SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Azienda Ospedaliera di Reggio Emilia
Arcispedale Santa Maria Nuova
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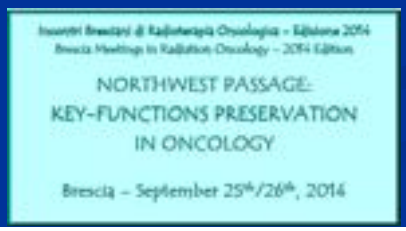
Rectal damage after radiotherapy +/- hormonal manipulation for advanced prostate cancer

E. Mazzeo - F. Bertoni

Radiotherapy department – Policlinic of Modena



Cancer registry: Modena

report 2013

Tab 1. Sintesi dei dati di incidenza e mortalità

	Incidenza	Mortalità
Numero casi	444	65
% sul totale dei casi	19,5	6,3
Tasso grezzo*	128,7	18,8
Tasso STD* (eur)	94,4	9,5
IC95% STD	*85,4-103,4*	*7,1-11,9*
Rischio cumulato (0-74 aa), %	9,3	0,3
Età mediana	69	83

** x 100 000*

Fig 1. Distribuzione per fascia d'età

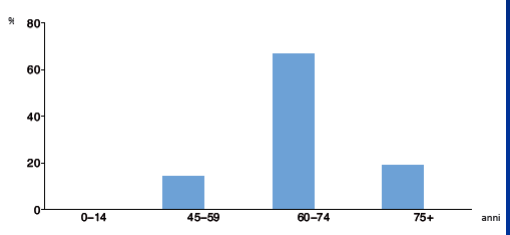
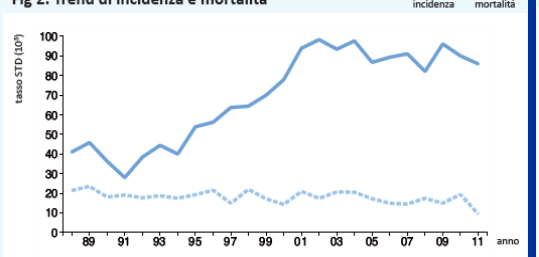
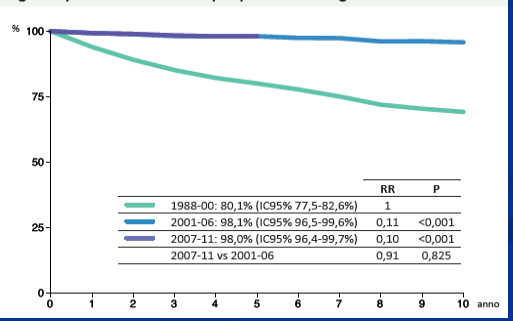


Fig 2. Trend di incidenza e mortalità



APC incidenza: 7,93 -0,57 (2002)*
*APC mortalità: -1,26**
** APC significativo (anno di cambio)*

Fig 5. Sopravvivenza relativa per periodo di diagnosi



Original Article

The Cost Implications of Prostate Cancer Screening in the Medicare Population

Characteristics of the Study Population (n = 94,652)

Patient Characteristics	n	Percent
Age in years on January 1, 2007		
66-69	23,827	25.2
70-74	25,401	26.8
75-79	20,112	
80-84	14,64	
85-99		
Race		
White		
Black		
Other		
Median household income		
<$33,000		
$33,000-$39,999		
$40,000-$49,999		
$50,000-$62,999		
≥$63,000		
Unknown		
Comorbid conditions		
0		51.1
1 to 2		34.1
≥3	14,045	14.8
Stage and risk classification*		
Localized, low-risk	388	17.2
Localized, intermediate-risk	877	38.9
Localized, high-risk	468	20.7
Regional/metastasized	138	6.1
Unknown	386	17.1

*Number of prostate cancer patients for stage and risk classification = 2257.

I R - H R: 60 – 70%
1,4 – 1,7%
screened patients

(CaP 1871/2257) /94652 paz. screenati

LR : 17 – 21%

IR: 39 – 47 %

HR: 21 – 25%

X. Ma et al.: Cancer 2013

Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy.
Results from the Prostate Cancer Results Study Group

TABLE 2 Criteria for inclusion of a study on treatment of localized prostate cancer

- Patients must be stratified into recognizable pretreatment risk groups, low, intermediate and high risk, using D'Amico, Zelefsky or NCCN stratification
- Standard endpoint used to measure biochemical relapse-free survival: ASTRO, Phoenix and PSA < 0.2 ng/mL (for surgery)
- Clinical staging conducted and not pathological staging alone
- EBRT must be minimum 72 Gy IMRT/conformal
- All treatment modalities considered: brachytherapy (including HDR), surgery, IMRT, HIFU, cryotherapy, protons
- Results published in peer-reviewed journals only
- Low risk accepted minimum number of patients was 100
- Intermediate risk accepted minimum number of patients was 100
- High risk accepted minimum number of patients was 50
- Minimum median follow-up was 5 years

NCCN, National Comprehensive Cancer Network; ASTRO, American Society for Radiation Oncology; IMRT, intensity modulated radiotherapy; HDR, high dose rate; HIFU, high intensity focused ultrasound

TABLE 3 Number of patients in each treatment group and according to risk group category

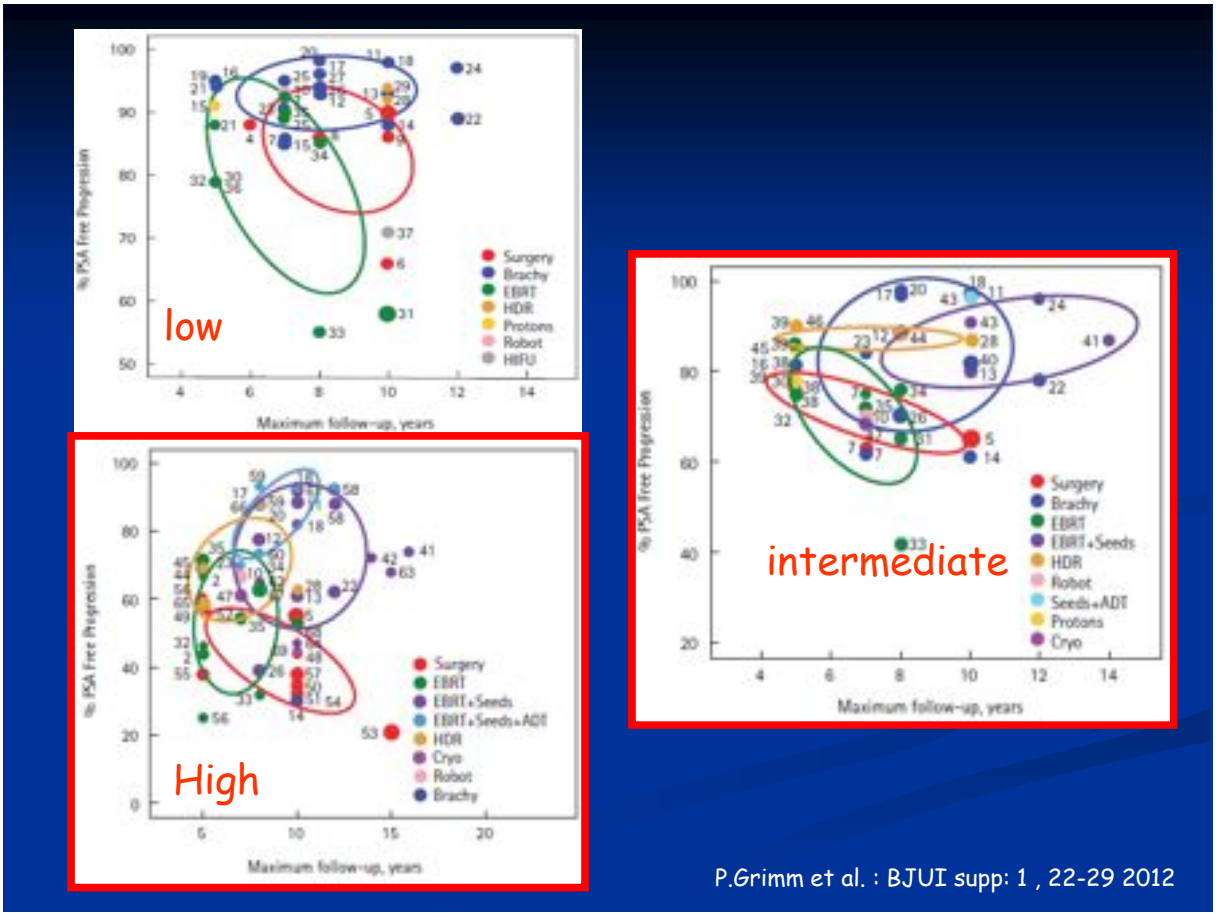
Treatment type	No. of patients (no. of studies) Low risk	Intermediate	High
RP	6447 (6)	3696 (4)	5149 (7)
Robotic RP	706 (1)	479 (1)	200 (1)
Seeds alone	8133 (17)	5808 (10)	396 (1)
Seeds + EBRT	726 (1)	1554 (6)	2864 (15)
EBRT + seeds + ADT	–	–	1231 (6)
HDR (seeds)	226 (2)	607 (4)	869 (3)
Protons	388 (2)	162 (1)	–
EBRT alone	4735 (8)	2969 (10)	3828 (11)
HIFU	227 (1)	–	–
Cryotherapy	–	175 (1)	357 (2)
Seeds + ADT	–	165 (1)	–

ADT, androgen deprivation therapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound; RP, radical prostatectomy; EBRT, external beam radiation

140/ 18000 abstracts→ 52087 pts

PCRSG criteria was as follows: high intensity focused ultrasound 1/30 (3%); robotic radical prostatectomy 3/59 (5%); radical prostatectomy 24/260 (9%); proton therapy 2/13 (15%); cryotherapy 5/31 (16%); EBRT 39/222 (18%)

P.Grimm et al. : BJUI supp: 1 , 22-29 2012



P.Grimm et al. : BJUI supp: 1 , 22-29 2012

Gastrointestinal and genitourinary radiotherapy late toxicity

Studio	Dose (Gy)	Tecnica RT	Tossicità tardiva (%) LENT-SOMA					
			Gastroenterica			Urinaria		
			2°	3°	4°	2°	3°	4°
MD Anderson Cancer Center [75]	70 vs 78	3D/CRT	15 vs 28	2 vs 10	0 vs 0	7 vs 11	7 5	0 0
MSCC [76]	81	IMRT	2	1	0	11	5	0
Gent University Hospital, Belgium [77]	74	IMRT	17			19	3	0
Dutch trial [78,79]	68 vs 78	3D/CRT (594 pz.) IMRT (41pz.)		3		41 vs 40	12 vs 13	
MRC RT01 [80]	64 vs 74	3D/CRT	24 vs 33	3 vs 10	0	57 vs 59	25 vs 26	5 vs 6

GI toxicity
•$G_{\geq 2}$ (2-35%)
•$G_{\geq 3}$ (1-10%)

AIOM guidelines, 2013

Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study

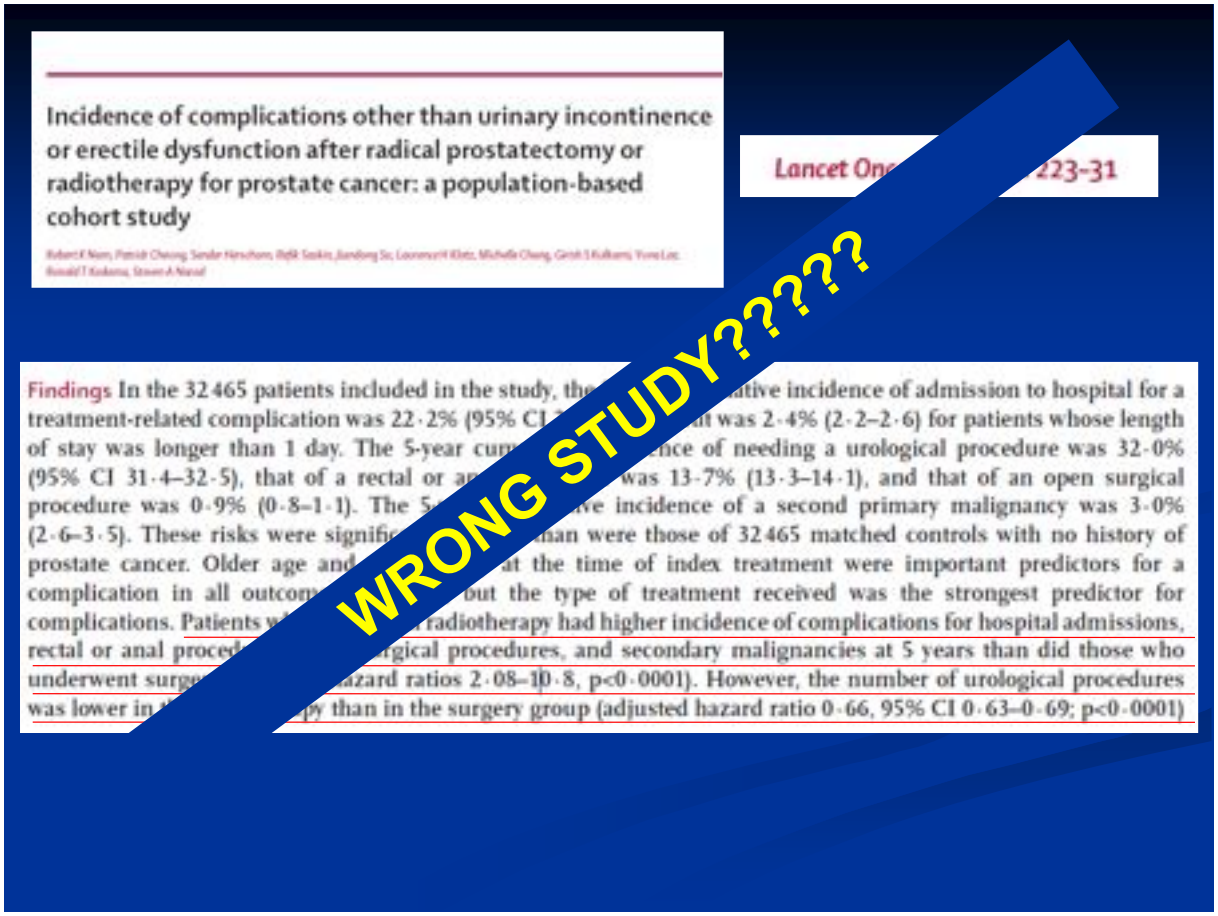
Robert K Nam, Patrick Cheung, Sender Herschorn, Refik Saskin, Jiandong Su, Laurence H Klotz, Michelle Chang, Girish S Kulkarni, Yuna Lee, Ronald T Kodama, Steven A Narod

Lancet Oncol 2014; 15: 223–31

Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study

Lancet Oncol 2014; 15: 223–31

	Radiotherapy group (N=16 595)		Radical prostatectomy (surgery) group (N=15 870)	
	Frequency distribution	Risk in person-years*	Frequency distribution	Risk in person-years*
Minimally invasive urological procedures				
Cystoscopy	2848 (61·8%)	48·0/1000	3103 (57·8%)	66·3/1000
Catheterisation	723 (15·7%)	12·2/1000	1184 (22·1%)	25·3/1000
Urethral dilation or incision	300 (6·5%)	5·1/1000	1014 (18·9%)	21·7/1000
Calculi or clot removal	61 (1·3%)	1·0/1000	67 (1·2%)	1·4/1000
Transurethral resection of prostate†	20 (0·4%)	0·3/1000	–	–
Prostate biopsy†	654 (14·2%)	11·0/1000	–	–
Admission to hospital				
Genitourinary or gastrointestinal fistula	12 (0·3%)	0·2/1000	30 (1·1%)	0·5/1000
Genitourinary bleeding	575 (14·3%)	11·1/1000	165 (6·0%)	2·8/1000
Gastrointestinal bleeding	553 (13·7%)	10·0/1000	0	0
Renal insufficiency	139 (3·5%)	2·7/1000	45 (1·6%)	0·8/1000
Infection	433 (10·8%)	8·3/1000	370 (13·5%)	6·2/1000
Urinary obstruction	487 (12·1%)	9·4/1000	2000 (72·8%)	33·5/1000
Radiation proctitis	1663 (41·3%)	31·7/1000	0	0
Radiation cystitis	160 (4·0%)	3·1/1000	0	0
Bladder stone	0	0	139 (5·1%)	2·3/1000



Biases of the study

- This study has generated much discussion because of several selection bias:
  - retrospective comparisons
  - patients given radiotherapy:
    - were older,
    - have more comorbidities,
    - have more advanced disease.
  - no differences between radiotherapy tecniques (EBRT, BRT)
  - no clear definitions of toxicities

Rectal damage: definitions

- Late rectal side effects include:
  - **rectal bleeding**
  - **fecal incontinence**
  - urgency
  - frequency
- Rectal bleeding and fecal incontinence are the better described and studied

Rectal damage: epidemiology

Only few (mostly retrospective) large studies report on rectal toxicity

The lack of explict definitions make difficult to have clear incidence data

Rectal damage: epidemiology

- Frequently is not correctly evaluated or misdiagnosed
- Scoring systems are quite inadequate
- Most of these scoring systems report about only rectal bleeding
- Few data about correlation with quality of life are available

Scales

RTOG

	Grade 1	Grade 2	Grade 3	Grade 4
GI	Mild diarrhoea Mild cramping Bowel movements 2–5 per day Slight rectal discharge or bleeding	Moderate diarrhoea Intermittent, severe cramping Bowel movements (5 per day) Moderate excessive, rectal discharge Intermittent, frequent bleeding (3; single laser treatments or transfusion)	Watery diarrhoea Obstruction requiring surgery Bleeding requiring surgery or 2 laser treatments or transfusions	Necrosis Perforation Fistula Abdominal pain or tenesmus requiring tube decompression or bowel diversion

CTCAE

Grade	Severity	Alternate Description[a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient''s daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient''s daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

Epidemiology
radical treatment

3D-CRT

Dose: 64 – 79.2 Gy

Late GI toxicity≥2 (%): **15 - 33**

No. of study patients	Treatment modality	Assessment	Median follow-up, mo	Late GI toxicity, grade, %	ADT
Zietmann [16]: 393	3DCRT 70.2 vs 79.2 Gy	RTOG scale	60	I 36 vs 43 II 8 vs 17 III 1 IV –	–
Peeters [31,33]: 669	3DCRT 68–78 Gy	RTOG/EORTC adopted	51	≥1 ≥2 23 vs 29 ≥3 2 vs 5 ≥4 0.3 vs 0.3	More symptoms in patients receiving ADT
MRC RT01 [125,126]: 843	3DCRT 64–74 Gy	RTOG scale	6	I 58–60 II 24–33 III 6–10	Yes (increased incidence of long-term adverse events)
Kuban [17]: 301	Initial conventional rather than 3DCRT 70 vs 78 Gy	RTOG/EORTC	100	≥1 42 vs 55 ≥2 15 vs 28 ≥3 2 vs 10 ≥4 –	–
Matzinger [24] (EORTC 22991): 791	3DCRT (n = 652) 70–78 Gy IMRT (n = 139) 74–78 Gy	CTCAE 2.0	–	–	6 mo

Buddaus L. Et al. European Urology 6 1 (2012) 112 – 127

Epidemiology
radical treatment

IMRT

Dose: 70 – 81 Gy

Late GI toxicity≥2 (%): **1.6 - 23**

No. of study patients	Treatment modality	Assessment	Median follow-up, mo	Late GI toxicity, grade, %
Zelefsky [44]: 561	IMRT 81 Gy	NCI-CTC for adverse events	96	I – II 1.6 III 0.1 IV –
Vora [46]: 145	IMRT 70–77Gy	RTOG scale	60	I 27 II 23 III 6
Kupelian [45]: 770	IMRT Hypofractionated 70Gy	RTOG/EORTC	45	≥1 5.9 ≥2 3.1 ≥3 1.3 ≥4 0.1

Buddaus L. Et al. European Urology 6 1 (2012) 112 – 127

Epidemiology
radical treatment

BRT

Dose: 70 – 81 Gy

Late GI toxicity≥2 (%): **9 – 11.7**

No. of study patients	Treatment modality	Assessment	Median follow-up, mo	Late GI toxicity, grade, %
Gomez-Iturriaga Pina [105]: 96	^{125}I LDR brachytherapy 160.4 Gy	CTCAE	≥30	I 38.3 II 11.7 III 3.2
Ishiyama [128]: 100	^{192}Ir HDR brachytherapy 31.5 Gy EBRT 30 Gy	RTOG scale	36	–
Gelblum [48]: 685	^{103}Pd LDR brachytherapy 120 Gy ^{120}I LDR brachytherapy 144 Gy	RTOG scale	48	I 8.9 II 6.5 III 0.4
Gelblum [48]: 140	^{103}Pd LDR brachytherapy 120 Gy ^{120}I LDR brachytherapy 144 Gy + EBRT 43 Gy	RTOG scale	48	I 10.5 II 7.1 III 0.7
Lee [129]: 130	EBRT 45 ^{125}I 108 Gy	RTOG scale	49	I – II – III 4 IV –
Zelefsky [47]: 248	^{125}I LDR brachytherapy	RTOG scale	60	I 33 II 9 III 0.4

Buddaus L. Et al. European Urology 6 1 (2012) 112 – 127

Epidemiology
post-operative treatment

Post-op

SWOG 8794	Rectal complications such as proctitis or rectal bleeding occurred in **7 (3.3%) of 214** men in the radiotherapy group
ARO 96-02	Two grade 2 GI adverse effects **(1.4%)** were seen in the RT arm
EORTC 22911	NOT REPORTED

Thompson I, et al. JAMA 296: 2329-2335, 2006
Bolla M, et al. EORTC trial 22911. Lancet 2005;366:572-4
Wiegel T, et al. J Clin Oncol 23:16s 2005

Epidemiology
Hypofractionation

HFRT

Dose: 66 – 80 Gy

Late GI toxicity≥2 (%): **1,9 – 14**

Reference	n	Risk groups	Median FU (months)	Total dose (Gy)	Total fractions	Gy/ fraction	BED (Gy), α/β =		RTOG late toxicity Grade ≥2 (%)	
							1.5	10	GU	GI
Lukka[21]	470	Low, intermediate, high	64	66	33	2	154	79	1.3	1.9
	466			52.5	20	2.63	144	66	1.3	1.9
Yeoh[22,23]	109	NR	90	64	32	2	149	77	NR	NR
	108			55	20	2.75	156	70	NR	NR
Arcangeli[24–26]	85	High	35	80	40	2	187	96	16	17
	83			62	20	3.1	190	81	11	14
Pollack[27,28]	152	Intermediate, high	>60	76	38	2	177	91	8.3	5
	151			70.2	26	2.7	197	89	18.3	6.8
Kuban[29]	102	Mostly low, intermediate	56	75.6	42	1.80	166	89	19	6
	102			72	30	2.40	187	89	19	14

Zaorsky,N. et al. *Cancer Treatment Reviews, vol. 39,no. 7,* 2013.

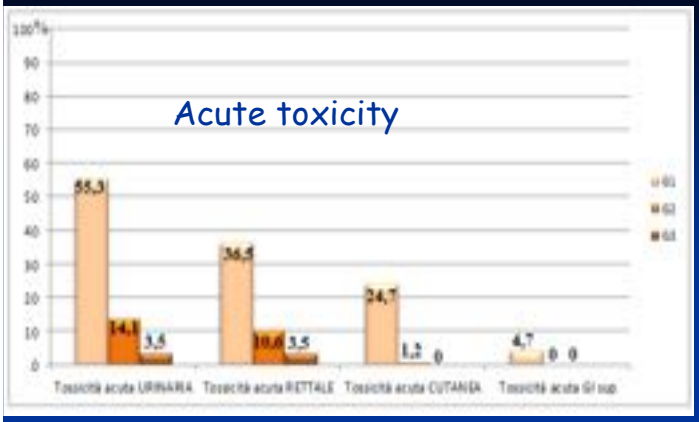
Epidemiology
Stereobody

SBRT

Dose: 66 – 80 Gy

Late GI toxicity≥2 (%): **2 – 8,2**

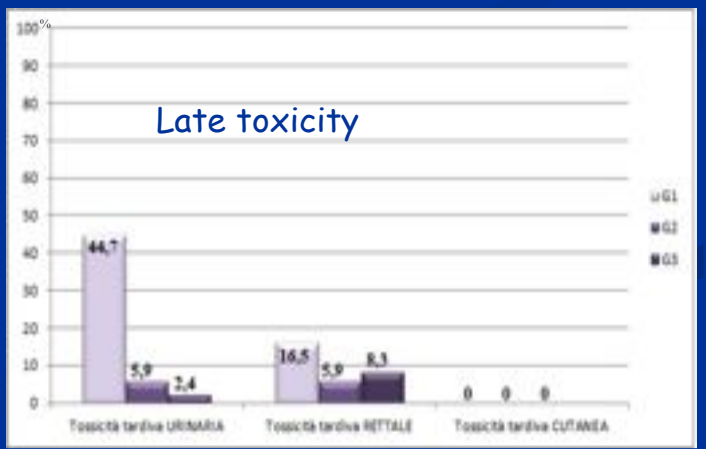
Reference	Numer of patients	Dose	Median follow-up	RTOG Late GI tox≥2
King et al. 2012	67	36.25 Gy in 5 fractions	2.7 years	2% (1/67)
Freeman et al. 2011	41	35–36.35 Gy in 5 fractions	5 years	2.5% (1/41)
Katz et al. 2010	73	35–36.25 Gy in 5 fractions	33 months	8.2% (6/73)
Madsen et al. 2007	40	33.5 Gy in 5 fractions	41 months	7.5% (3/40)



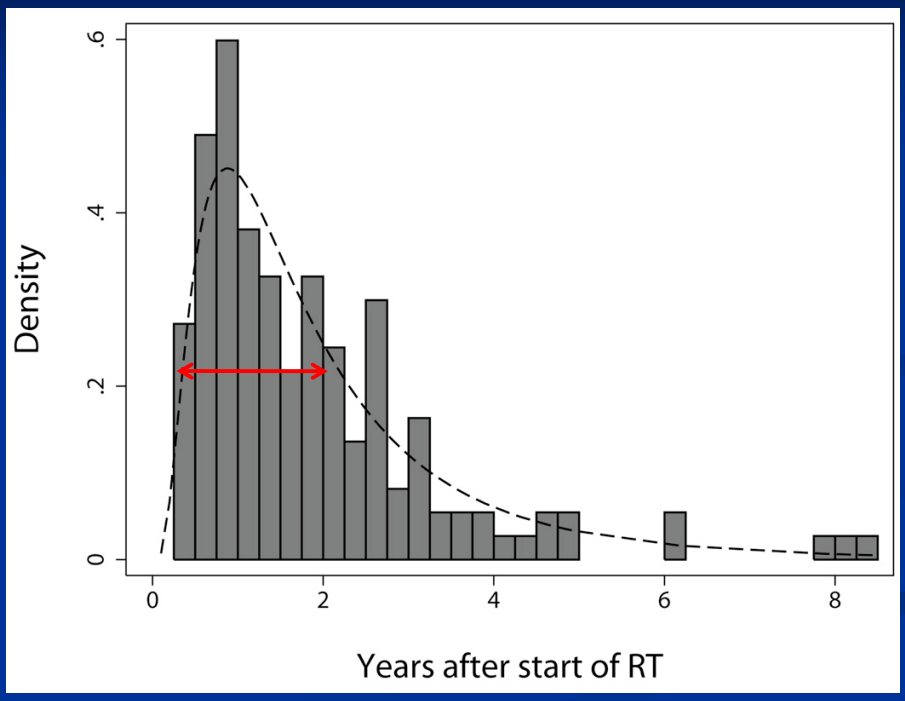
HR prostate cancer patients:

Tomotherapy Modena

RTOG scale



Clinical presentation



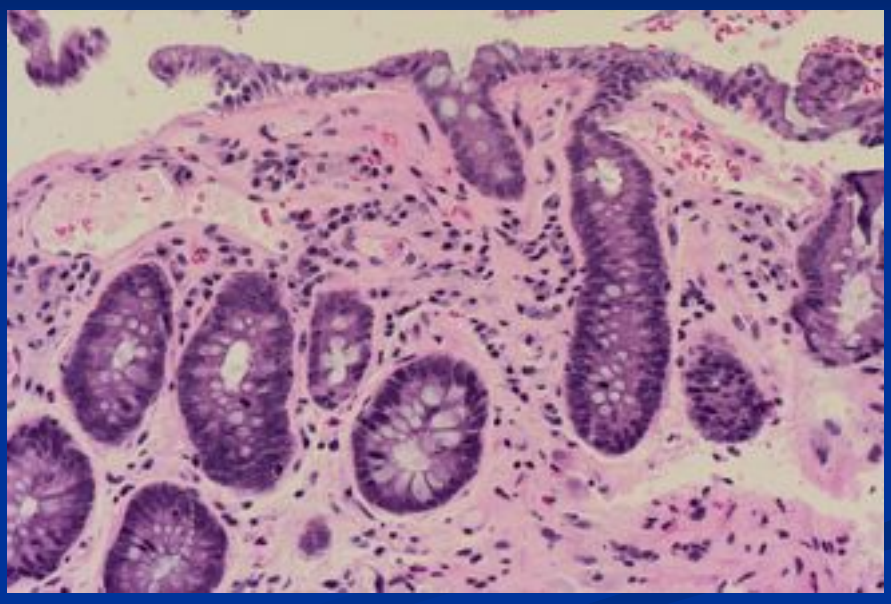
Tucker SL Int J Radiat Oncol Biol Phys. Nov 15, 2010; 78(4):1253-1260

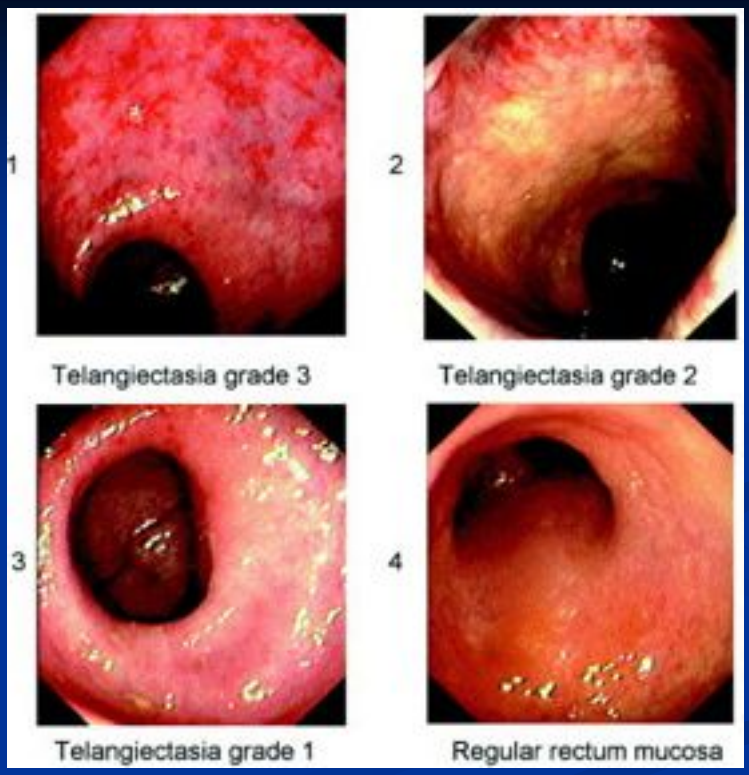
Physiopathology

- Acute toxicity:
  - Epithelium inability to replace adequately because of **damage to progenitor cells**
  - **Mucosa becomes denuded** within a few days after irradiation
  - Cellular changes can be detected in crypts of the colon and rectum, and include: neutrophilic infiltrates, mucosal congestion, and atrophy of villi
- Late toxicity:
  - Result of progressive **obliterative endarteritis** that leads to ischaemia and fibrosis

Histology

- **DISORDERLY CRYPTS**
- **FIBROSIS OF LAMINA PROPRIA**
- **VASCULAR DILATATION**





Wachter S. et al. Radiotherapy and Oncology 54 (2000) 11-19

Endoscopy

- **Endoscopy** can show a **spectrum** of **late changes as defined** by *World Organization for Digestive Endoscopy (OMED)*, **including**:
  - **Telangiectasia**: grade 0, none; grade 1, single telangiectasia; grade 2, multiple non-confluent telangiectasia; grade 3, multiple confluent telangiectasia.
  - **Congested mucosa**: grade 0, none; grade 1, focal reddening of the mucosa combined with an edematous mucosa; grade 2, diffuse not confluent reddening of the mucosa combined with an edematous mucosa; grade 3, diffuse confluent reddening of the mucosa combined with an edematous mucosa.
  - **Ulceration**: grade 0, none; grade 1, microulceration superficial <1 cm^2 ; grade 2, superficial >1 cm^2; grade 3, deep ulceration; grade 4, fistula, perforation.
  - **Stricture**: grade 0, none; grade 1>2/3 of regular diameter; grade 2, 1/3-2/3 of regular diameter; grade 3<1/3 regular diameter; grade 4, complete obstruction
  - **Necrosis**: grade 0, none; grade 1, necrosis.

Crespi M. Et al. Am. J. ESGE (European Society for Gastrointestinal Endoscopy) Gastroenterol. 1996;91:191±216.

ELSEVIER

Radiotherapy and Oncology 54 (2000) 11–19

RADIOTHERAPY & ONCOLOGY

www.elsevier.com/locate/radonline

Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma

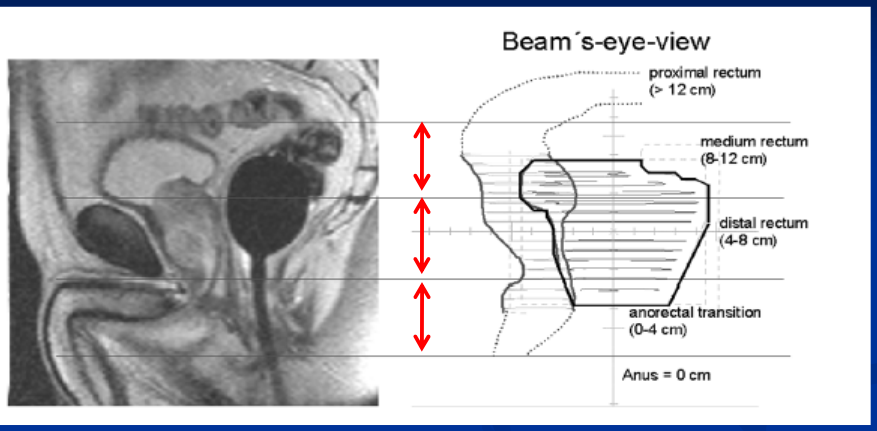
Stefan Wachter[a,*], Natascha Gerstner[a], Gregor Goldner[a], Regina Pötzi[b], Andre Wambersie[c,1], Richard Pötter[a]

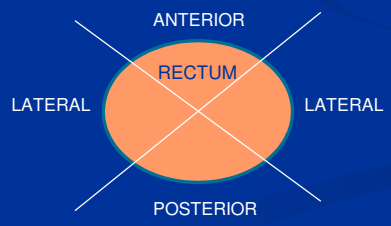
Vienna Rectoscopy Score published by Wachter *et al.*

VRS	Congested mucosa	Telangiectasia	Ulceration	Stricture	Necrosis
0	Grade 1	None	None	None	None
1	Grade 2	Grade 1	None	None	None
2	Grade 3	Grade 2	None	None	None
3	Any	Grade 3	Grade 1	None	None
4	Any	Any	Grade 2	Grade 1	None
5	Any	Any	Grade ≥3	Grade ≥2	Yes

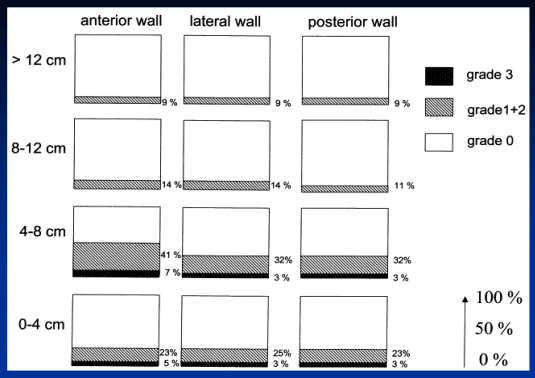
Abbreviation: VRS = Vienna Rectoscopy Score.

Vienna rectoscopy score

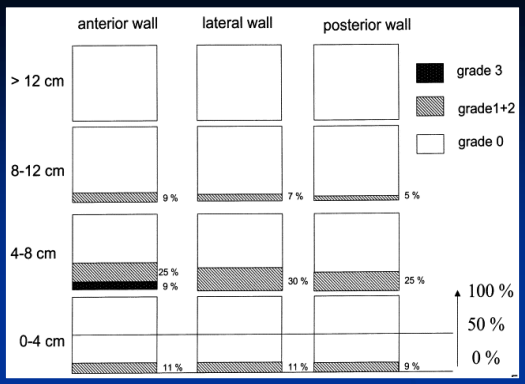




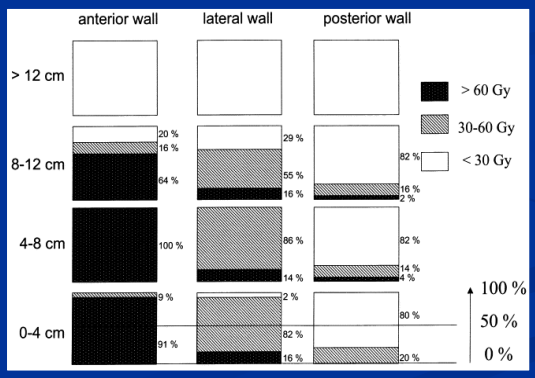
Wachter S. et al. Radiotherapy and Oncology 54 (2000) 11-19



CONGESTED MUCOSA DISTRUBUTION



TELEANGECTASIA DISTRUBUTION



DOSE DISTRUBUTION

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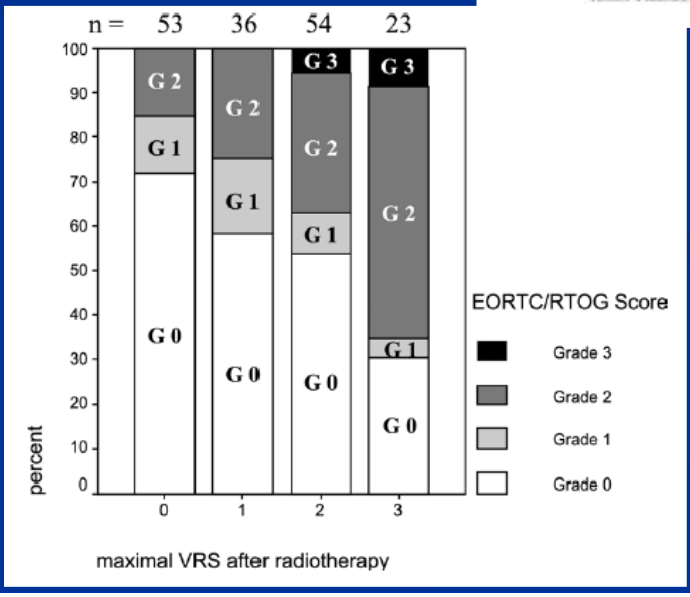
Endoscopy and clinical correlation

CLINICAL INVESTIGATION — Prostate

PROCTITIS AFTER EXTERNAL-BEAM RADIOTHERAPY FOR PROSTATE CANCER CLASSIFIED BY VIENNA RECTOSCOPY SCORE AND CORRELATED WITH EORTC/RTOG SCORE FOR LATE RECTAL TOXICITY: RESULTS OF A PROSPECTIVE MULTICENTER STUDY OF 466 PATIENTS



...The VRS and EORTC/RTOG showed a high coherence. However the VRS was significantly more sensitive.

Clinical and objective findings

LENT-SOMA score

ORIGINAL ARTICLE

Acta Oncologica, 2013; 52: 727–735

Late radiation effects to the rectum and anus after treatment for prostate cancer; validity of the LENT/SOMA score

JO-Å LUND[1,2], STEIN KAASA[1,2], ARNE WIBE[3,4], ANDERS WIDMARK[5] & PER FRANSSON[6]

Table III. Contents of the Subjective Objective Management/Late Effects Normal Tissue (SOMA/LENT) tables for rectum.

Domain/Item	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Subjective					
Tenesmus	No toxicity	Occasional urgency	Intermittent	Persistent	Refractory
Mucosal loss	No toxicity	Occasional	Intermittent	Persistent	Refractory
Sphincter control	No toxicity	Occasional	Intermittent	Persistent	Refractory
Stool frequency	No toxicity	2–4 per day	4–8 per day	>8 per day	Uncontrolled diarrhea
Pain	No toxicity	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Objective					
Bleeding	No toxicity	Occult	Occasionally >2/week	Persistant/daily	Gross hemorrhage
Ulceration	No toxicity	Superficial ≤ 1 cm²	Superficial >1 cm²	Deep ulcer	Perforation, Fistulae
Stricture	No toxicity	>2/3 normal diameter with dilatation	1/3–2/3 normal diameter with dilatation	<1/3 normal diameter	Complete obstruction
Management					
Tenesmus & frequency	No toxicity	Occasional, ≤2 antidiarrheals/ week	Regular, >2 antidiarrheals/ week	Multiple, >2 antidiarrheals/ day	Surgical intervention/ Permanent colostomy
Pain	No toxicity	Occasional, non-narcotic	Regular, non-narcotic	Regular, narcotic	Surgical intervention
Bleeding	No toxicity	Stool softener, iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention/ Permanent colostomy
Ulceration	No toxicity	Diet modification, stool softener	Occasional steroids	Steroids per enema, hyperbaric oxygen	Surgical intervention/ Permanent colostomy
Stricture	No toxicity	Diet modification,	Occasional dilatation	Regular dilatation	Surgical intervention/ Permanent colostomy
Sphincter control	No toxicity	Occasional use of incontinence pads	Intermittent use of incontinence pads	Persistent use of incontinence pads	Surgical intervention/ Permanent colostomy
Analytic					
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				

S

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Table V. SOMA/LENT* and EORTC/RTOG† toxicity score for rectum in 103 patients randomized to hormonal therapy (HT) alone versus HT plus radiotherapy (RT).

HT 55
HT+RT 48

Grade	SOMA/LENT HT (n)	SOMA/LENT HT + RT (n)	EORTC/RTOG HT (n)	EORTC/RTOG HT + RT (n)
0	38	4	42	33
1	12	19	10	12
2	4	15	1	5
3	1	4	0	0
4	0	6	0	0
5	NA	NA	0	0
Difference between groups Mann-Whitney U (p)	<0.001		0.138	

31% ≥G_2 9%

91% ≥G_2 52%

20% ≥G_2 2,3%

35% ≥G_2 10,4%

*Subjective Objective Management Analytic/Late Effects Normal Tissue.
†The European Organisation for Research and Treatment of Cancer and the Radiation Therapy Oncology Group.

Table IV. Correlation coefficients (Spearman's rho) for SOMA/LENT† vs QlQ-C30/QUFW-94†† single items in 103 patients randomized to hormonal treatment alone or hormonal treatment + radiotherapy for prostate cancer.

	S Tenesmus	S Frequency	S Pain	O Bleeding	M Tene/ Freq	M Pain	M Bleeding
Have you had pain? (QLQ-C30)	0.309		0.470*			0.015	
Did pain interefere with your daily activities?(QLQ-C30)	0.169		0.297		0.250	0.093	
How many stools per 24 hours did you have?(QUFW-94)	0.276	0.760*			0.043		
Did you have cramp/pain when passing stools?(QUFW-94)			0.300			0.087	
Did you have blood in your stools?(QUFW-94)				0.671*			0.149

*Correlations with values above the pre-determined correlation limit highlighted.
†Subjective Objective Management Analytic.
††Health-related quality of life questionnaires EORTC QLQ-C30 and QUFW-94.

ORIGINAL ARTICLE

Acta Oncologica, 2013; 52: 727–735

Late radiation effects to the rectum and anus after treatment for prostate cancer; validity of the LENT/SOMA score

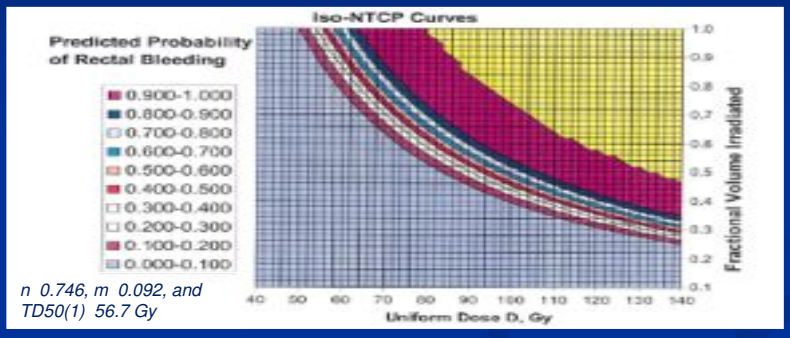
JO-Å LUND[1,2], STEIN KAASA[1,2], ARNE WIBE[3,4], ANDERS WIDMARK[5] & PER FRANSSON[6]

Content/face validity, sensitivity and inter-rater reliability of the LENT/SOMA tables for rectum were analyzed. *Results.* Content/face analysis of LENT/SOMA revealed serious problems. Significant correlations (Spearman's rho >0.4) were found between three of 15 LENT/SOMA items and similar HRQOL items. LENT/SOMA score made it possible to detect significant differences between the two groups of patients ($p < 0.001$), EORTC/RTOG toxicity score did not ($p = 0.138$). Inter-rater reliability was acceptable. *Conclusions.* LENT/SOMA scoring system for recto-anal side effects after radiotherapy for prostate cancer displays serious difficulties in the present study. Replacement of LENT/SOMA tables for rectum by a combination of patient-reported HRQOL questionnaires, clinical examination and objective physiological measurements might be called for.

Dosimetric predictors

NTCP models

***Lyman-Kutcher-Burman* model**
(NTCP fit based on DVH reduction to effective homogeneous dose given to total volume (EUD)



n 0.746, m 0.092, and TD50(1) 56.7 Gy

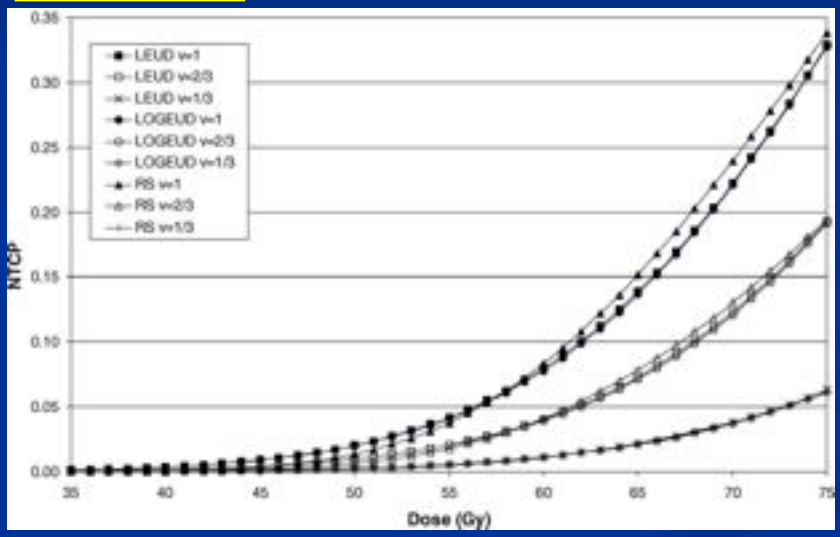
Cheun R. et al. Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 5, pp. 1513–1519, 2004

Ref.	No. of pts	Dose range 1.8–2 Gy/fr	LKB model parameters (68% confidence intervals)			Comments
			n	D_{50} (Gy)	m	
Rancati [9]	547	64–79.2 Gy	0.24 (−0.09; +0.19)	81.9 (−5.1; +9.3)	0.19 (−0.04; +0.06)	G2–G3 late rectal bleeding; solid rectum including filling; including 90 non-conformal patients
Rancati [9]	547	64–79 Gy	0.06 (±0.01)	78.6 (±3.7)	0.06 (±0.005)	G3 late rectal bleeding; solid rectum including filling; including non-conformal patients
Peeters [11]	468	68–78 Gy	0.13 (−0.09; +0.12)	80.7 (−6.0; +6.0)	0.14 (−0.03; +0.05)	G3 late rectal bleeding; rectal wall
Soehn [12]	319	70.2–79.2 Gy	0.08 (−0.02; +0.04)	78.4 (±2.1)	0.11 (±0.03)	G2–G3 late rectal bleeding; rectal wall defined starting from solid rectum contours + 3–4 mm thickness
Tucker [13]	1023	68.4–79.2 Gy	0.08 (−0.04; +0.18)	78 (±6.0)	0.14 (−0.04; +0.12)	G2–G3 late rectal bleeding; solid rectum including filling
Rancati [14]	1119	64–81.6 Gy	0.085 (±0.047)	97.7 (±1.8)	0.27 (±0.13)	G2–G3 late rectal bleeding; solid rectum including filling; including 90 non-conformal patients

Fiorino C. et al. Radiotherapy and Oncology 93 (2009) 153–167

Dosimetric predictors

NTCP models



Lyman with DVH reduction to EUD (LEUD)

Logistic model with DVH reduction using EUD (LOGEUD)

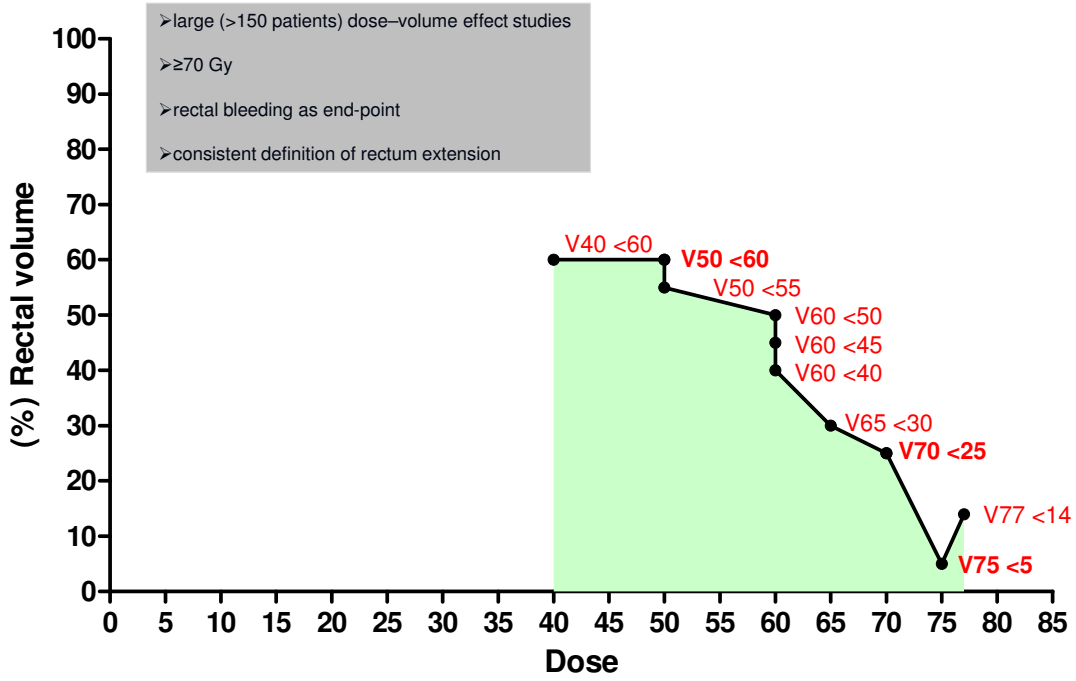
Relative seriality model (RS)

NO DIFFERENCE
SIMILAR LIKELIHOOD VALUES

Rancati T. et al. Radiotherapy and Oncology 73 (2004) 21–32

Dose volume constraints

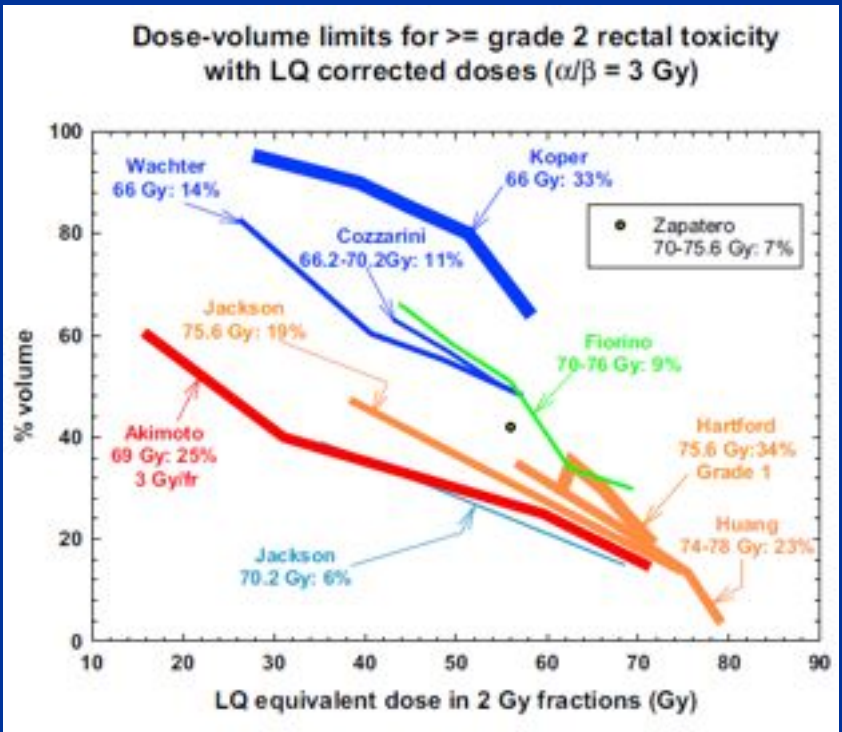
- large (>150 patients) dose–volume effect studies
- ≥70 Gy
- rectal bleeding as end-point
- consistent definition of rectum extension



Fiorino C. et al. Radiotherapy and Oncology 93 (2009) 153–167

Dose volume constraints

QUANTEC: Michalski M.J. et al. IJROBP, Vol. 76, No. 3, Supplement, pp. S123–S129, 2010



Dose volume constraints

QUANTEC: Michalski M.J. et al. IJROBP, Vol. 76, No. 3, Supplement, pp. S123–S129, 2010

Vdose<45 Gy: no difference in rectal toxicity with a few exception

Data from multiple centers converge at the high dose range

V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 <15%.

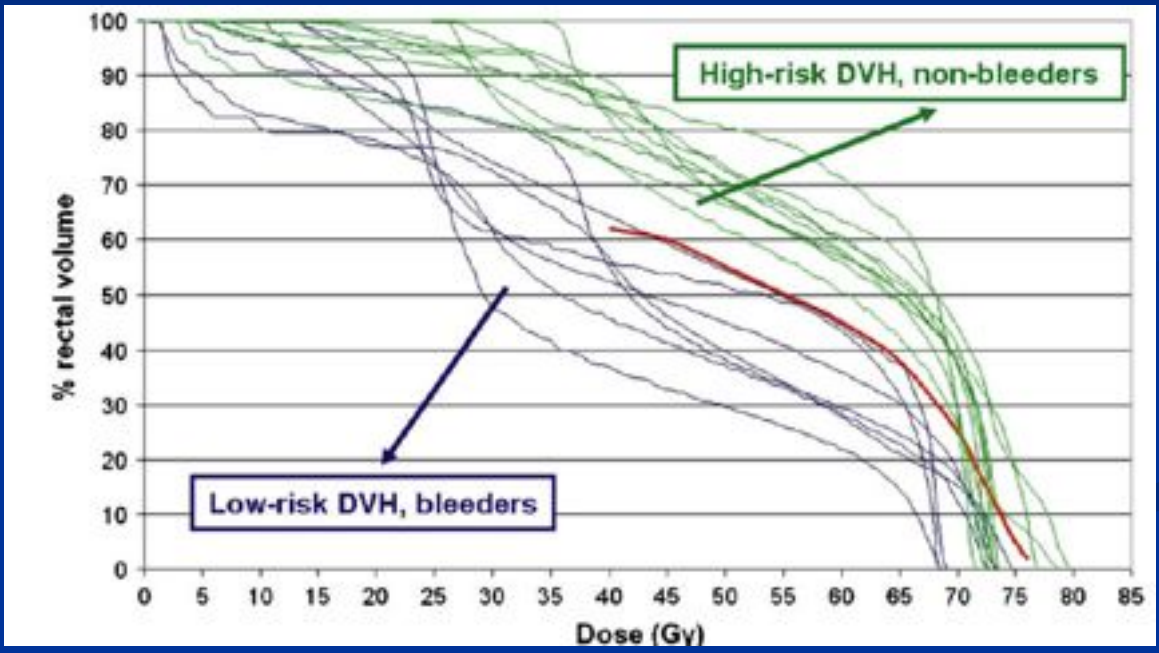
Following these constraints should limit
Grade >2 late rectal toxicity <15%
Grade >3 late rectal toxicity <10%
for prescriptions up to 79.2 Gy in standard 1.8- to 2-Gy fractions.

Higher doses in the VDose parameter have more impact on the complication probability.

Clinicians should strive to minimize the V70 and V75

Reducing the V75 by just 5% from 15% to 10% has a significant impact In the predicted complication probability, whereas reducing the V50 from 50% to 45% makes relatively little difference.

DVH: the only predictor?



α/β ratio: rectal toxicity

For Hypofractionation

"DVH dose bins should be adjusted to conventional 1.8- or 2-Gy fractions using the linear-quadratic model with an **α/β ratio of 3** for the rectum. Whereas some have proposed a rectal a/b ratio of 5.4 Gy, the choice of a/b ratio of 3 is a reasonably conservative estimate"

QUANTEC: Michalski M.J. et al. IJROBP, Vol. 76, No. 3, Supplement, pp. S123–S129, 2010

Fowler J.F. Et al. Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 4, pp. 1093–1104, 2003

Gene espression

CLINICAL INVESTIGATION Prostate

TO BLEED OR NOT TO BLEED. A PREDICTION BASED ON INDIVIDUAL GENE PROFILING COMBINED WITH DOSE–VOLUME HISTOGRAM SHAPES IN PROSTATE CANCER PATIENTS UNDERGOING THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY

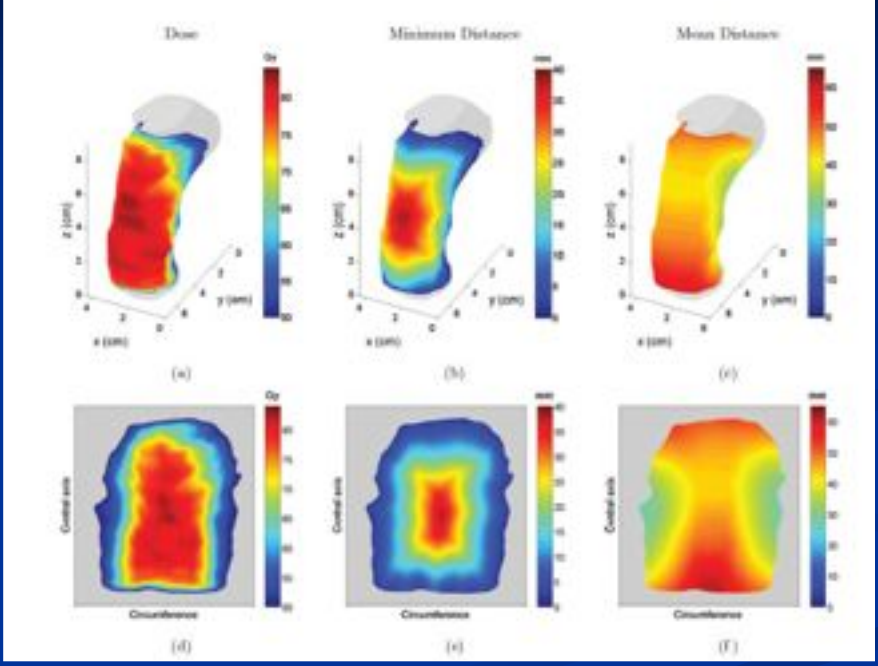
Riccardo Valdagni, M.D., Ph.D.,*† Tiziana Rancati, Ph.D.,* Marco Ghilotti, Ph.D.,†§ Cesare Cozzarini, M.D.,‡ Vittorio Vavassori, M.D.,* Gianni Fellin, M.D.,** Claudio Fiorino, Ph.D.,¶ Giuseppe Girelli, M.D.,†† Salvina Barra, M.D.,‡‡ Nadia Zaffaroni, Ph.D.,§ Marco Alessandro Pierotti, Ph.D.,§§ and Manuela Garibaldi, Ph.D.§§

Down-regulated genes in low-risk bleeder group:
AKR1B1
BAZ1B
LSM7
MRPL23
NUDT1
PSMB4
PSMD1
SEC22L1
UBB000

Upregulated in the high-risk nonbleeder group :
DDX17
DRAP1
RAD23
SRF

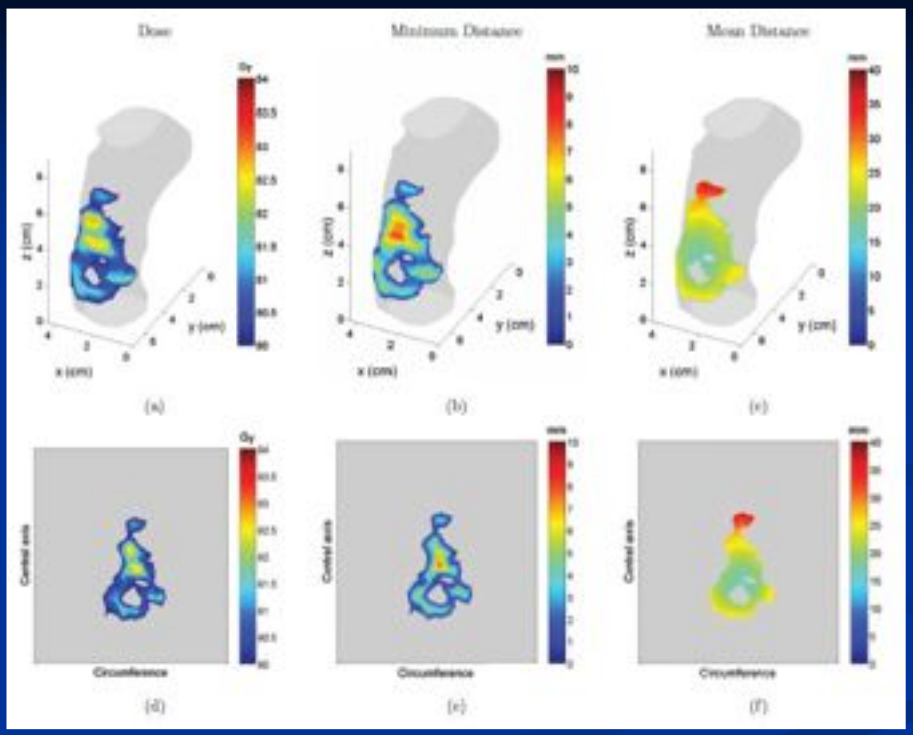
Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 5, pp. 1431–1440, 2009

Quantifying cell migration distance as a contributing factor to the development of rectal toxicity after prostate radiotherapy



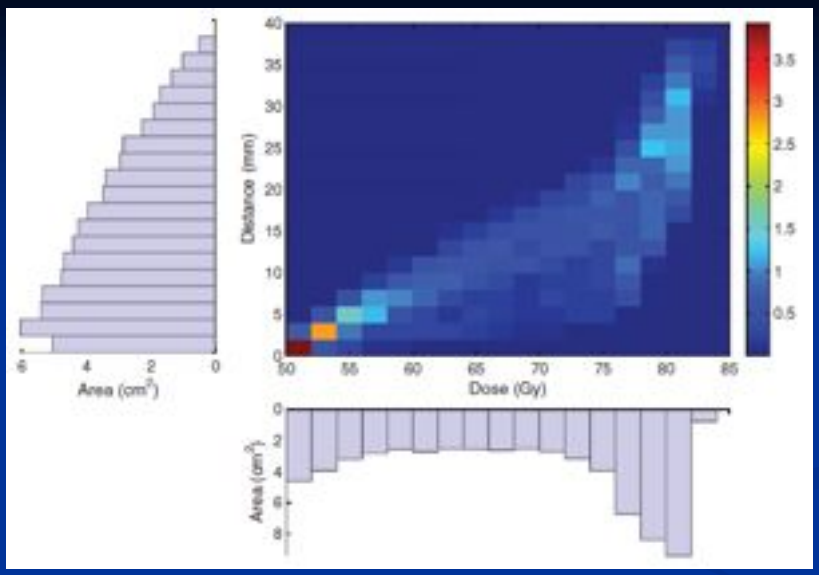
Distance maps for the region receiving at least 50 Gy to the 50 Gy isodose contour

Munbodh R. et al. Med. Phys. 41 (2), February 2014



Distance maps for the region receiving at least 80 Gy to the 80 Gy isodose contour

Munbodh R. et al. Med. Phys. 41 (2), February 2014



(DSH)
dose surface histogram

(DiSH)
distance surface histogram

(DDSH)
distance dose surface histogram

"The method provides a means to evaluate the hypothesis that **distances between lower and higher dose regions on the rectum influence radiation damage repair** due to the **migration of normal cells** into damaged areas, and may be a contributing factor to the development of radiation-induced toxicity in patients treated with radiation for prostate cancer."

Munbodh R. et al. Med. Phys. 41 (2), February 2014

Factors affecting risk

Impact of clinical variables

- Diabetes mellitus
- Hemorrhoids
- Inflammatory bowel disease
- Advanced age
- Androgen deprivation therapy
- Rectum size
- Prior abdominal surgery
- Severe acute rectal toxicity

Summary of main studies investigating the impact of clinical variables on rectal bleeding

Organ: Rectum; End-point: Late rectal toxicity (bleeding)

Ref.	No. of pts	Covariate	Stratification	HR	*P* value
Herold [57]	944	Diabetes	Yes vs No	–	<0.01
Skwarchuk [34]	743	Diabetes	Yes vs No	1.8	0.04
Feinberg [50]	1204	Androgen Deprivation	>6 months vs < 6 months	1.3	<0.01
Sanguineti [49]	182	Androgen deprivation	Yes vs No	2.2	0.02
Peeters [11]	641	Abdominal Surgery	Yes vs no	2.7	<0.01
Fiorino [15]	506	Abdominal Surgery	Yes vs no	4.4	0.06

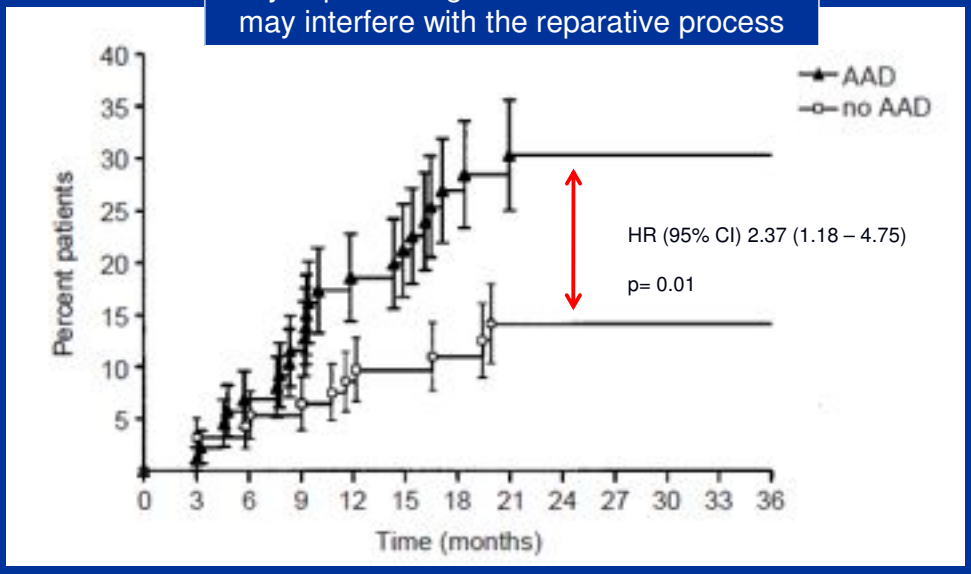
QUANTEC: Michalski M.J. et al. IJROBP, Vol. 76, No. 3, Supplement, pp. S123–S129, 2010

Fiorino C. et al. Radiotherapy and Oncology 93 (2009) 153–167

Androgen deprivation therapy

The underlying mechanism of such phenomenon is not known

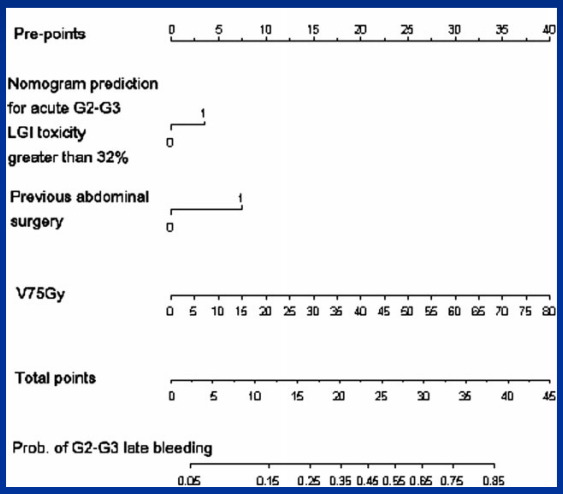
may expose a higher volume of the rectum
may interfere with the reparative process

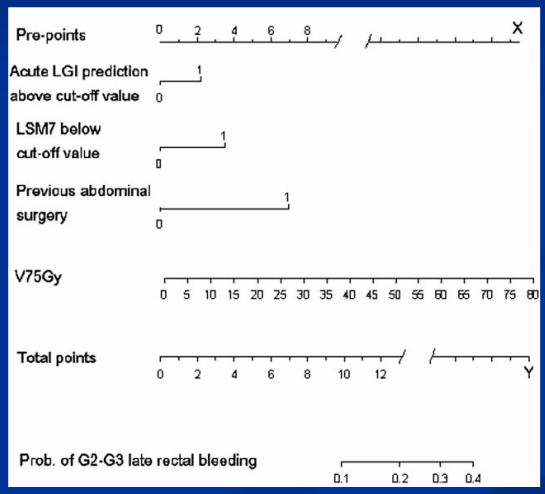


Actuarial incidence (+s.e.) of grade 2 – 4 late rectal toxicity by adjuvant hormonal treatment

AAD: adiuvant androgen deprivation

Nomograms





Including hypothetical gene-profile

Valdagni R. et al. Cancer July 1, 2009

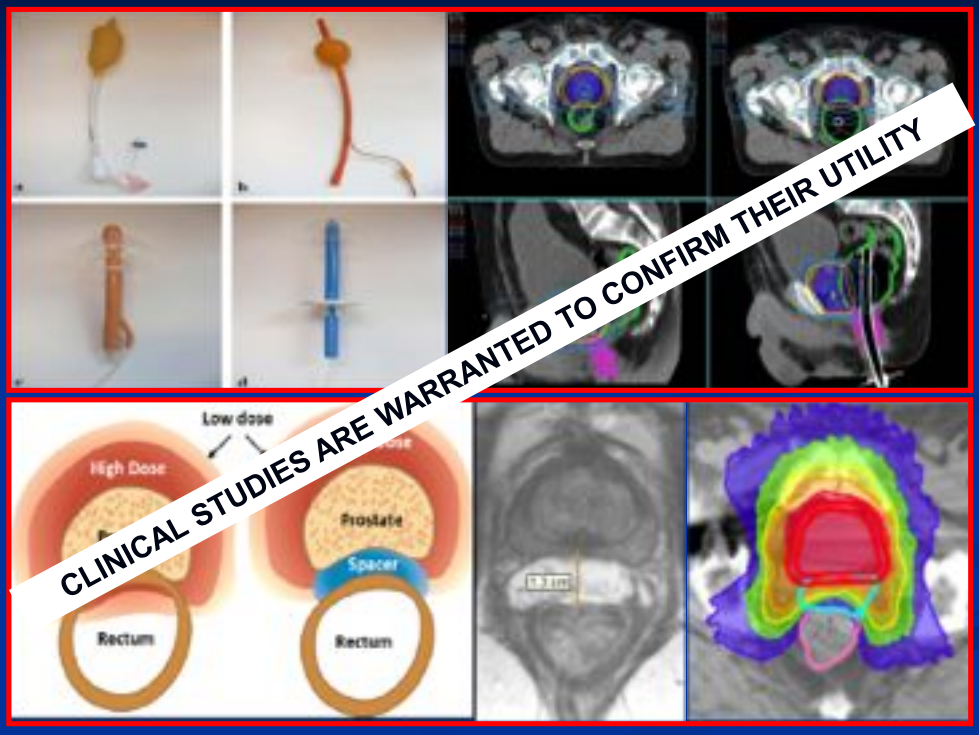
Rectal bleeding: treatments

- Aminosalicylic acid derivatives
- Corticosteroids
- Sucralfate
- Argon plasma coagulation (APC)
- Short chain fatty acids (Sodium Butyrate)
- Hyperbaric oxygen
- Formalin

No randomized trials tested these approaches

Henson C, Ther Adv Gastroenterol (2010) 3(6) 359365
Samalavicius NE, World J Gastroenterol 2013 August 14; 19(30): 4944-4949

Devices To Reduce Rectal Toxicity



CLINICAL STUDIES ARE WARRANTED TO CONFIRM THEIR UTILITY

Smeenk RJ et al. Radiotherapy and Oncology 95 (2010) 277–282
Uhl M. et al Heidelberg, Germany.

Fecal incontinence

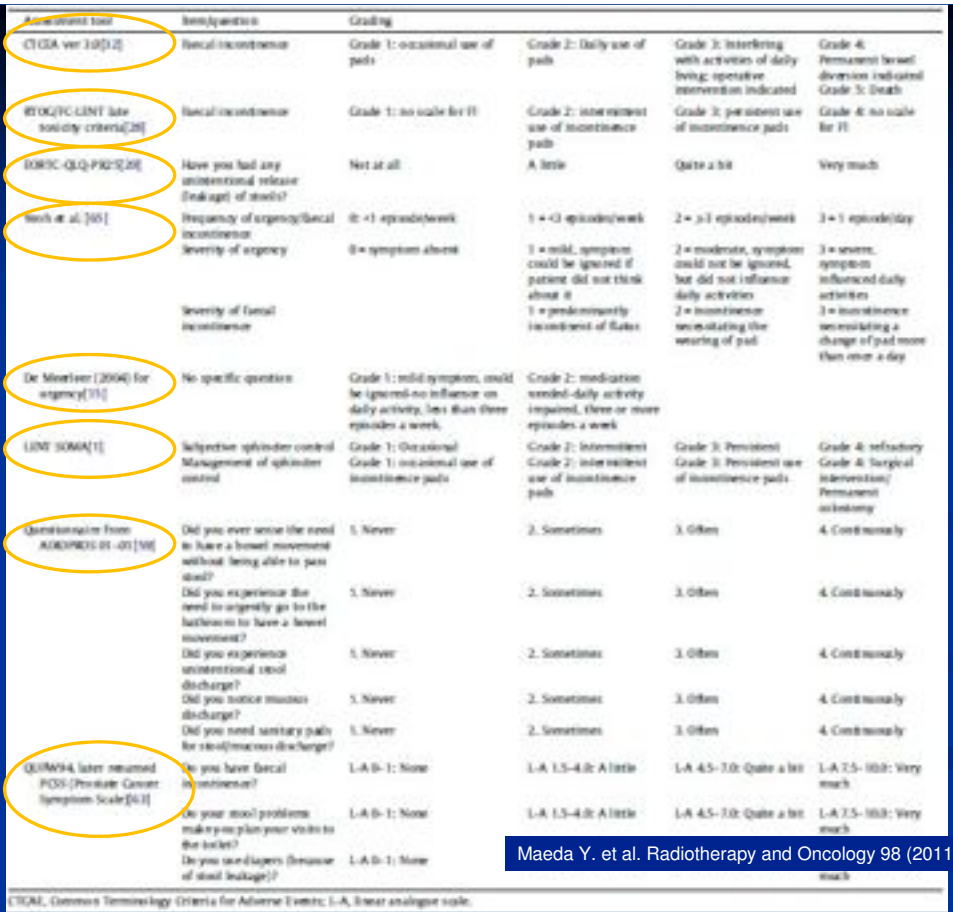
- Fecal incontinence:
  - Large populations prospectively followed for 2 – 3 years after high-dose conformal radiotherapy (3D-CRT) showed an incidence as great as **8%** when considering the peak score during the entire follow-up period
  - Other report an incidence of **1.6–58%** in patients receiving 3D conventional RT

Fiorino C et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 38e45, 2012
Maeda Y. et al. Radiotherapy and Oncology 98 (2011) 145–153

Fecal incontinence

- Lack of knowledge about incidence clinical and dosimetric predictors:
  - difficulty in scoring the incontinence symptoms using questionnaires or objective measurements
  - the need to know baseline situation
  - the natural increase in incontinence risk with age in population
  - the relatively rare occurrence of severe incontinence requiring large groups of patients to study

Fiorino C et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 38e45, 2012
Maeda Y. et al. Radiotherapy and Oncology 98 (2011) 145–153



Assessment tool	Item/question	Grading			
CTCAE ver 3.0[12]	Fecal incontinence	Grade 1: occasional use of pads	Grade 2: Daily use of pads	Grade 3: Interfering with activities of daily living; operative intervention indicated	Grade 4: Permanent bowel diversion indicated Grade 5: Death
RTOG/EC LENT late toxicity criteria[28]	Fecal incontinence	Grade 1: no scale for 1!	Grade 2: intermittent use of incontinence pads	Grade 3: persistent use of incontinence pads	Grade 4: no scale for 1!
EORTC-QLQ-PR25[29]	Have you had any unintentional release (leakage) of stools?	Not at all	A little	Quite a bit	Very much
Stelzer et al. [65]	Frequency of urgency/fecal incontinence Severity of urgency Severity of fecal incontinence	0: <1 episode/week 0 = symptom absent	1 = <3 episodes/week 1 = mild, symptom could be ignored if patient did not think about it 1 = predominantly incontinent of flatus	2 = ≥1 episodes/week 2 = moderate, symptom could not be ignored, but did not influence daily activities 2 = incontinence necessitating the wearing of pad	3 = ≥1 episode/day 3 = severe, symptom influenced daily activities 3 = incontinence necessitating a change of pad more than once a day
De Meerleer (2004) for urgency[35]	No specific question	Grade 1: mild symptom, could be ignored-no influence on daily activity, less than three episodes a week	Grade 2: medication needed-daily activity impaired, three or more episodes a week		
LENT SOMA[1]	Subjective sphincter control Management of sphincter control	Grade 1: Occasional Grade 1: occasional use of incontinence pads	Grade 2: Intermittent Grade 2: intermittent use of incontinence pads	Grade 3: Persistent Grade 3: Persistent use of incontinence pads	Grade 4: refractory Grade 4: Surgical intervention/ Permanent colostomy
Questionnaire from ASKOPROS 01-03[59]	Did you ever sense the need to have a bowel movement without being able to pass stool?	1. Never	2. Sometimes	3. Often	4. Continuously
	Did you experience the need to urgently go to the bathroom to have a bowel movement?	1. Never	2. Sometimes	3. Often	4. Continuously
	Did you experience unintentional stool discharge?	1. Never	2. Sometimes	3. Often	4. Continuously
	Did you notice mucous discharge?	1. Never	2. Sometimes	3. Often	4. Continuously
	Did you need sanitary pads for stool/mucous discharge?	1. Never	2. Sometimes	3. Often	4. Continuously
QUFM94, later renamed PCSS (Prostate Cancer Symptom Scale)[63]	Do you have fecal incontinence?	L-A 0-1: None	L-A 1.5-4.0: A little	L-A 4.5-7.0: Quite a bit	L-A 7.5-10.0: Very much
	Do your stool problems make you plan your visits to the toilet?	L-A 0-1: None	L-A 1.5-4.0: A little	L-A 4.5-7.0: Quite a bit	L-A 7.5-10.0: Very much
	Do you use diapers (because of stool leakage)?	L-A 0-1: None			

CTCAE, Common Terminology Criteria for Adverse Events; L-A, linear analogue scale.

Maeda Y. et al. Radiotherapy and Oncology 98 (2011) 145–153

Fecal incontinence

- Potential mechanism:
  - direct nerve damage
  - muscle damage in the anal sphincter
  - loss of storage capacity of rectal ampulla owing to fibrosis
  - reduced ability of absorption of rectal mucosa
  - data suggest that, at least for persistent incontinence (including moderate symptoms), the origin could be mostly vascular
  - the effect of antihypertensive drugs supports the hypothesis of vascular damage

Fiorino C et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 38e45, 2012
Maeda Y. et al. Radiotherapy and Oncology 98 (2011) 145–153

Fecal incontinence

- Objective findings:

Anal pressures after EBRT and sphincter morphology

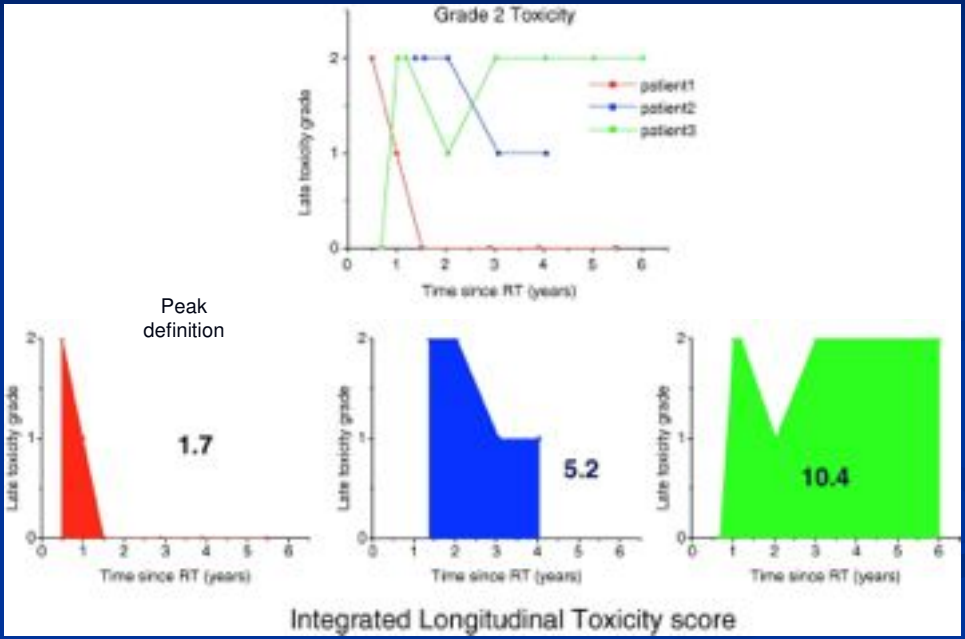
References			Anal pressures		Anal morphology	
Author	Year	Mean follow-up	Resting pressure	Squeeze pressure	IAS	EAS
Varma	1986	3.5 years	Decreased	NS	–	–
Yeoh	2000	1.5 year	Increased	NS[a]	NS	NS
Berndtsson	2002	2 years	Decreased	Decreased	–	–
Kushwaha	2003	6 months	Decreased	Decreased	–	–
Yeoh (1 year/2 years)	2004	2 years	Decreased/decreased	Decreased/decreased[a]	NS/NS	NS/increased
Yeoh (2D/3D)[b]	2009	2 years	Decreased/decreased	Decreased/decreased[a]	NS/NS	NS/decreased
Yeoh	2010	1 year	NS	Decreased[a]	NS	NS
Smeenk	2012	2.5 years	Decreased	NS	–	–
Krol	2012	1 year	NS	NS	–	–

IAS maximum thickness of internal anal sphincter, **EAS** maximum thickness of external anal sphincter

Krol R. et al. Int J Colorectal Dis (2014) 29:273–283

Fecal incontinence

longitudinal definition



Gulliford SL et al. Radiotherapy and Oncology (94) 241–247, February 2010

Fecal incontinence

longitudinal definition

Clinical Investigation: Genitourinary Cancer

Late Fecal Incontinence After High-Dose Radiotherapy for Prostate Cancer: Better Prediction Using Longitudinal Definitions

Claudio Fiorino, Ph.D.,* Tiziana Rancati, Ph.D.,† Gianni Fellin, M.D.,‡ Vittorio Vavassori, M.D.,§ Emanuela Cagna, M.D.,¶ Valeria Casanova Borca, Ph.D.,‖ Giuseppe Girelli, M.D.,# Loris Menegotti, Ph.D.,** Angelo Filippo Monti, Ph.D.,†† Francesca Tortoreto, M.D.,‡‡ Stefania Delle Canne, Ph.D.,§§ and Riccardo Valdagni, M.D.†

- Longitudinal definition:
  - the average (mean) score of late incontinence using the four-grade scale of the specific questions in the AIROPROS 0102 questionnaire concerning incontinence
  - correlation between this score and
    - dose-volume predictors
    - clinical predictors

Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 38–45, 2012

Fecal incontinence

longitudinal definition

Multivariate analysis

Variable	Coefficient	SE	p	OR
M_INC ≥1 (V_{40} continuous)				
Previous bowel symptoms	1.4353	0.7031	.0412	4.2010
Antihypertensive agents	−1.2678	0.5520	.0216	0.2814
V_{40} (continuous)	0.0341	0.0148	.0212	1.0346
Previous abdominal surgery	0.9232	0.6771	.1727	2.5173
Constant	−5.5696		.0034	
M_INC ≥1 (V40 ≥80%)				
Previous bowel symptoms	1.5097	0.7118	.0339	4.5255
Antihypertensive agents	−1.3437	0.5621	.0168	0.2609
V_{40} (dichotomic, ≥80%)	1.3368	0.5067	.0083	3.8069
Previous abdominal surgery	1.0160	0.6838	.1373	2.7623
Constant	−3.6616		.0018	

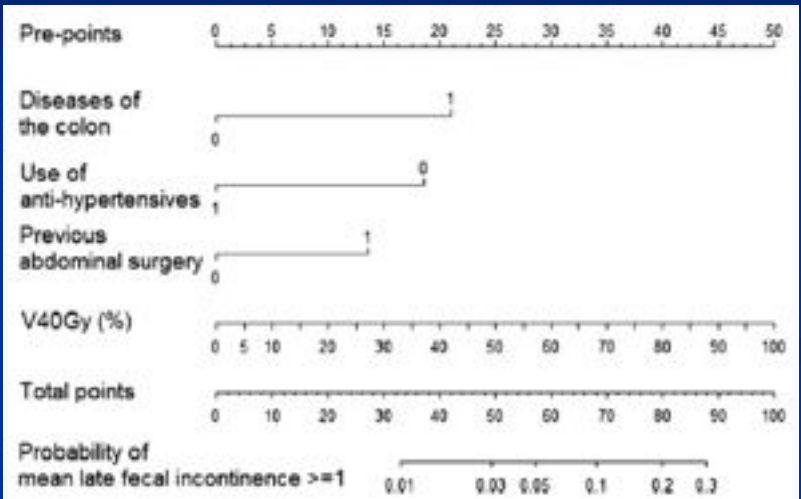
M_INC = mean incontinence score

- Previously report **V40 < 65-70%** to reduce the risk of persistent late incontinence (defined as "use of pads") to **under 1.5%.**
- Antihypertensive drugs (protective factor)
- Abdominal/pelvic surgery
- Bowel symptoms were found to be a very important baseline

Fiorino C et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 38e45, 2012

Fecal incontinence

longitudinal definition



Nomogram for calculation of risk of mean incontinence score ≥1 (with percentage of the rectal volume receiving >40 Gy [V_{40Gy}] as continuous variable). Mean incontinence score is average incontinence score for first 3 years of follow-up.

Fiorino C et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 38e45, 2012

Fecal incontinence:
treatments

- No standardized treatment
  - topical phenylephrine, α1-adrenoceptor agonist used in a small non-randomised case series
  - anal plug
  - constipating agents
  - retrograde irrigation
  - artificial bowel sphincter
  - dietary advice and anti-diarrhoeal medication
  - sacral nerve stimulation: implanting a lead and pulse generator which stimulates sacral nerve roots and modulates bowel motility
  - implantation of an artificial bowel sphincter
  - colostomy

Fiorino C et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 38e45, 2012
Maeda Y. et al. Radiotherapy and Oncology 98 (2011) 145–153

Conclusions

- Rectal bleeding & fecal incontinence:
  - Incidences are not clearly reported (1.6-33-50%??) and depend on many factors (techniques, doses, comorbidities, therapies.....) particularly the scoring system used
  - A spontaneous improvement over time is described for rectal bleeding
  - No standardized treatment for symptomatic patients has been established,
  - Rectal devices are under investigation
  - Radiation oncologists should approach these patients in a multidisciplinary team within a gastroenterology unit
  - Many uncertainties heavily influence ”dose–volume modelling” of rectal toxicity

Conclusions

- Radiation oncologists should better clarify dosimetric and clinical predictors to reduce risk of rectal toxicity
- We generally base our evaluations on DVHs and OAR dose-constraints

BUT

We don't have completely reliable:

1. widely accepted definition of "what and how" contour rectum and anal canal to be applied to planning process

2. dose–volume constraints

Conclusions

Avalaible data are weak in terms of quality of evidence (EBM)

Our current practice is generally based on old, retrospective and extrapoleted data on **inhomogeneously prescribed doses**

Only since 2010 we have a more standardized way to prescribe dose

Conclusions

How can we enhance our knowledge?

1. Retrospective mono or multinstituitional studies?

using the new prescription dose modalities

Tipical biases of this kind of studies

2. Phase III prospective mulicenter trials?

designed explicitly to assess toxicities

Usually not feasible and reliable because of the small number of events

Use of artificial neural networks to predict biological outcomes for patients receiving radical radiotherapy of the prostate

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Radiotherapy and Oncology 71 (2004) 3–12

The future: ?

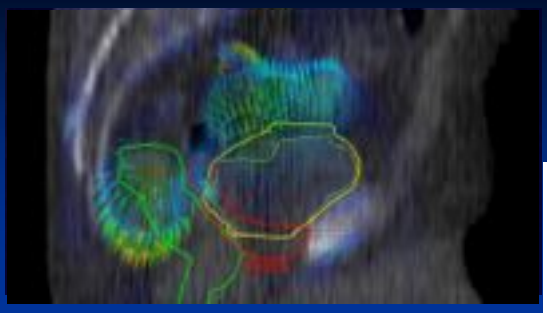
MULTINSTITUTIONAL LARGE DATABASE

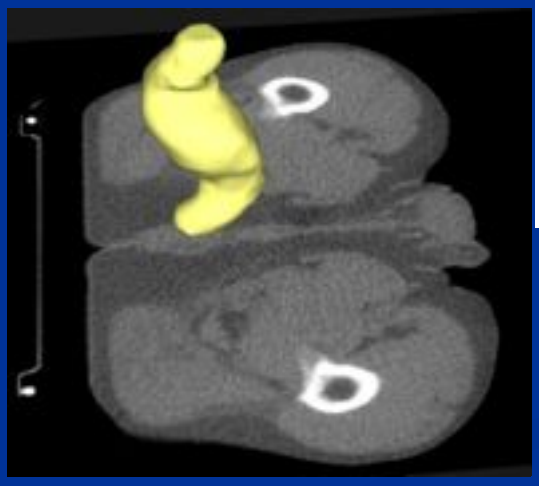
ARTIFICIAL NEURAL NETWORKS

MACHINE LEARNING BASED METHODS

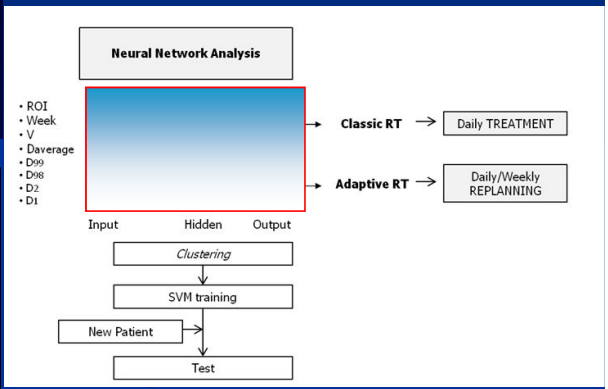
(pitfalls: over sampling, undersamplping, used algorithms)

PREDICTIVE ANALYSIS WITH NEURAL NETWORKS : EXPERIENCE MODENA





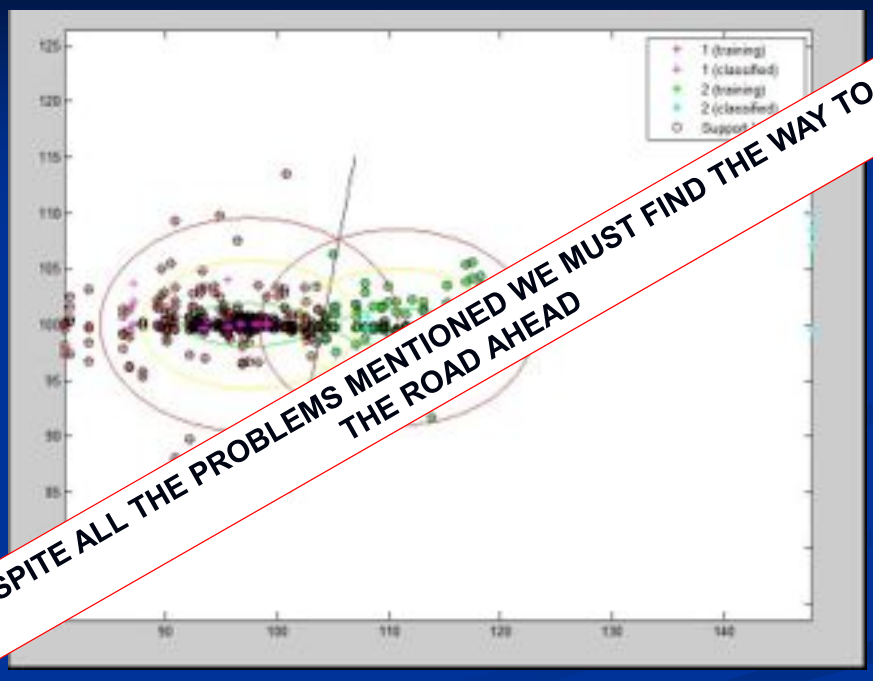
ART
Experience of Modena for dose evaluation and need for replanning



D1 (dose to 1% of volume)
D2 (dose to 2% of volume)
D 98 (dose to 98% of volume)
D99 (dose to 99% of volume)
D average
V (volume)

Courtesy of Maffei N., Guidi G., Modena

Neural Networks: clusterization



se normalized to prescribed dose

DESPITE ALL THE PROBLEMS MENTIONED WE MUST FIND THE WAY TO SET THE ROAD AHEAD

Volume normalized to initial MVCT

Courtesy of Maffei N., Guidi G., Modena

THANK YOU