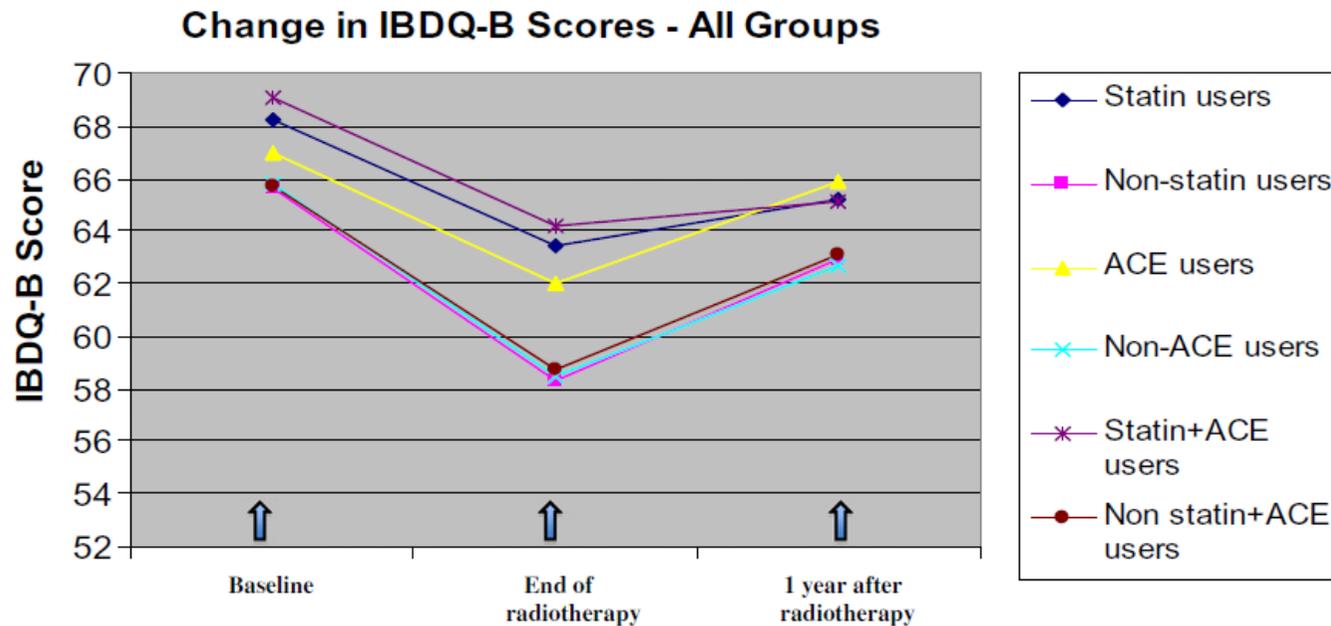
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# Tools to reduce toxicity

## DRUGS



# Statins and ACE-inhibitors



- User subgroups experienced less severe peaks in acute toxicity (worst IBDQ-B) than non-user sub-groups and reduced overall acute severity of toxicity (lesser IBDQB AUC scores).
- The difference in scores was greatest between statin + ACEi users compared to non-statin+ACEi users.
- Analysis of variance showed statin use to be significantly associated with acute IBDQ-B AUC ( $p = 0.04$ ) whilst ACEi use was not ( $p = 0.20$ ).
- Combined statin + ACEi use was more strongly associated with IBDQ-B AUC ( $p = 0.008$ ).

# Amifostine

- Organic thiophosphate cytoprotective agent
- Detoxifies the reactive metabolites and scavenges reactive oxygen species generated by tissue irradiation
- IV, SC, intrarectally
- RCTs: 340mg/m<sup>2</sup> IV or 500mg SC administered during the whole period of treatment **may prevent acute but not late on-set symptoms**
- Nausea and vomiting are common side effects
- **RCTs:** 1-2 g/d intrarectal during the whole period of treatment **may prevent acute symptoms**
- No systemic side effects

# Aminosalicylates

- Contain 5-ASA
  - Inhibitor of the synthesis and release of pro-inflammatory mediators (NO, leukotrienes, PAF, thromboxanes)
  - Inhibitor of the function of several cells implicated in the acute inflammatory and immune response (NK cells, mast cells, neutrophils...)
- Prodrugs: sulfasalazine, balsalazide
- Active compound: mesalazine

# Sulfasalazine

- Prodrug of mesalazine with a high concentration of 5-ASA in the distal colon after metabolisation by the colonic flora
- Oral (daily dose of 6 capsules may reduce compliance)
- **RCTs: possible beneficial effect** on early on-set toxicity.
- No data for the prevention of late-onset radiation disease.

# Balsalazide

- Prodrug that is metabolized to its active component 5-ASA by intestinal microflora, therefore ensuring a high concentration of the active drug in the distal colon
- Oral
- **RCTs:** a dose of 1000mg/d **significantly reduces the risk of developing diarrhea** during radiation treatment

# Mesalazine

- 5-ASA, active compound of aminosalicylates
- Oral or rectal
- **RCTs:** no beneficial or even harmful effects on acute symptoms, **should be avoided** as a preventive agent

# Beclomethasone

- Non-systemic glucocorticoid
- Works as an anti-inflammatory agent
- Rectal
- **RCTs: possible preventive effect** on late-onset rectal bleeding and cost-effective preventive strategy

# Misoprostol

- Methylester analog of prostaglandin E1
- Capability to stimulate mucus production, to prevent cellular shedding and lysosomal enzyme release. Also induction of sulfhydryl compounds, which may act as free radical scavengers.
- Rectal
- **RCTs: conflicting results**, not a treatment of choice.

# Sucralfate

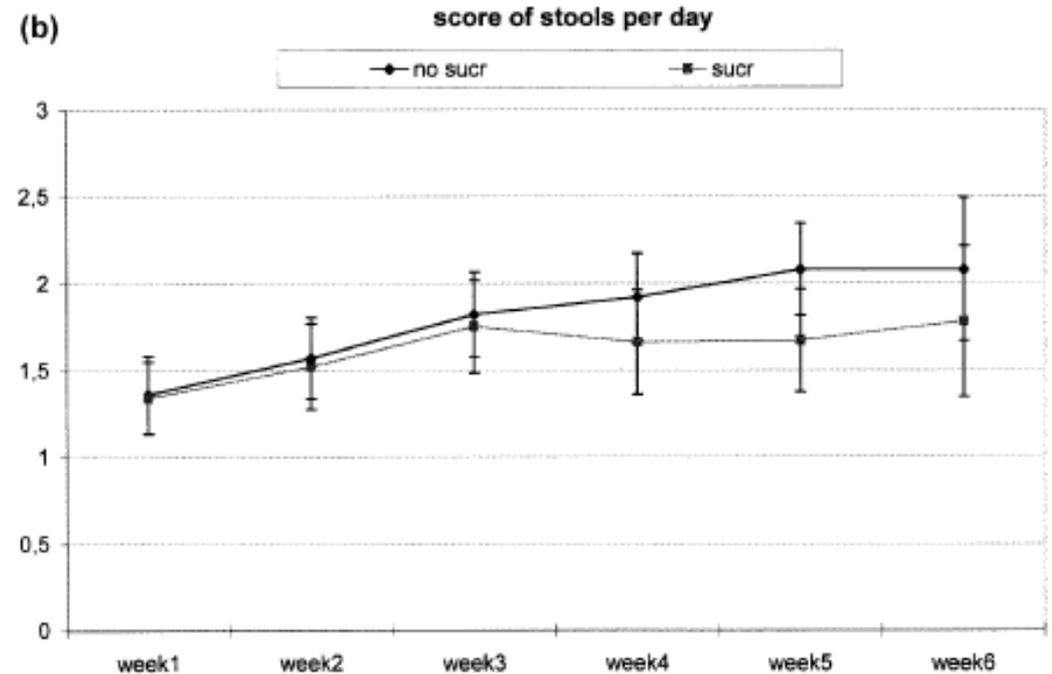
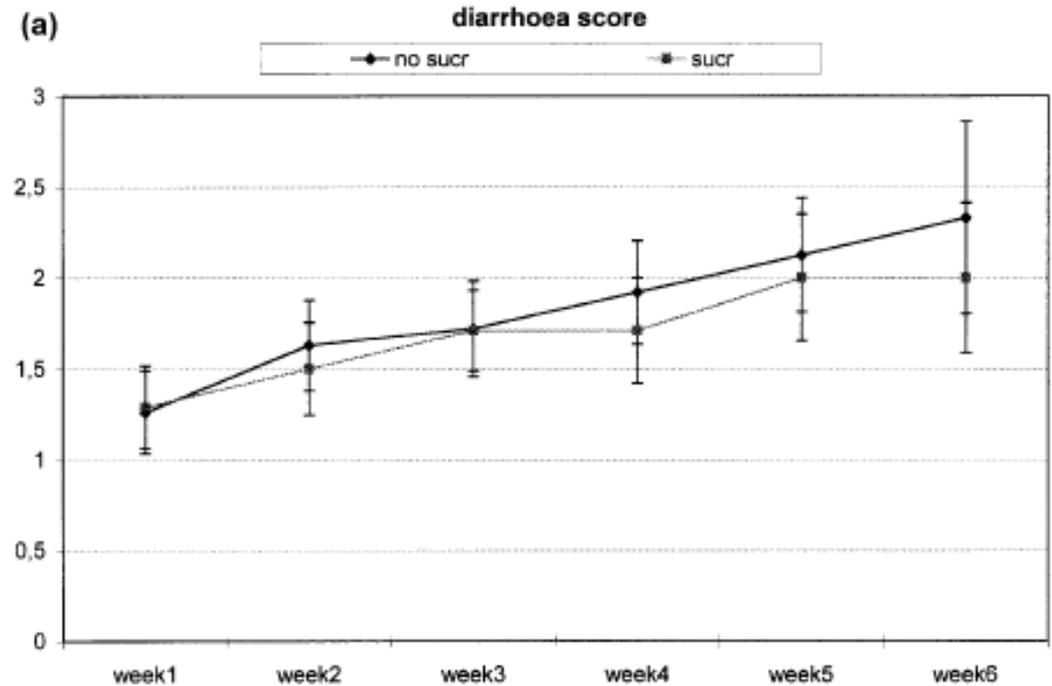
- Alkaline aluminium hydroxide of sulfated sucrose
- Preventive effect by protection of the mucosa by formation of a viscous superficial coating and by stimulation of mucosal healing by its angiogenic effect
- Oral or rectal
- **RCTs: no beneficial or even harmful effect** as preventive agents on both acute and late-onset symptoms
- Useful for treating rectal bleeding

# Sucralfate

Double-blind placebo-controlled  
Pelvic tumor irradiation (GI, GYN)

38 pts sucralfate (oral 4 x 2g/day)  
42 pts placebo

No significant difference between  
sucralfate and placebo



# Probiotics

- Radiation can change the microbial ecosystem of the large intestine, which can contribute to the development of GI side effects.
- Can prevent/treat radiation-induced diarrhea by
  - Composition of indigenous intestinal flora
  - Enhancement of mucosal barrier function
  - Prevention of bacterial overgrowth
  - Prevention of colonization by pathogens
  - Stimulation of hosts immune defenses
- Oral
- **RCTs: possible beneficial effect**, large high-quality studies are required
- CAVE: immunocompromised patients

# Toxicity management

- Nutritional interventions
  - Elemental formula: reduce pancreatic and biliary secretions that may aggravate pre-existing mucosal inflammation (promising)
  - Probiotics
- Specific symptomatic treatment
  - e.g. rectal bleeding (sucralfate enema, lasering, hyperbaric oxygen)

# Toxicity management

Underlying pathophysiology	Therapeutic options
Nutritional deficits	Correction
	Low fat diet
	Lactose-free diet
	Elemental diet
	Total parenteral nutrition
Intestinal dysmotility	Loperamide
	Octreotide
	Prokinetic agents
Bile acid malabsorption	Cholestyramine
Bacterial overgrowth	Antibiotics

# Toxicity management

- 218 patients, pelvic radiotherapy
- Urological, gynaecological, gastrointestinal

**Usual care  
Self-help booklet  
N=68**

**Gastroenterologist  
-led algorithm  
N=70**

**Nurse-led  
algorithm  
N=80**

- Difference in change in IBDQ-B score:
  - nurse vs. booklet: 4,12 (p=0,04)
  - gastroenterologist vs. booklet: 5,47 (p=0,01)
- Outcomes nurse group not inferior to gastroenterologist group

# Surgery

- Highly individualized
- Resection
- Bypass
- Caution with side-to-side staplers



# Conclusions

- A substantial number of cancer patients have become long-term survivors
- Radiation-induced toxicity is a frequent and underestimated problem
- Technological advances have substantially decreased toxicity
- Drugs and diet may be applied in toxicity prevention and management

# Future prospects

- Prediction of treatment-related toxicity
  - Individualized risk-adapted treatment
- Toxicity of new treatment schedules can shed new light on toxicity profiles in cancer treatment

