Fattori predittivi di tossicità nella radioterapia del carcinoma prostatico

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FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

PROSTATE CANCER PROGRAM

UNIVERSITÀ DEGLI STUDI DI MILANO

Considerazioni preliminari

1. In Medicine, we are facing an increasing need and wish to move from evaluation of "*mean effect*" as derived from the present **"philosophy of clinical trial",** i.e. of group comparison,

to the *"philosophy of models"* which

- **takes most of what we know about the individual patient into account (more pt-centered), to try**
- **to produce an estimate of patient's present condition (e.g., pos. lymphnodes) and/or his/her future outcome (e.g., clinical results or radioinduced toxicity)**

Predicting Radio-induced Toxicity

2. Treatment planning procedures greatly benefitted
from the routine utilization
of sophisticated dosimetric predictive models.
This resulted in a very limited incidence of radio-induced side effects
exhibited by our patients
However,

it is becoming more and more evident that
dosimetric-only predictive tools are scantly helpful
in anticipating the knowledge of the risk of developing
that specific toxic event in the individual patient

Factors predicting radio-induced toxicity in prostate cancer

What have we learned?

Predictive Factors of Radio-induced Toxicity
What have we learned? The three Ingredients

Modifiers of dose-response relationship:
Ingredients to be considered are given the same dose levels, the followings:
subgroups of pts have greater (less) probabilities of tox events

Dosimetric factors

Clinical factors

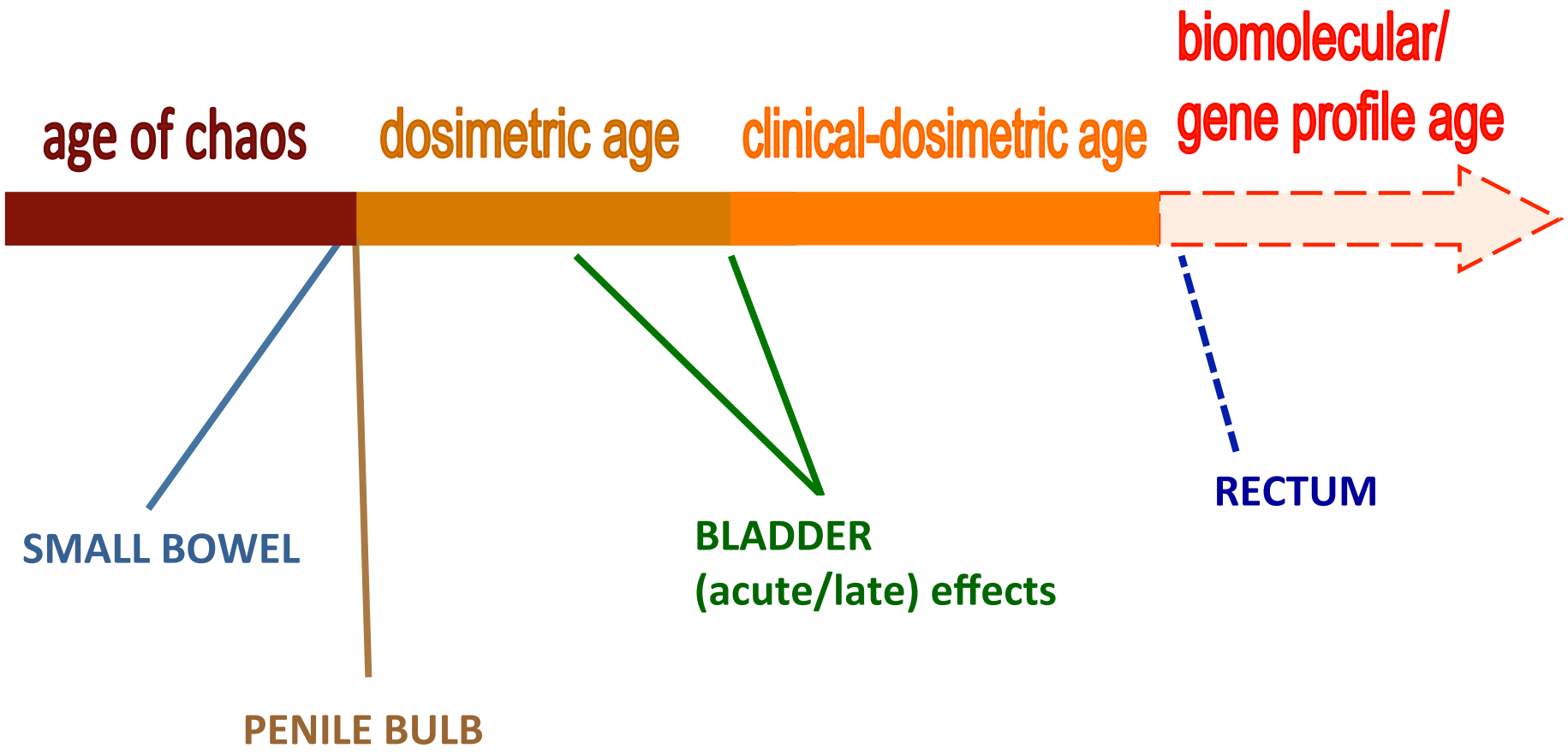
Genetic factors

There is a dose-response relationship:
↑ Dose to OaRs = ↑ probability of tox events

Factors predicting radio-induced toxicity in prostate cancer

Historical scenario

Every time the role of a variable and its relationship with toxicity were determined, at the same time the role of a new type of variable was unveiled

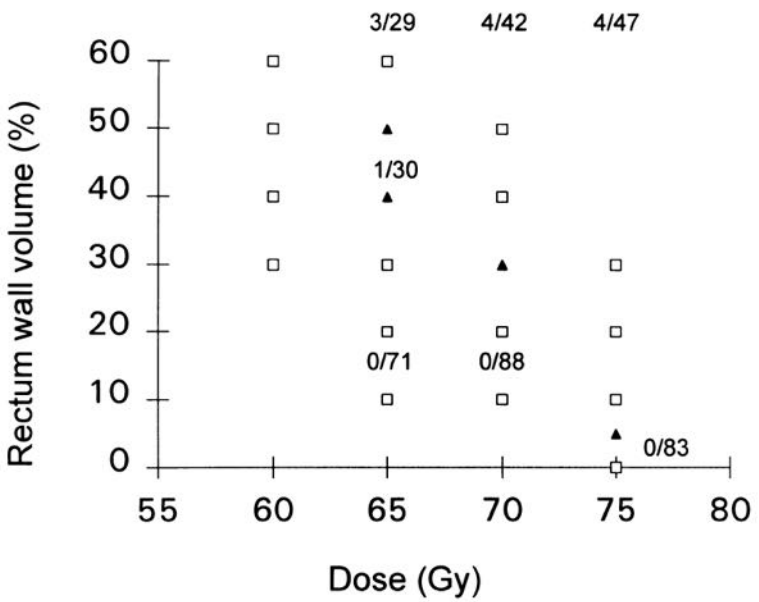


Factors predicting radio-induced toxicity in prostate cancer

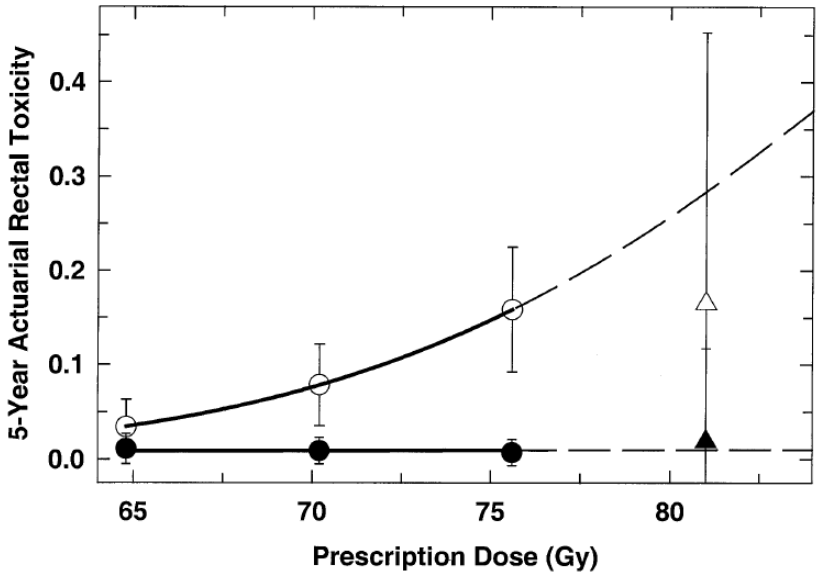
The rectum paradigm

1995 → 2000 The Age of Chaos

Boersma, IJROBP, 1998



Skwarchuk, IJROBP, 2000



Late Rectal Toxicity

No dose-volume relationship for grade ≥ 2 toxicity ↔ Dose-volume relationship for grade ≥ 2 toxicity

Dose-volume relationship for grade 3 toxicity ↔ No dose-volume relationship for grade 3 toxicity

1995 → 2000 The Age of Chaos

Late Rectal Toxicity

Dale, IJROBP, 1999

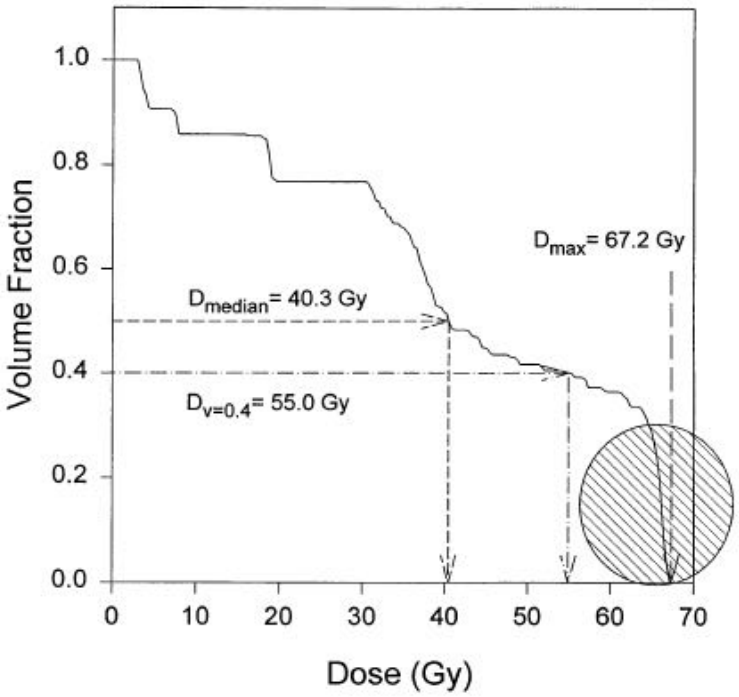
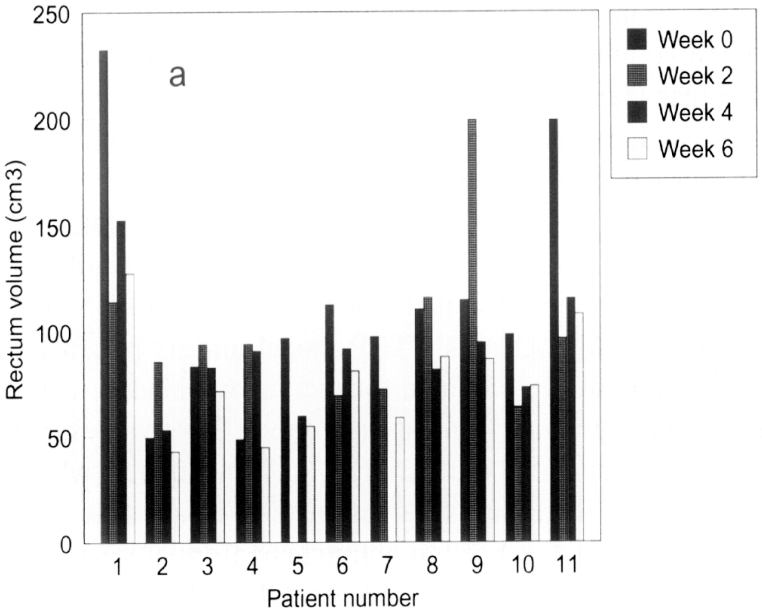


Fig. 2. Example of a cumulative whole rectum dose-volume histogram. The hatched circle, indicates the part of the histogram with the best predictive ability for risk (Results).

"The maximum rectal dose is the only parameter correlated to late rectal bleeding (G1+)"

1995 → 2000 Reasons for Chaos

Lebesque, IJROBP 1995



The major problem was related to the reliability and reproducibility of rectal DVHs:

- hollow organ
- variable volume
- variable shape
- variable position

But also mixing toxicity end points in scoring systems:

can we expect the same dose-volume effect for:

- ✓rectal bleeding
- ✓faecal incontinence
- ✓abdominal pain

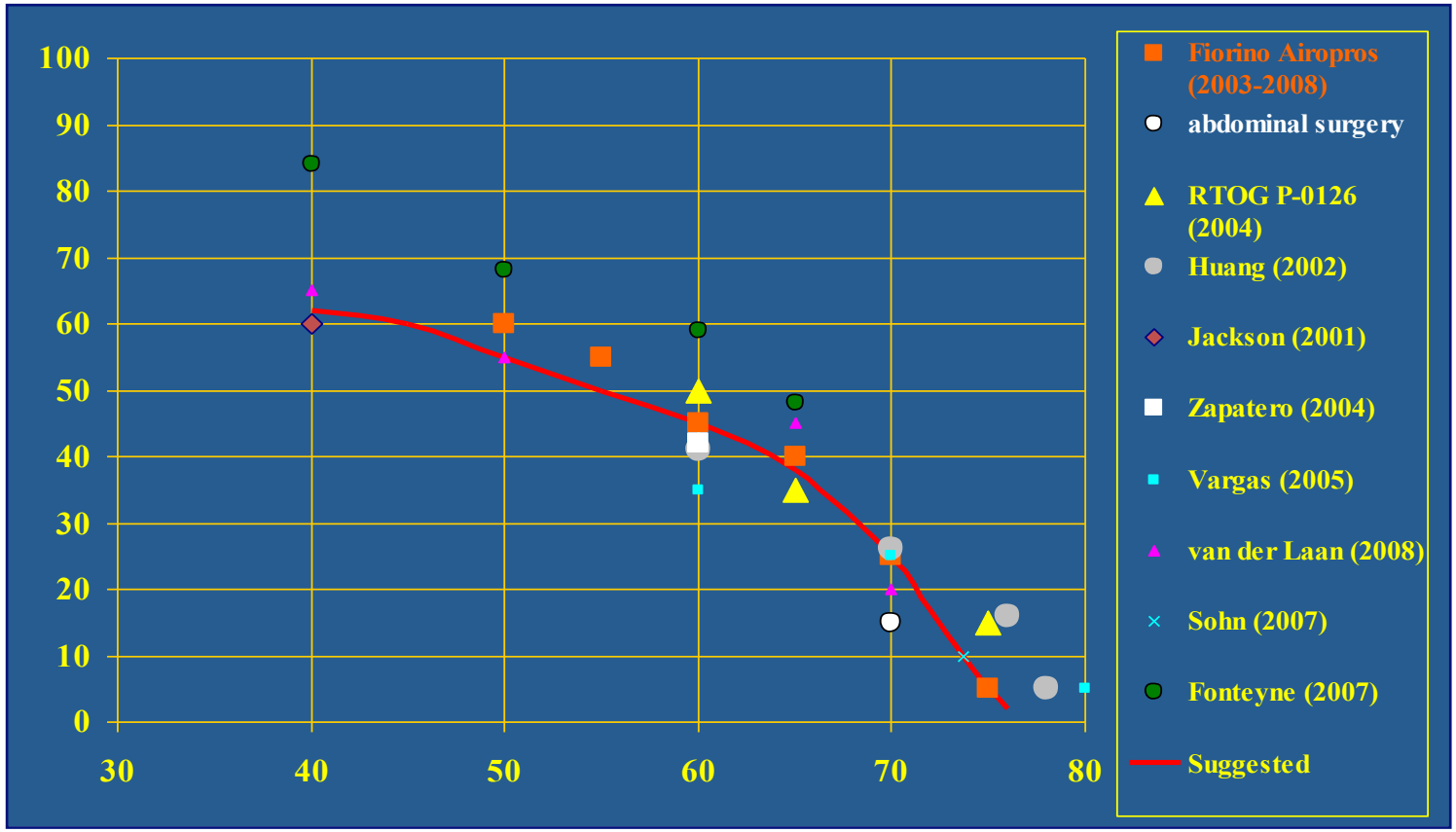
?

≥2000 Emerging from Chaos: Problem Solving

1. Sharing rules for rectum contouring
2. Reducing the spacing between CT slices
3. Emptying the rectum
4. Selecting different endpoints for different symptoms
5. Using self-assessed questionnaires, systematically
6. Choosing adequate follow-up

And the first studies with comparable results on dose-volume effects evaluating late rectal bleeding became available

2000-2009 The Dosimetric Age: towards a Consensus



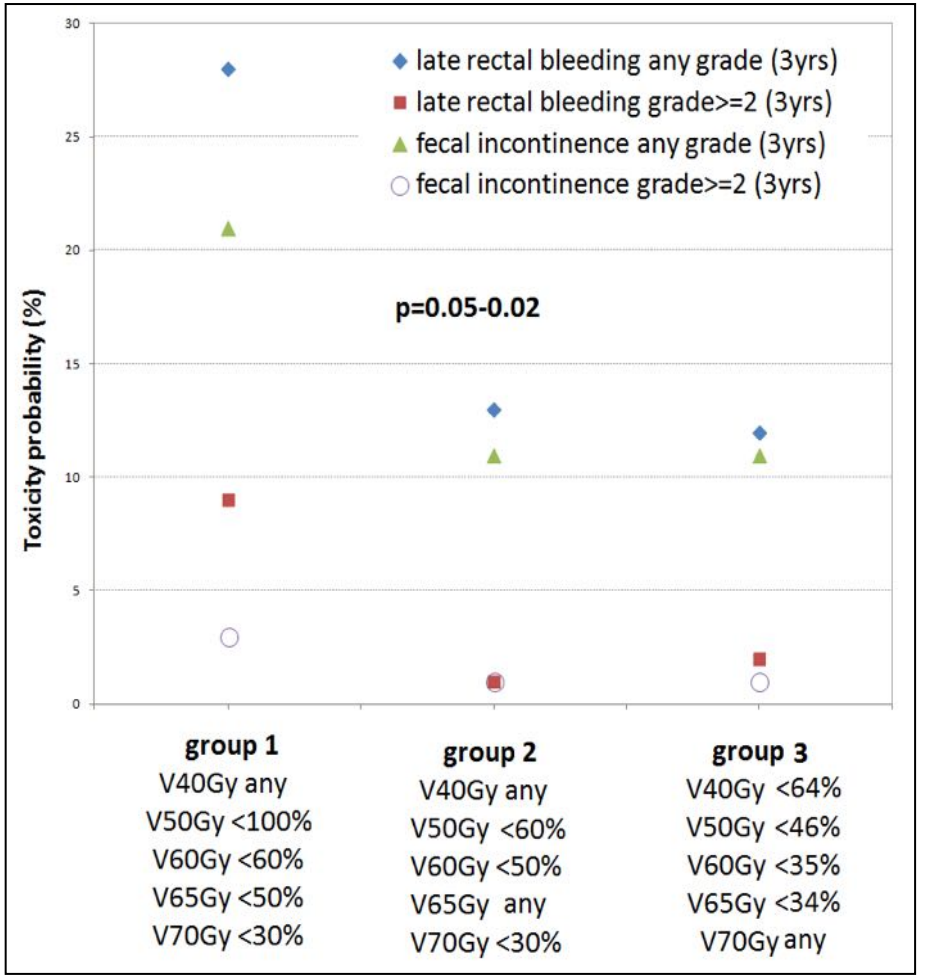
C. Fiorino, T. Rancati and R. Valdagni, Cancer, 2009

- ✓ Late rectal bleeding: keeping grade 2-3 below 5-10%
- ✓ A cut-off DVH derived from the literature was proposed

DVH constraints to reduce late rectal bleeding: Evidence Based? Maybe …

Indirect evidence:
Fonteyne et al, Acta Oncol 2015
Single centre experience (≈600 pts)

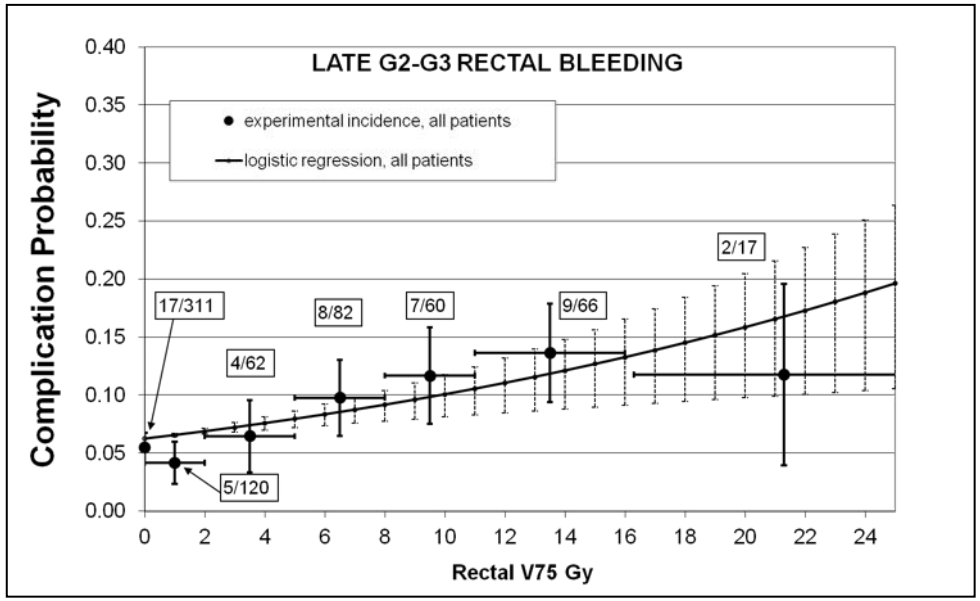
Stricter DVH constraints resulted in significantly lower toxicity rates



2000-2009 The Dosimetric Age: towards a Consensus

More sophistication than single dose-volume constraints:
Normal Tissue Complication Probability modeling
for non-uniform irradiation of the rectum in the single patient

C. Fiorino et al, AIROPROS 0102, Rad&Oncol, 2008



S. Peeters et al, Dutch trial, IJROBP, 2006

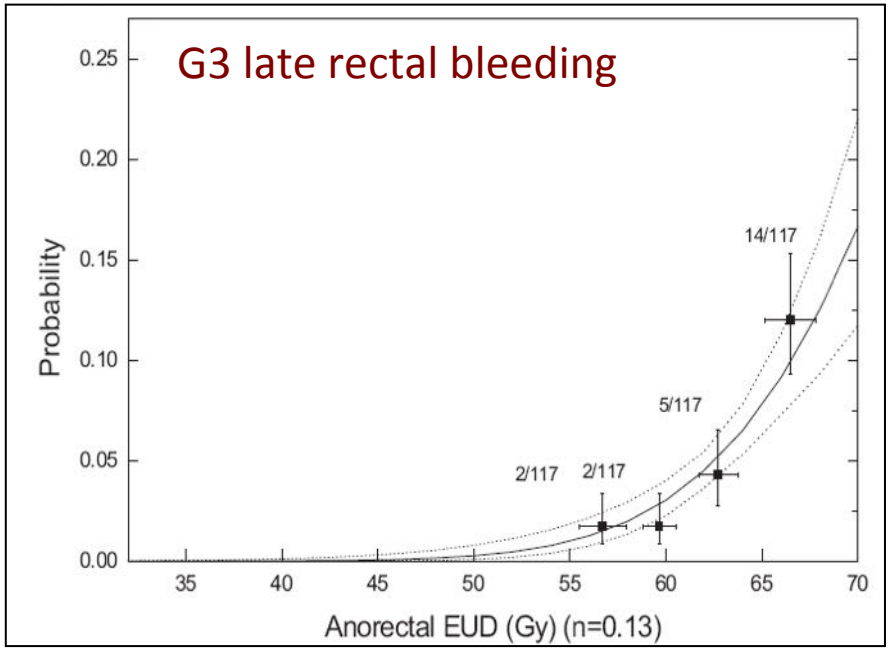


Fig. 1. Probability of late gastrointestinal toxicity as a function of the equivalent uniform dose (EUD) Lyman-Kutcher-Burman (LKB) models: rectal bleeding

2000-2009 The Dosimetric Age: Consensus

- ✓ Use of a set of solid dose-volume constraints (V40Gy, V50Gy, V70Gy, V75Gy)
- ✓ Use of logistic curves (prob. of rectal injury vs V40Gy, V50Gy, V70Gy, V75Gy)
- ✓ Use of DVH reduction to EUD
- ✓ Use of NTCP models

Radiotherapy and Oncology 93 (2009) 153–167

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

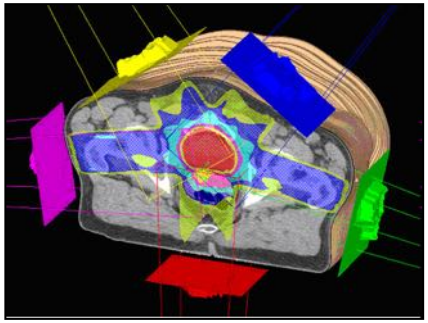
Dose–volume effects for normal tissues in external radiotherapy: Pelvis

Claudio Fiorino [a,*], Riccardo Valdagni [b], Tiziana Rancati [b], Giuseppe Sanguineti [c]

[a] Medical Physics Department, San Raffaele Scientific Institute, Milan, Italy
[b] Prostate program, Scientific Directorate Fondazione IRCCS – Istituto Nazionale dei Tumori, Milan, Italy
[c] Radiotherapy Department, The John Hopkins University, Baltimore, MD, USA

2004 → 2009: The Clinical-Dosimetric Age

From anatomy/dose- based treatment planning



Reductionism

to patient/disease/dose- based treatment tailoring

The Tailor, GB Moroni, c. 1570, National Gallery, London

Holism

2004 → 2009: The Clinical-Dosimetric Age

Whenever possible, the application in the RT planning of

- well defined dose-volume constraints and of
- NTCP models

promotes the reduction of both

1. the incidence of late radio-induced toxicity
2. the impact of dosimetric factors and →

2004 → 2009: The Clinical-Dosimetric Age

New risk factors can be unveiled:

- ✓ clinical risk factors (or protective factors*), such as
  - haemorrhoids
  - anticoagulants*
  - antihypertensives*
  - hormonal therapy*
  - previous abdominal surgery
- ✓ radiobiological factors, such as
  - the sequential relationship between acute and late damage

Radiotherapy and Oncology 93 (2009) 197–202

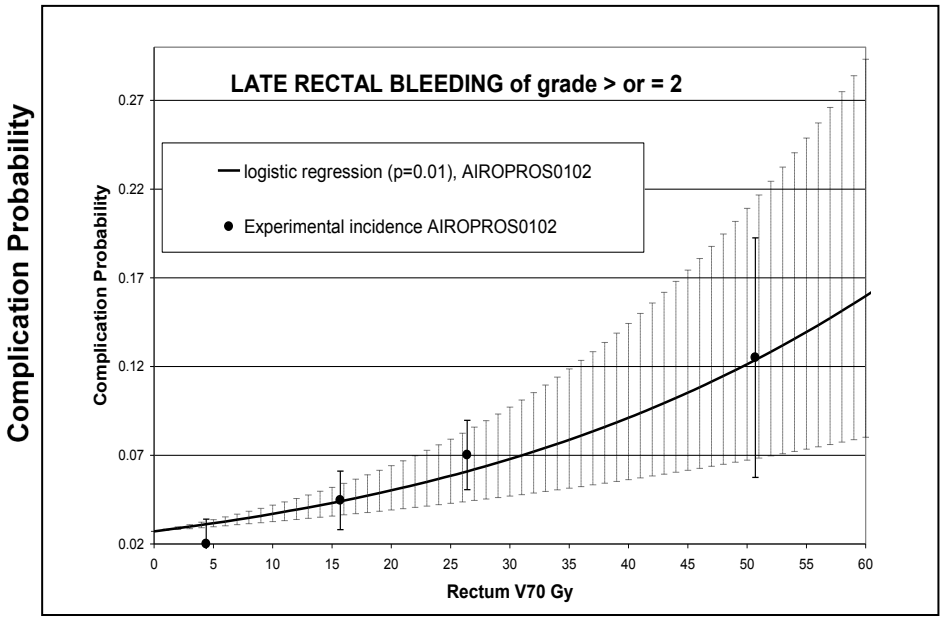
Prostate radiotherapy

Clinical and dosimetric predictors of late rectal toxicity after conformal radiation for localized prostate cancer: Results of a large multicenter observational study

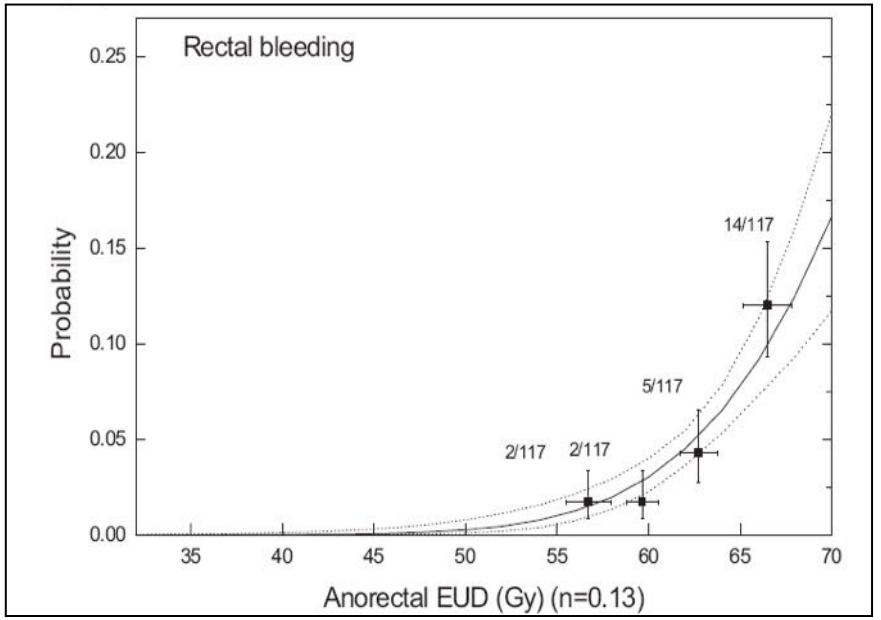
Gianni Fellin [a], Claudio Fiorino [b,*], Tiziana Rancati [c], Vittorio Vavassori [d], Micaela Baccolini [g], Carla Bianchi [d], Emanuela Cagna [e], Pietro Gabriele [f], Floranna Mauro [g], Loris Menegotti [a], Angelo Filippo Monti [e], Michele Stasi [f], Riccardo Valdagni [c]

2004 → 2009: The Clinical-Dosimetric Age

G. Fellin et al, AIROPROS 0102, Rad&Oncol, 2009



DeFraene et al, Dutch trial, IJROBP 2011

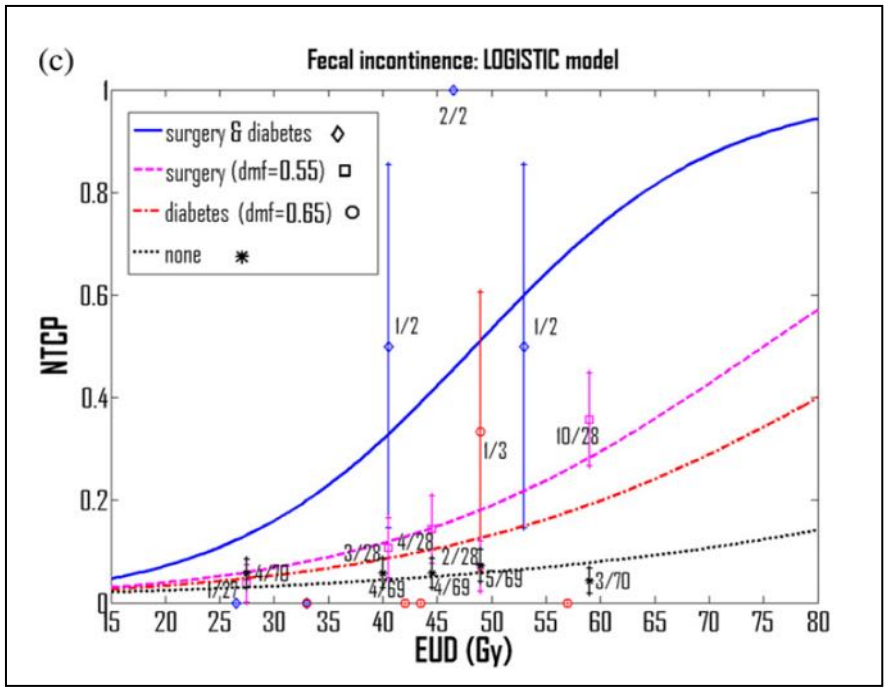


Identifying subgroups of patients with an enhanced risk of late rectal bleeding (e.g. abdominal surgery) and developing different dose-volume curves (and constraints) for these sub-population of patients

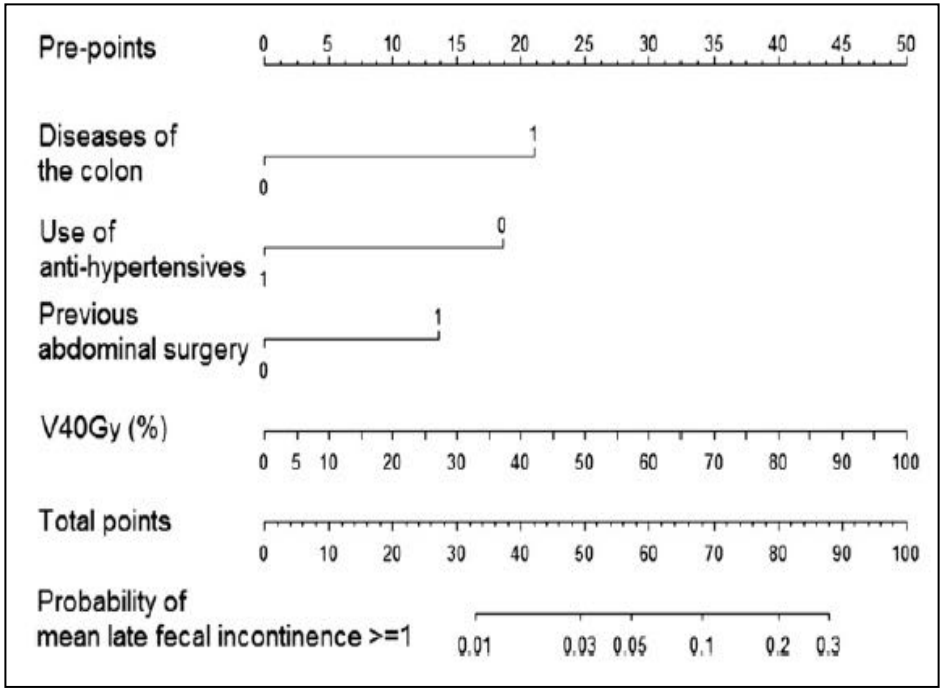
2004 → 2009: The Clinical-Dosimetric Age

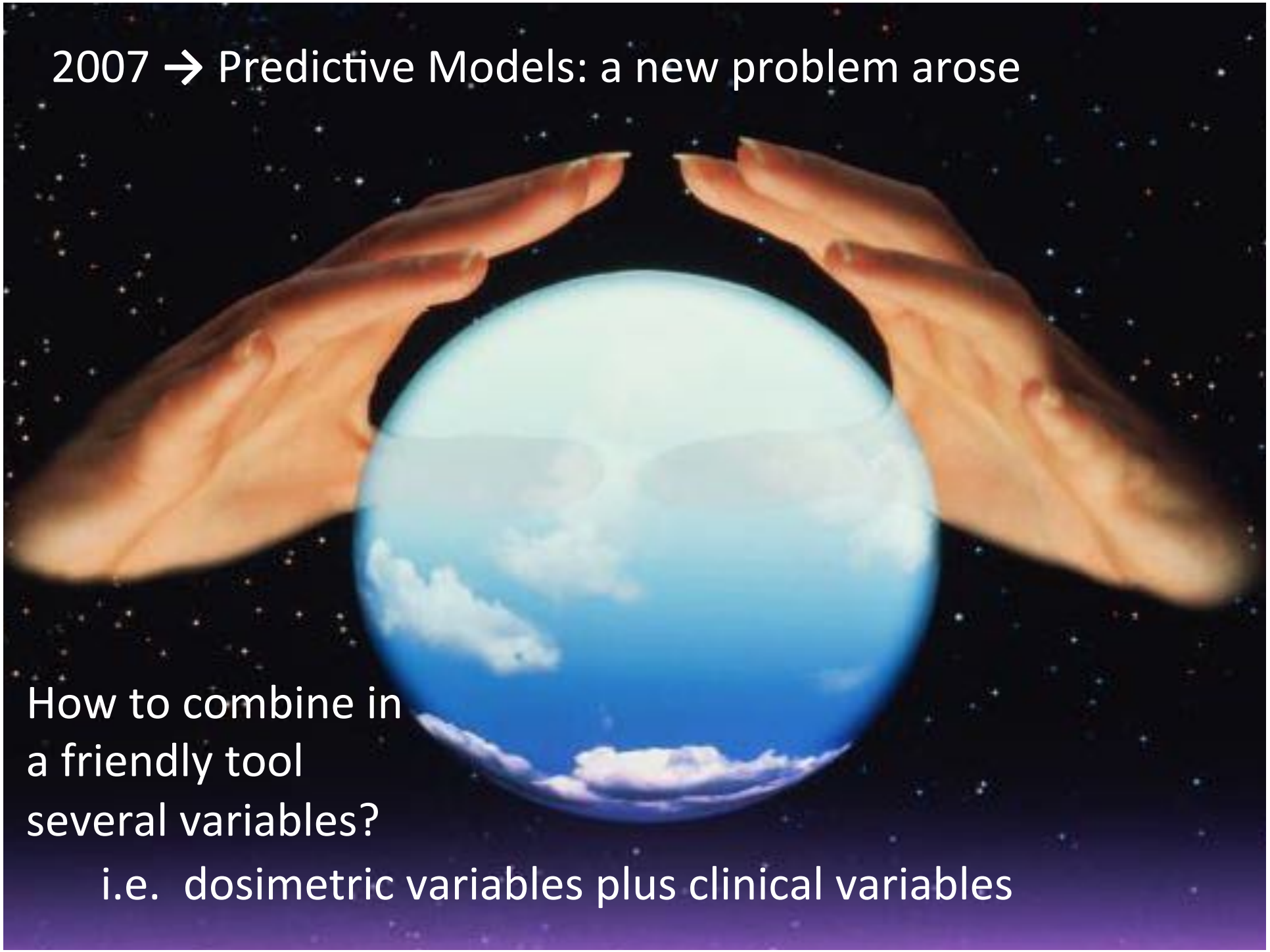
Late fecal incontinence, clinical risk factors: abdominal surgery, diabetes, use of antihypertensives and previous disease of the colon

DeFraene et al, Dutch trial IJROBP 2011



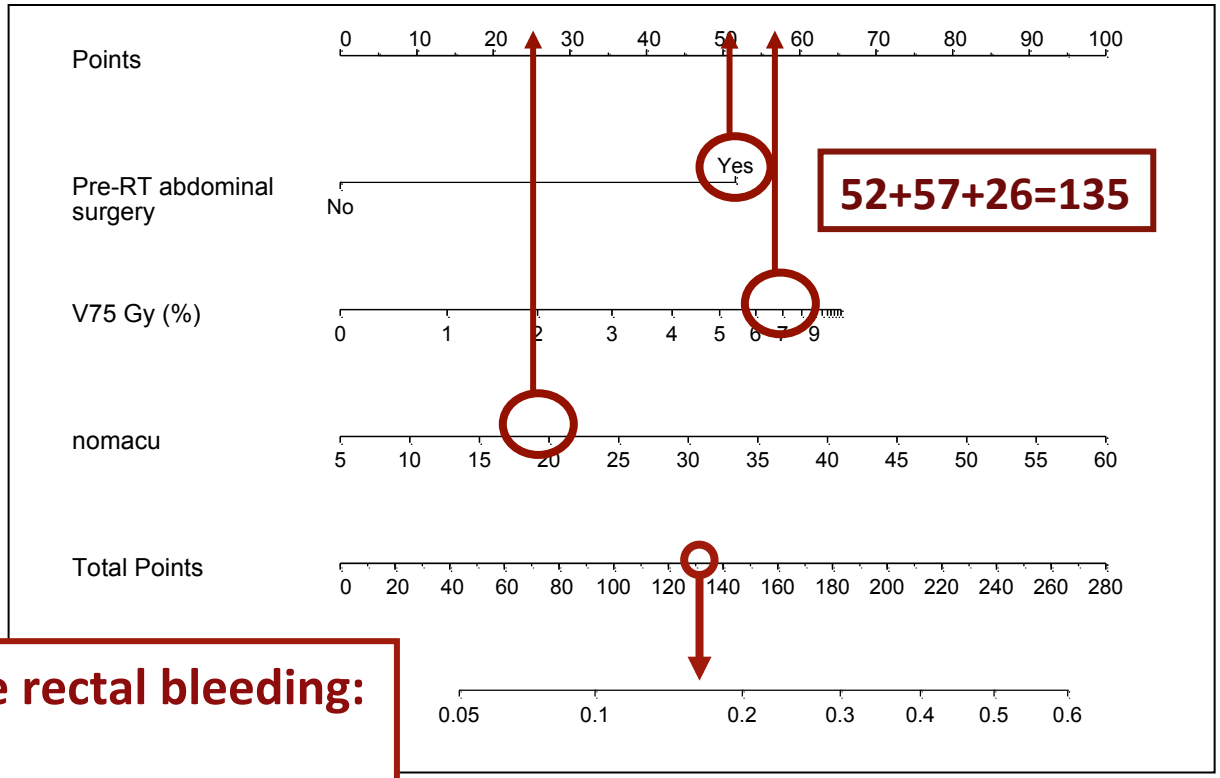
Fiorino et al, AIROPROS 0102, IJROBP 2012




2007 → Predictive Models: a new problem arose
How to combine in
a friendly tool
several variables?
i.e. dosimetric variables plus clinical variables

Nomograms

Analyse the combined effects of multiple independent factors found to be prognostically valuable, helping evaluate a single patient's clinical-dosimetric parameters and provide a tailored, *easy to calculate,* probability for a particular outcome



Probability of G2-G3 late rectal bleeding: ~ 18%

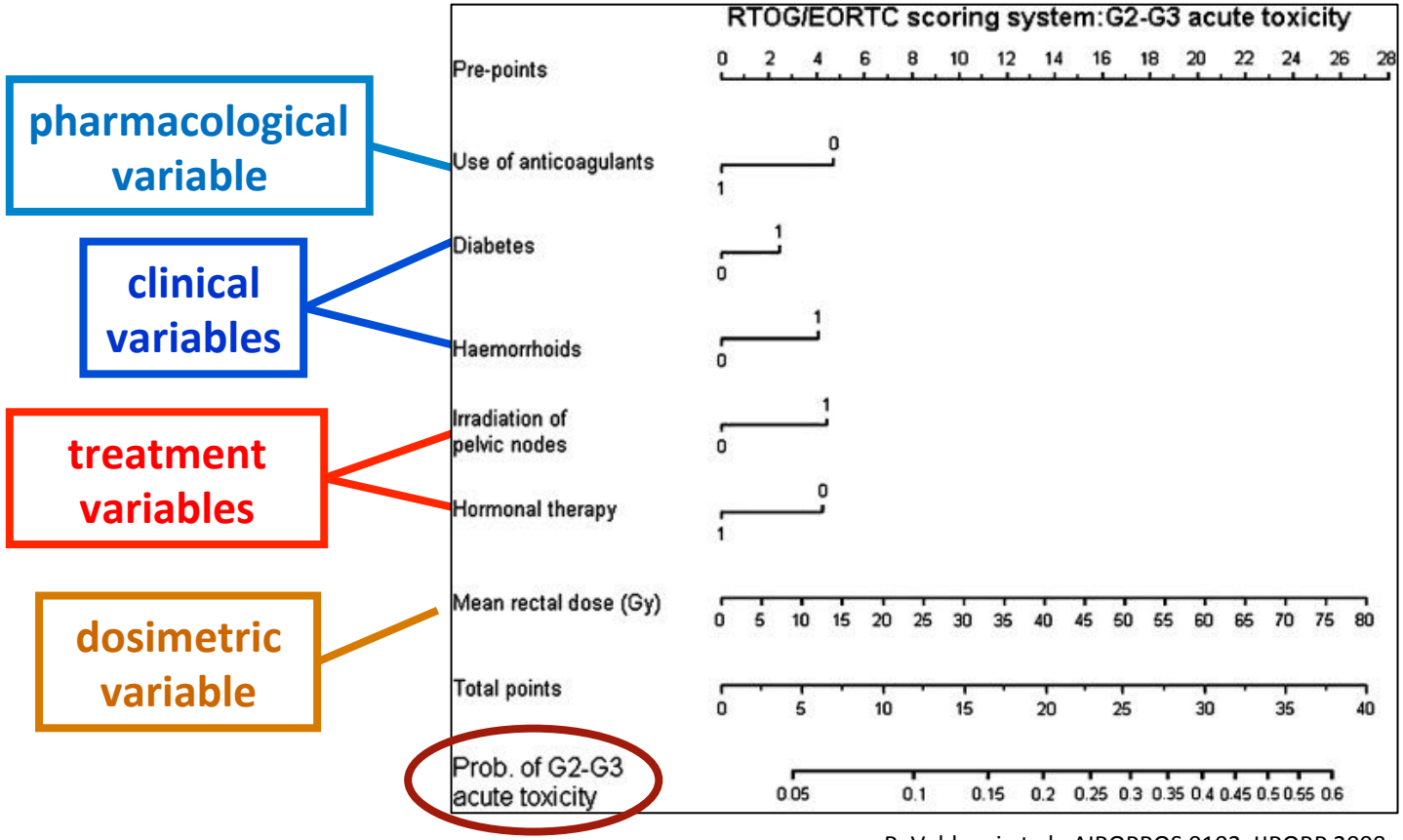
R. Valdagni, M. Kattan, T. Rancati et al, IJROBP 2010

2004 → 2009: The Clinical-Dosimetric Age

CLINICAL INVESTIGATION **Prostate**

DEVELOPMENT OF A SET OF NOMOGRAMS TO PREDICT ACUTE LOWER GASTROINTESTINAL TOXICITY FOR PROSTATE CANCER 3D-CRT

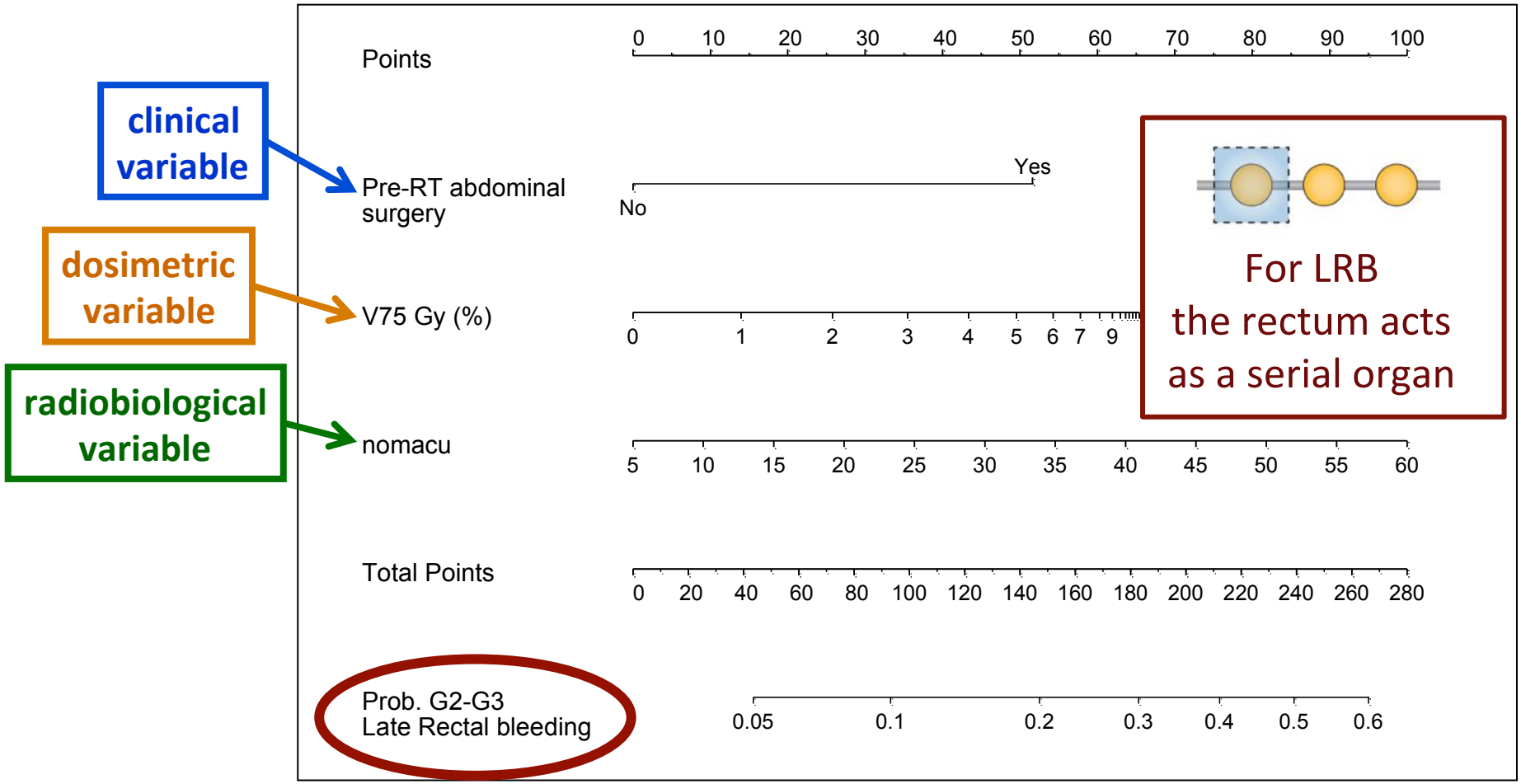
Riccardo Valdagni, M.D., Ph.D.,* Tiziana Rancati, Ph.D.,* Claudio Fiorino, Ph.D.,† Gianni Fellin, M.D.,‡ Alessandro Magli, M.D.,§ Michela Baccolini, Ph.D.,‖ Carla Bianchi, Ph.D.,¶ Emanuela Cagna, M.D.,# Carlo Greco, M.D.,** Flora A. Mauro, M.D.,†† Angelo F. Monti, Ph.D.,‡‡ Fernando Munoz, M.D.,§§ Michele Stasi, Ph.D.,‖‖¶¶ Paola Franzone, M.D.,## and Vittorio Vavassori, M.D.§



R. Valdagni et al., AIROPROS 0102, IJROBP 2008

2004 → 2009: The Clinical-Dosimetric Age

Large prospective studies allow the detailed evaluation of relatively uncommon toxicity, e.g. **G2-3 late rectal bleeding**

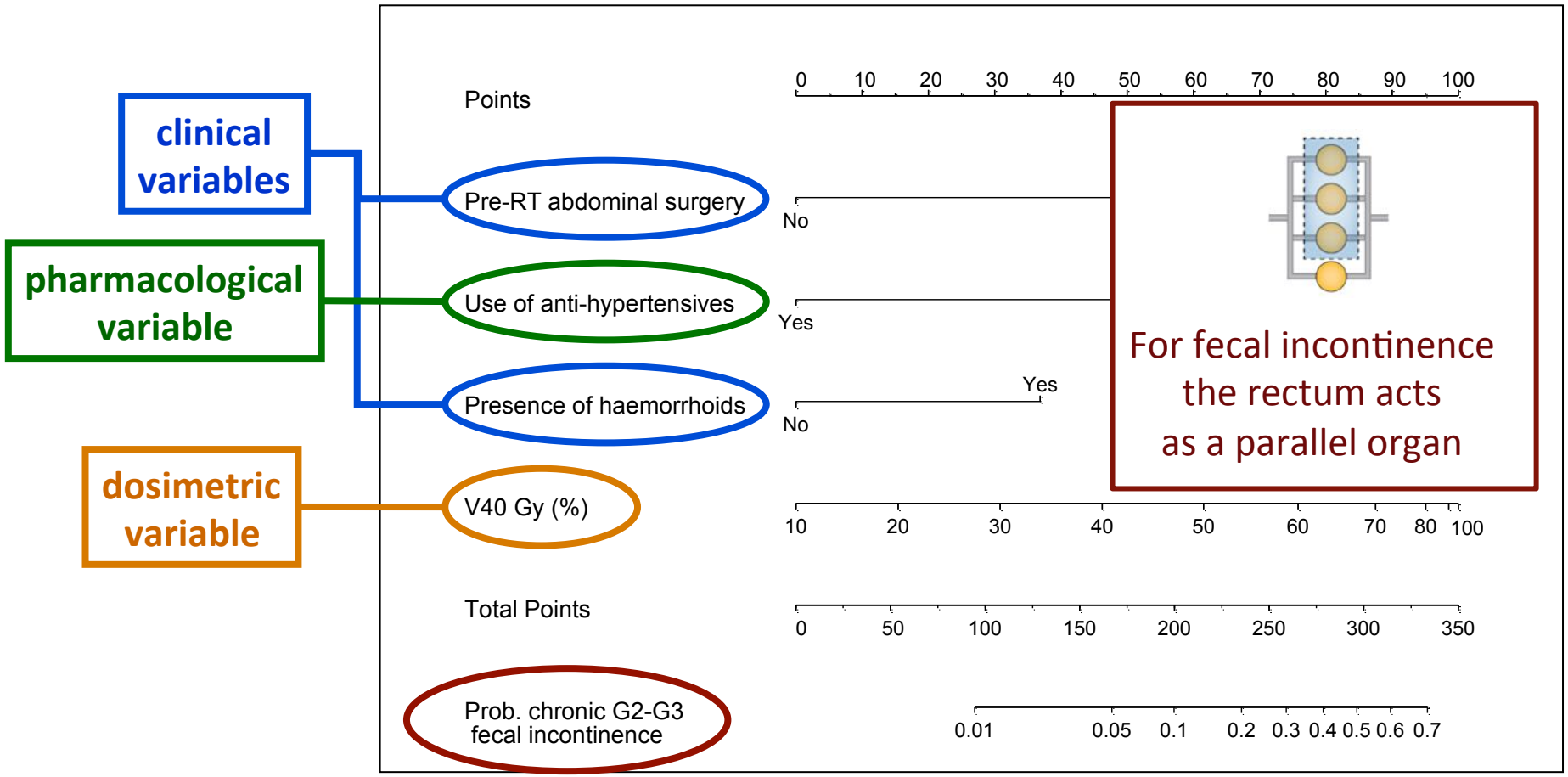


R. Valdagni, M. Kattan, T. Rancati et al, AIROPROS 0102, IJROBP 2010

2004 → 2009: The Clinical-Dosimetric Age

Large prospective studies allow the evaluation of unusual toxicity, e.g.

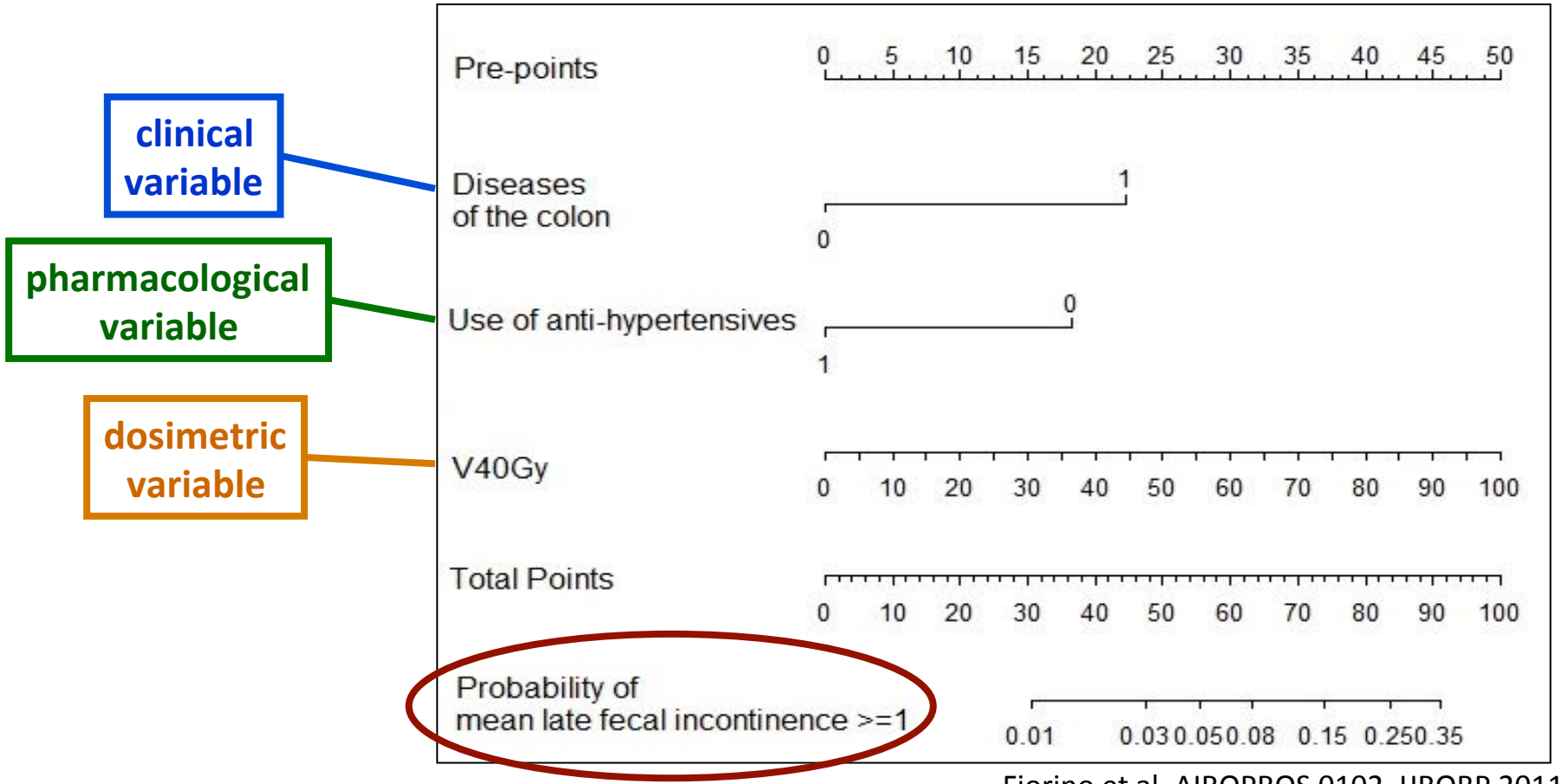
G2-3 late faecal incontinence



R. Valdagni, M. Kattan, T. Rancati et al, AIROPROS 0102, IJROBP 2010

2004 → 2009: The Clinical-Dosimetric Age

Changing perspective:
from peak definition of grade ≥ 2 late fecal incontinence, to a longitudinal definition, i.e. **persistent, ≥ mild fecal incontinence**

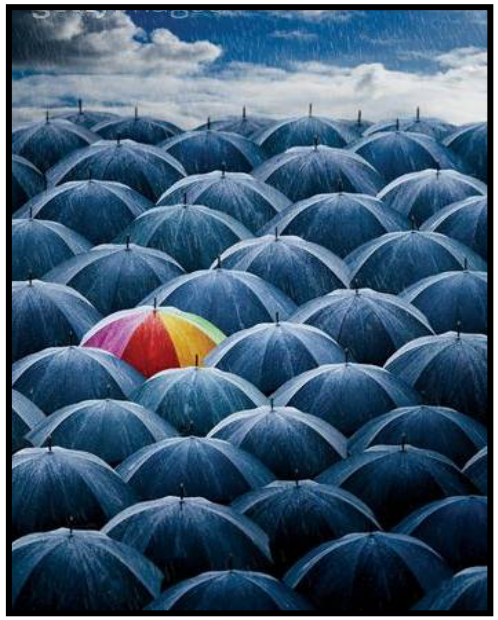


Fiorino et al, AIROPROS 0102, IJROBP 2011

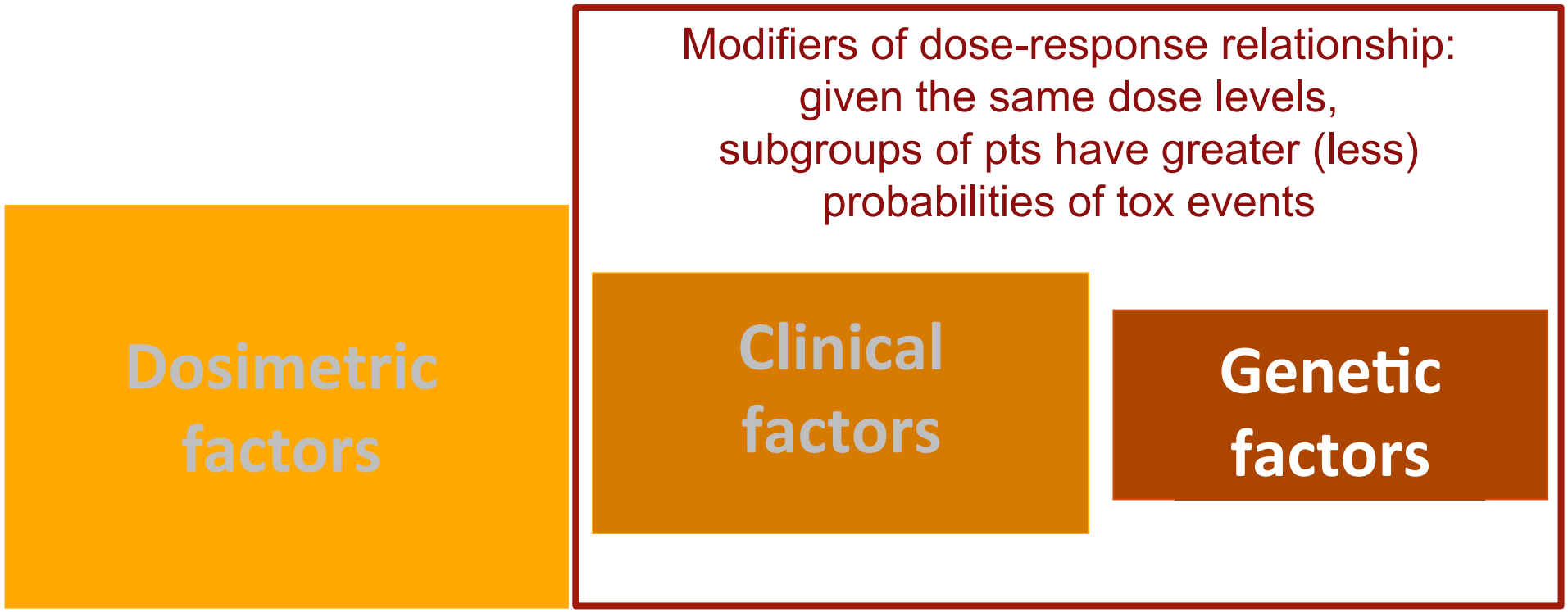
Bleeders despite good DHVs and absence of clinical risk factors?

There are a number of hints from human studies underlining that the assumption of uniform radiosensitivity is incorrect.

Inter-patient variability in the expression of radio-induced toxicity could be explained by a genetically driven, enhanced radiosensitivity



Years 2009 → 2020?
The Genetic/Biomolecular Age



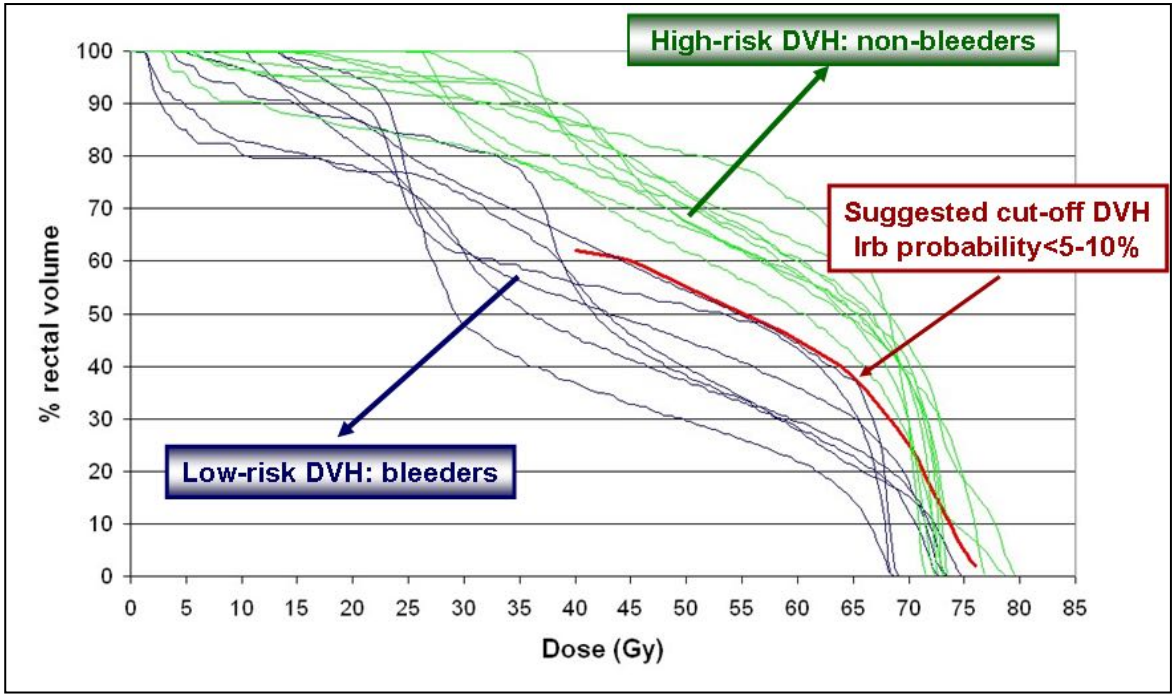
The influence of genetic makeup on radio-induced late rectal bleeding has not yet been unveiled: we are still in the Stone Age!

2009 → 2020? The genetic/biomolecular age

Bleeders despite good DHVs and absence of clinical risk factors?

<u>Working hypothesis:</u>

might gene expression profile concur to unveil the individual radio-sensitivity/resistance?



2009 → 2020? The genetic/biomolecular age

CLINICAL INVESTIGATION Prostate

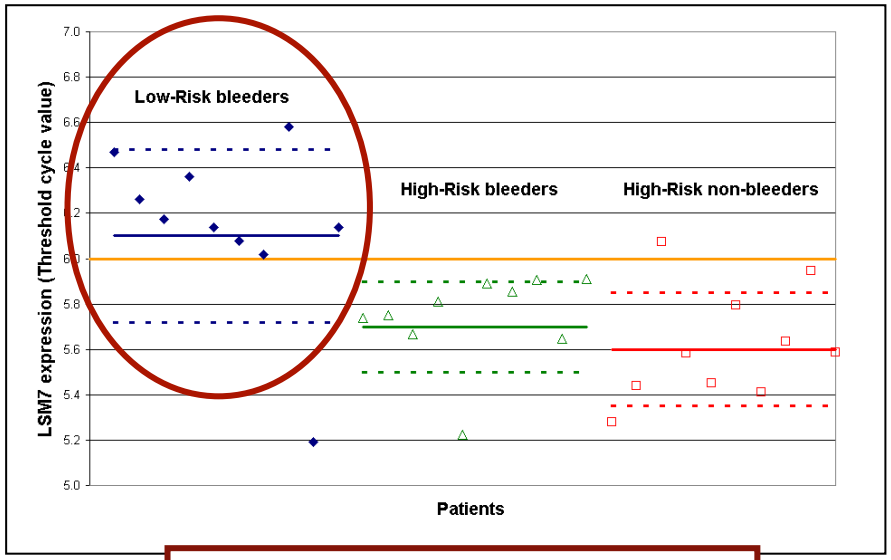
TO BLEED OR NOT TO BLEED. A PREDICTION BASED ON INDIVIDUAL GENE PROFILING COMBINED WITH DOSE–VOLUME HISTOGRAM SHAPES IN PROSTATE CANCER PATIENTS UNDERGOING THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY

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 Gariboldi, Ph.D.‡§

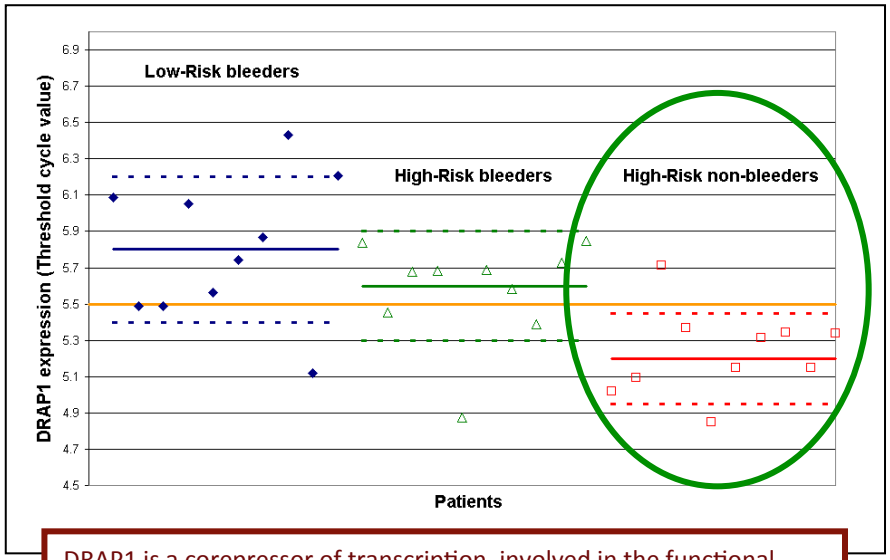
Int. J. Radiation Oncology Biol. Phys., 2009

Bleeders with optimal DVHs? Genetically radiosensitive patients

Non-bleeders with bad DVHs? Genetically radioresistant patients



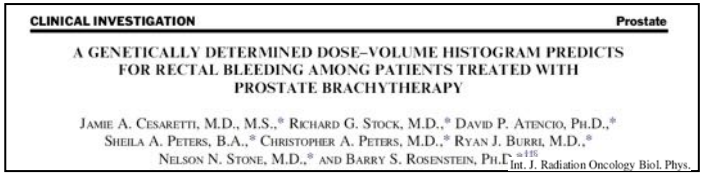
LSM7 is a protein with RNA binding activity, involved in RNA splicing and mRNA processing



DRAP1 is a corepressor of transcription, involved in the functional repression of class II genes (genes that are transcribed by DNA polymerase II)

2009 → 2020? The genetic/biomolecular age

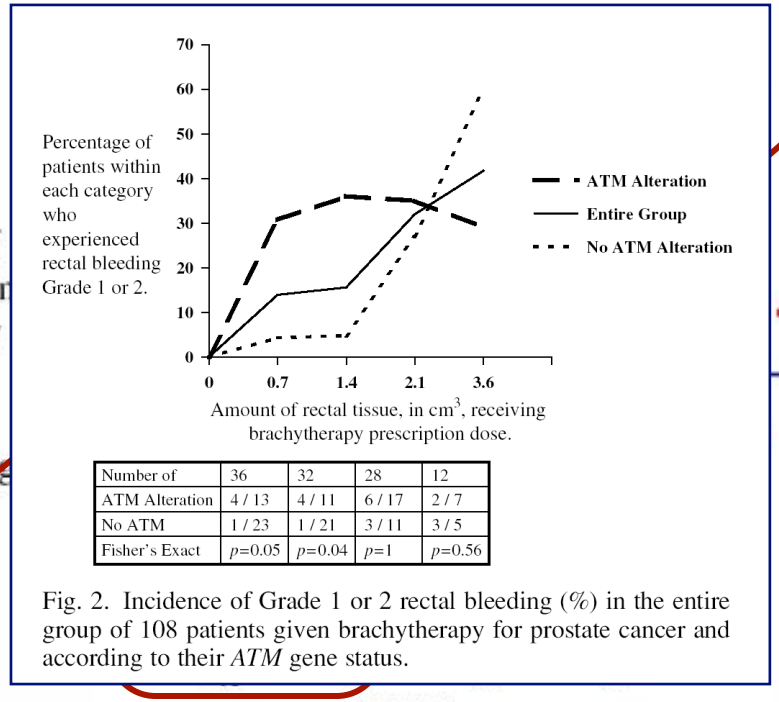
Our data seem to confirm Cesaretti et al's findings (BCT) on the possible genetic component of rectal bleeding



CLINICAL INVESTIGATION Prostate

A GENETICALLY DETERMINED DOSE–VOLUME HISTOGRAM PREDICTS FOR RECTAL BLEEDING AMONG PATIENTS TREATED WITH PROSTATE BRACHYTHERAPY

Jamie A. Cesaretti, M.D., M.S.,* Richard G. Stock, M.D.,* David P. Atencio, Ph.D.,* Sheila A. Peters, B.A.,* Christopher A. Peters, M.D.,* Ryan J. Burri, M.D.,* Nelson N. Stone, M.D.,* and Barry S. Rosenstein, Ph.D.† Int. J. Radiation Oncology Biol. Phys.



Number of	36	32	28	12
ATM Alteration	4 / 13	4 / 11	6 / 17	2 / 7
No ATM	1 / 23	1 / 21	3 / 11	3 / 5
Fisher's Exact	p=0.05	p=0.04	p=1	p=0.56

Fig. 2. Incidence of Grade 1 or 2 rectal bleeding (%) in the entire group of 108 patients given brachytherapy for prostate cancer and according to their *ATM* gene status.

High-dose region: the genetic makeup plays a minor role and the dose the major role

Low-dose region: the genetic makeup might play the major role

- LSM7 alteration ?
- Entire population ?
- no LSM7 alteration ?

EUD (Gy)

When more pts are available, it might be reasonable to unveil the double nature of the dose-response relationship also for EBRT

We are aware of the influence of genetic signature.
Nevertheless, investigation in this field
is still leading to controversial results

Lancet Oncol 2012

Independent validation of genes and polymorphisms
reported to be

Gene signature:
lot of clinical research still to be done!
Use of genetic profiles will help better identify
patients at high risk of exhibiting toxicity

Negative Study:
no replication of previously reported association between late tox & SNPs was shown

Models predicting radio-induced toxicities in prostate cancer

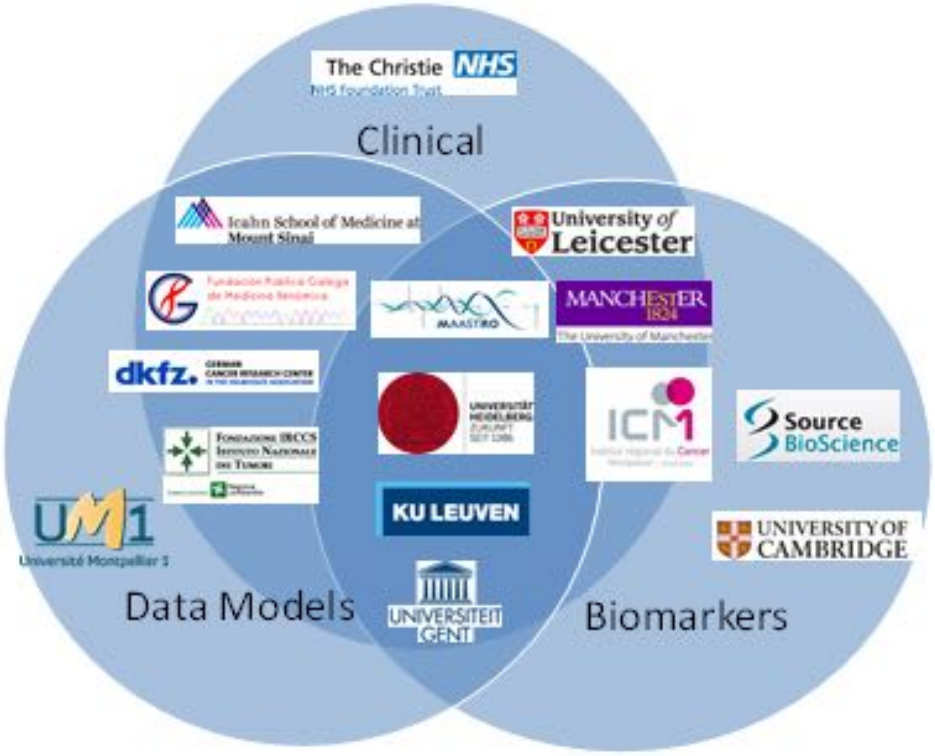
Validation?

2014 → 2020? The Validation Age

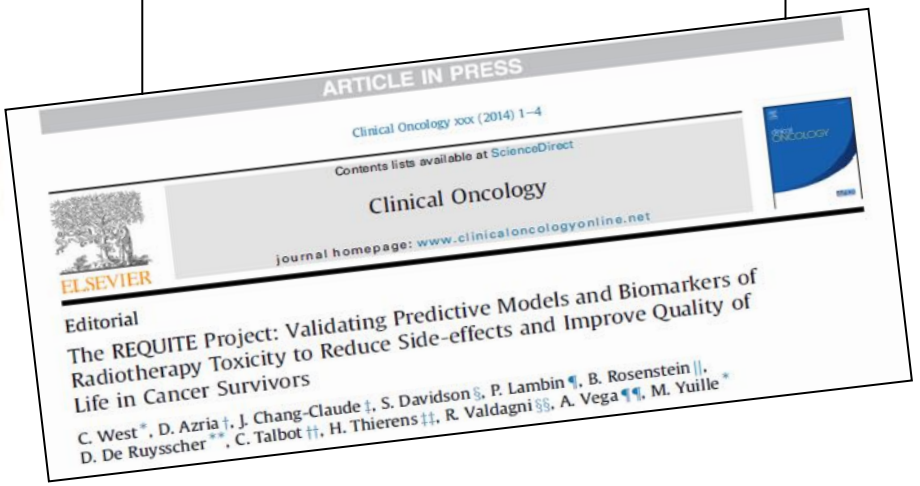
REQUITE

grant agreement no 601826

Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality-of-Life in Cancer Survivors



2100 Pca prospectively collected pts in 2.5 yrs (open: April 2014) 1032 pts (October 2015)



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ELSEVIER

Editorial

The REQUITE Project: Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-effects and Improve Quality of Life in Cancer Survivors

C. West *, D. Azria †, J. Chang-Claude ‡, S. Davidson §, P. Lambin ¶, B. Rosenstein ||, D. De Ruysscher **, C. Talbot ††, H. Thierens ‡‡, R. Valdagni §§, A. Vega ¶¶, M. Yuille *

2014 → 2020? The Validation Age

IG 16087 AIRC

Modelling toxicity after high dose RT for prostate cancer: validating clinical, dosimetric and molecular factors

Aims of the project

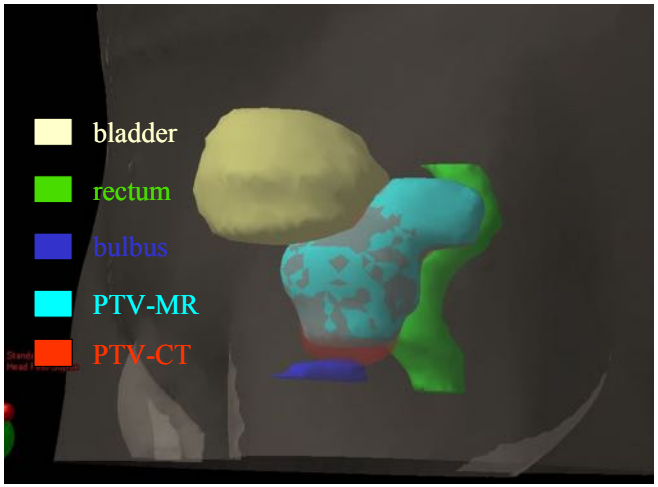
1. External cross-validation of models for prospectively assessed toxicity symptoms based on independent data sets
2. Development of models for acute and late GI and acute GU toxicity from the joined population (≈ 2000 patients)
3. Inclusion of molecular features into the external validated models

Group	study	patients	RT type and dose	endpoint	follow-up
INT+HSR	AIROPROS0102	1124	3DCRT 70-80 Gy	RTOG; SOMA/LENT questionnaire	acute, 1 month
INT+HSR	AIROPROS0102	718	3DCRT 70-80 Gy	SOMA/LENT questionnaire	minimum: 36 mos
INT+HSR	AIROPROS0102	515	3DCRT 70-80 Gy	SOMA/LENT questionnaire	minimum: 72 mos
HSR	DUE-01	500	3DCRT+IMRT 70-80 Gy	SOMA/LENT questionnaire (IPSS/ICIQ/IIEF)	open to recruitment
IRE	IRE-HYPO	186	3DCRT 80Gy conv/62 Gy Hypo	Modified "clinical" SOMA/LENT	median 96 mos
France	STIC-IGRT	130	IMRT+ IGRT 78-80 Gy	acute and late toxicity (SOMALENT and CTCAE v4)	median 31 mos
France	GETUG_Rennes	170	IMRT 70-80 Gy	SOMA/LENT; CTCAE v4	median 65 mos
France	Rennes	63	3DCRT and IMRT 70-80 Gy	SOMA/LENT; CTCAE v4	median 68 mos
France	IGR	97	3DCRT 70 Gy	RTOG; SOMA/LENT	median 92 mos
Australia	TROG 03.04 RADAR	754	3DCRT 66, 70 and 74 Gy	EORTC QLQ-PR25; SOMA/LENT; CTC v2; IPSS	acute, 1 month
Australia	TROG 03.04 RADAR	754	3DCRT 66, 70 and 74 Gy	EORTC QLQ-PR25; SOMA/LENT; CTC v2; IPSS	late 72 mos

Factors predicting radio-induced toxicities in prostate cancer

Organs at Risk

Organs at Risk



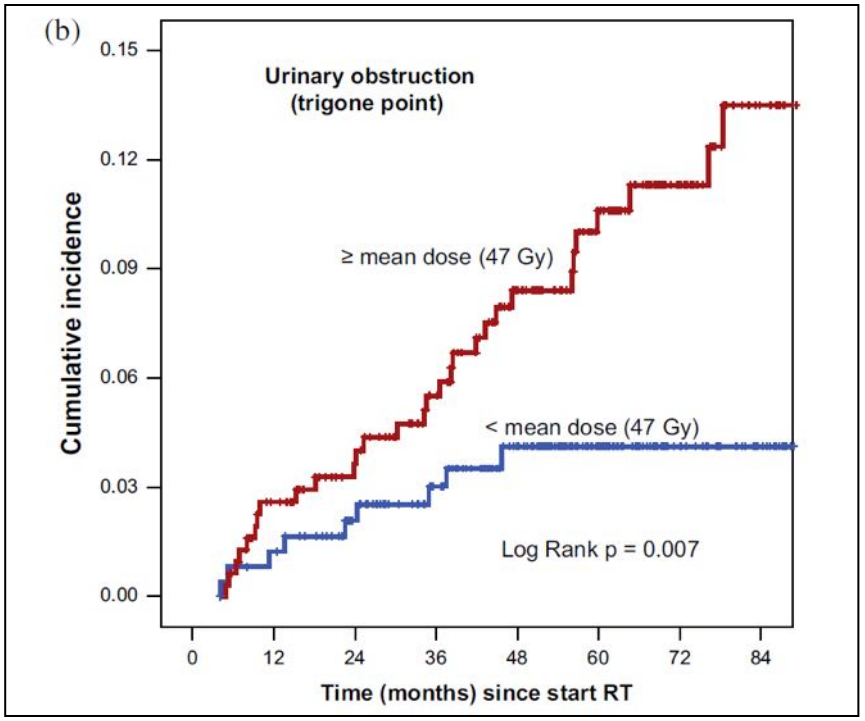
- Gastro-intestinal toxicity
- **Genito-urinary toxicity**
- **Erectile dysfunction**

- Rectum
- Anal canal
- Bladder
- Urethra
- Penile Bulb
- Testicles
- Bone marrow
- Second cancers

Genitourinary toxicity: towards the Dosimetric Age

Urinary obstruction: relationship with dose to the trigone

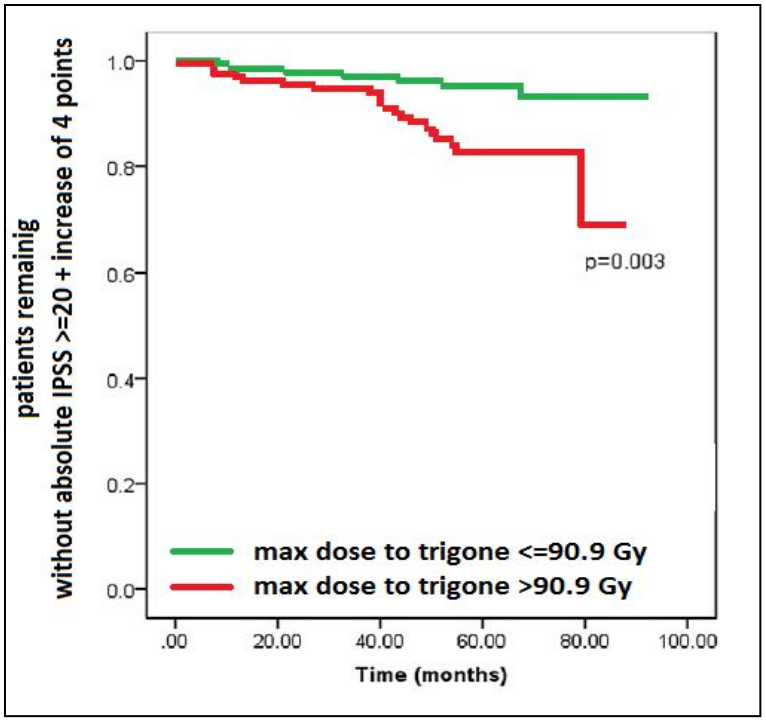
(68 vs 78 Gy: 3DCRT !)



Dutch dose escalation trial
Heemsbergen et al, IJROBP 2010

IPSS increase: relationship with dose to the trigone

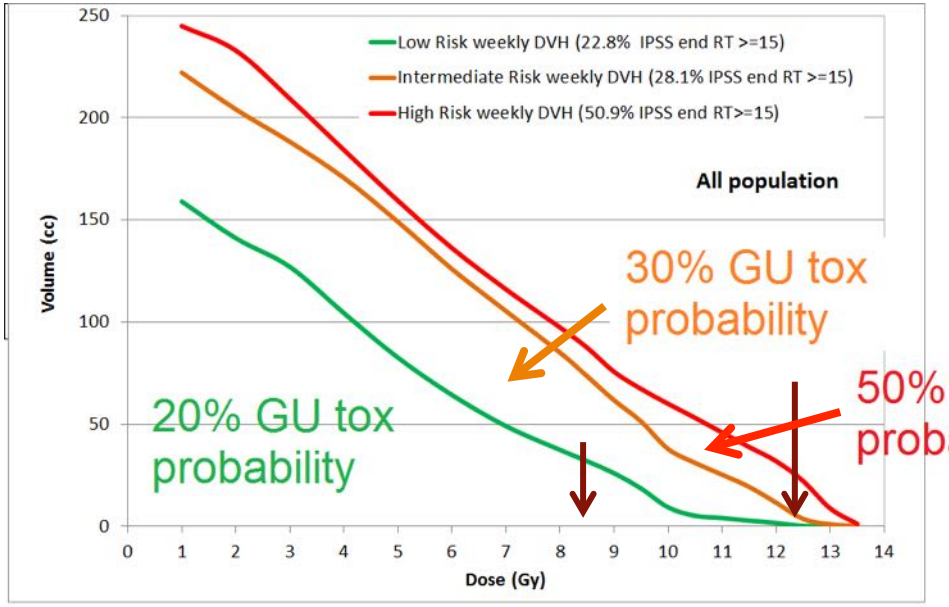
(86.4 Gy IMRT)



MSKCC data
Ghadjar et al, IJROBP 2014

Genitourinary toxicity: towards the Dosimetric Age

If robust DVH constraints for bladder not (yet) available ... first proofs of evidence are coming for <u>acute GU toxicity</u>



A dose-response relationship is becoming evident together with the possibility of stratifying dose-volume histograms, leading to low/int/high probabilities of acute GU tox

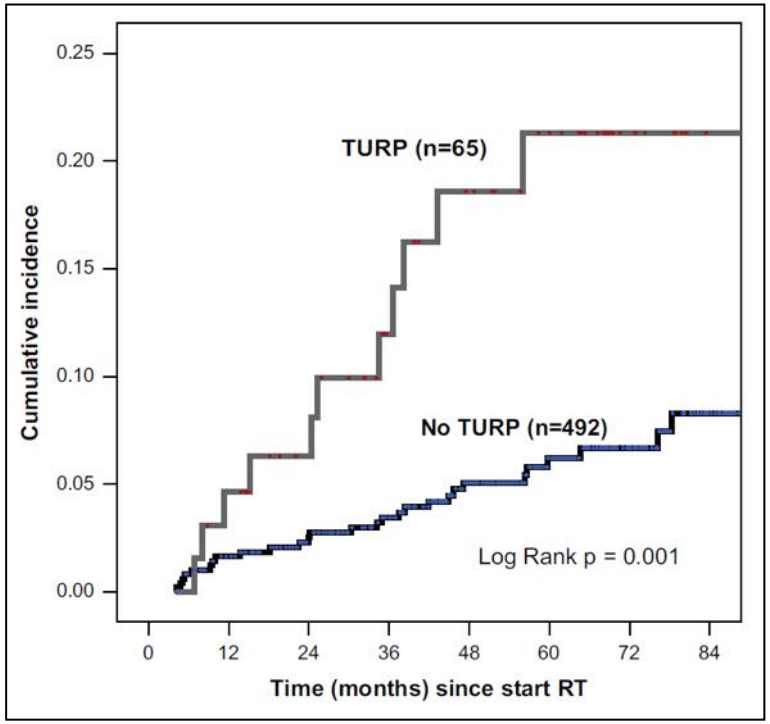
First results of the DUE01 multicenter trial, C*arillo et al, Radioth Oncol, 2014*

HSR	Milan
INT	Milan
Humanitas Gavazzeni	Bergamo
Arcispedale SMN	Reggio E
Ospedale ASL 9	Ivrea
Ospedale Bellaria	Bologna
Ospedale Parini	Aosta
IRCCS	Candiolo

GU toxicity: some hints for Clinical-Dosimetric Age

Clinical variables: Urinary Obstruction endpoint
Relation between RT acute tox and baseline characteristics

Parameter/endpoint	Urinary obstruction (40 events) HR	*p*
Baseline		
TURP (yes vs. no)	3.6	.001
Urinary leakage (yes vs. no)	2.7	.007
Acute toxicity		
Pain passing urine*	3.4	<.001
Dose parameter		
Surface >80 Gy (<0.5 vs. >2 cm^2)	3.5	.006
Trigone point (<47 vs. >47 Gy)	2.6	.02

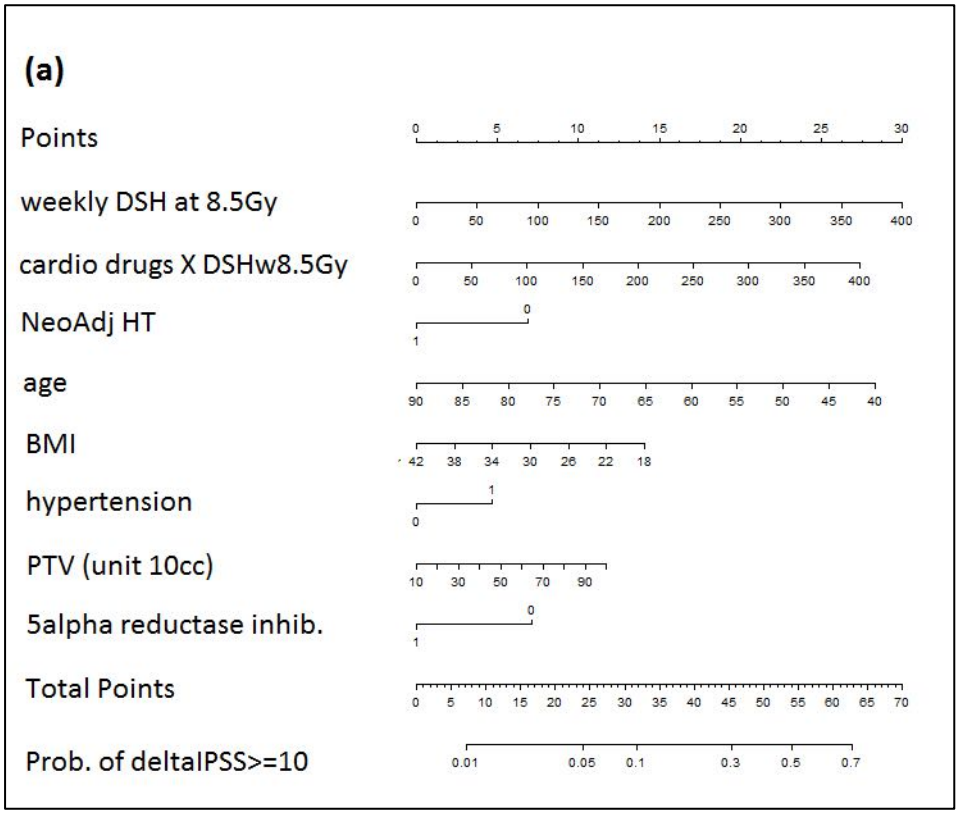


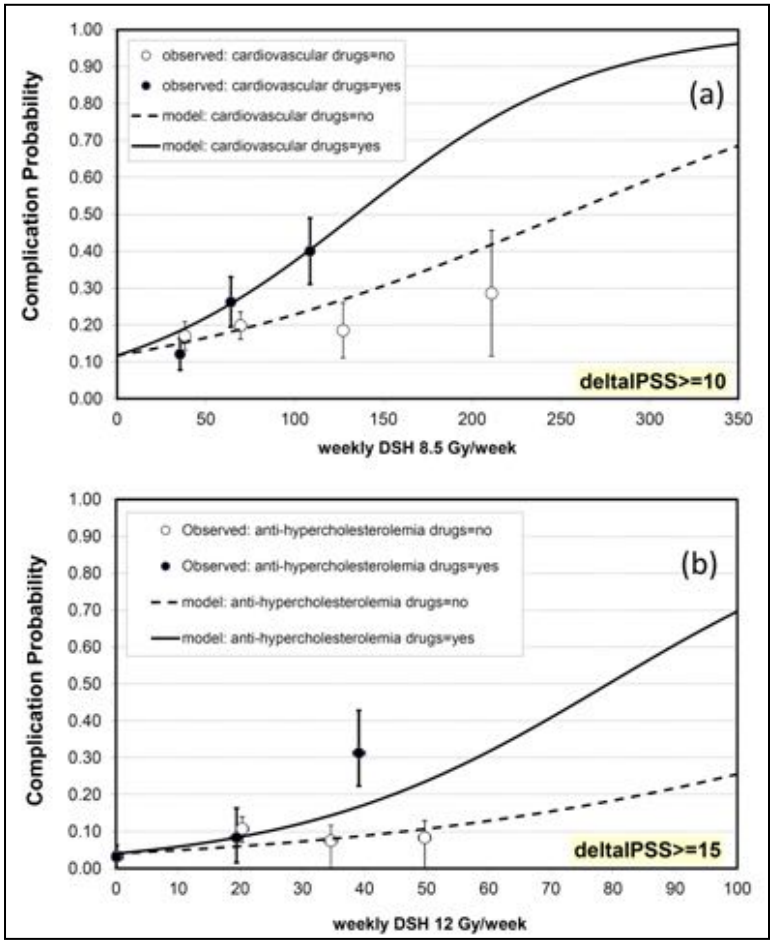
Results from the Dutch dose escalation trial, *Heemsbergen et al, IJROBP 2010*

GU toxicity: some hints for Clinical-Dosimetric Age

... but first deep knowledge of influence of clinical factors on acute GU toxicity syndrome is coming

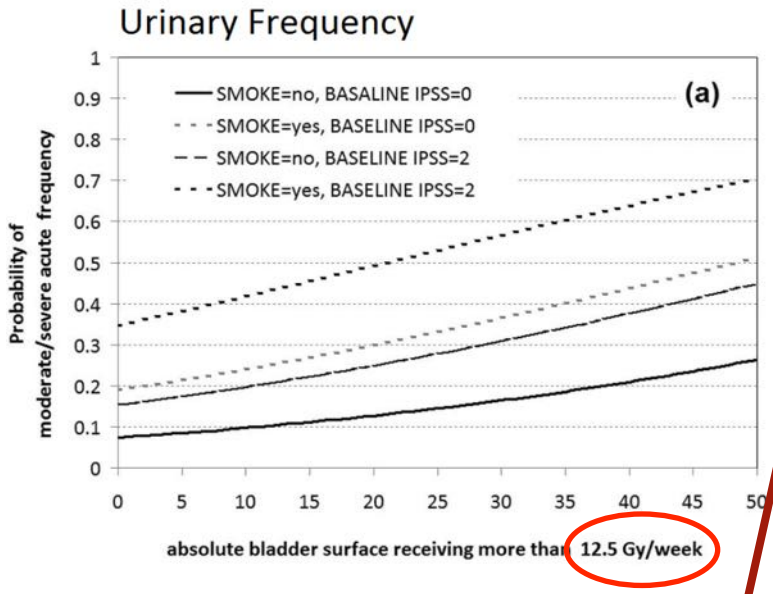
TOX GU= IPSS increase of at least 10





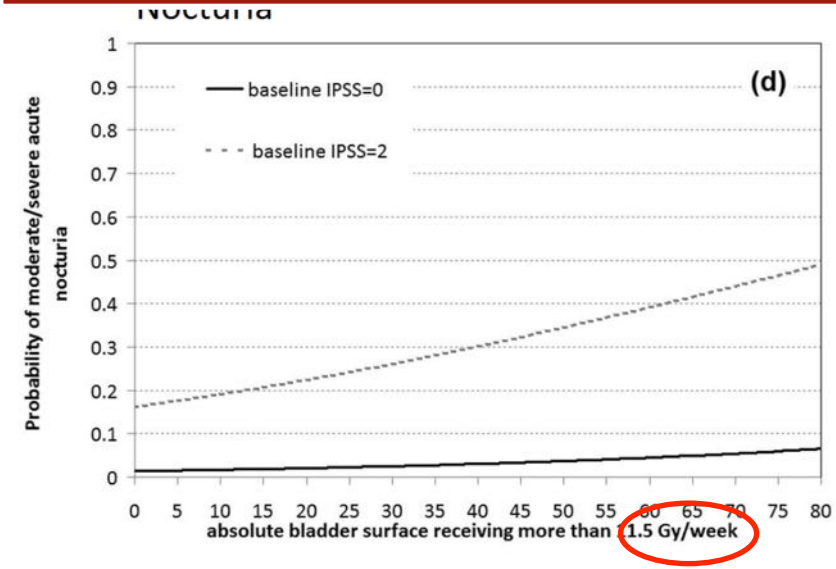
Palorini et al, DUE01, R&O submitted

GU tox syndrome: some hints for Clinical-Dosimetric Age



Should we pay attention to bladder volume included in medium doses in pts harbouring clinical risk factors (smoking, slight urinary sympt, etc)?

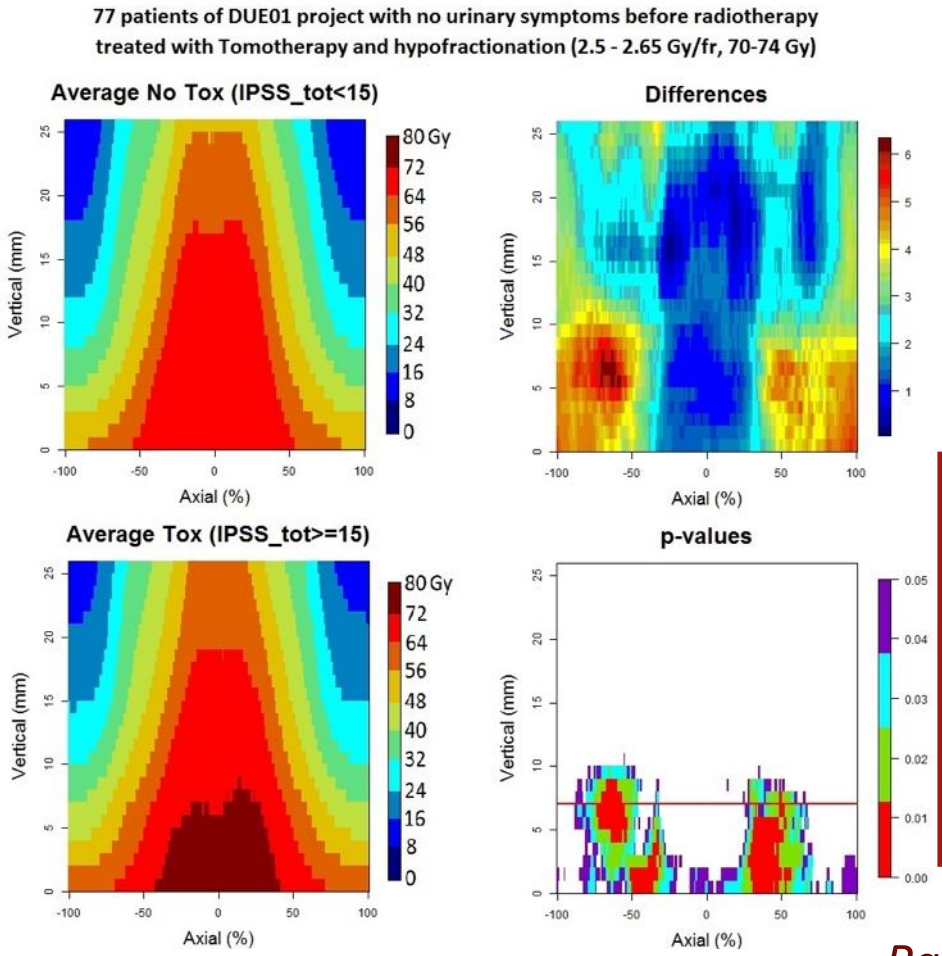
Should we avoid moderate hypofractionation in patients harbouring clinical risk factors (smoking, slight urinary sympt, etc)?

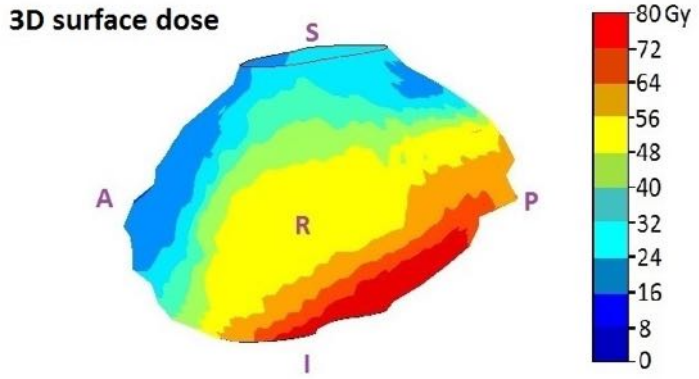


Cozzarini et al, DUE 01, RO 2015

Considering sensitive sub-volumes

Identification of specific bladder regions correlated to GU acute toxicity



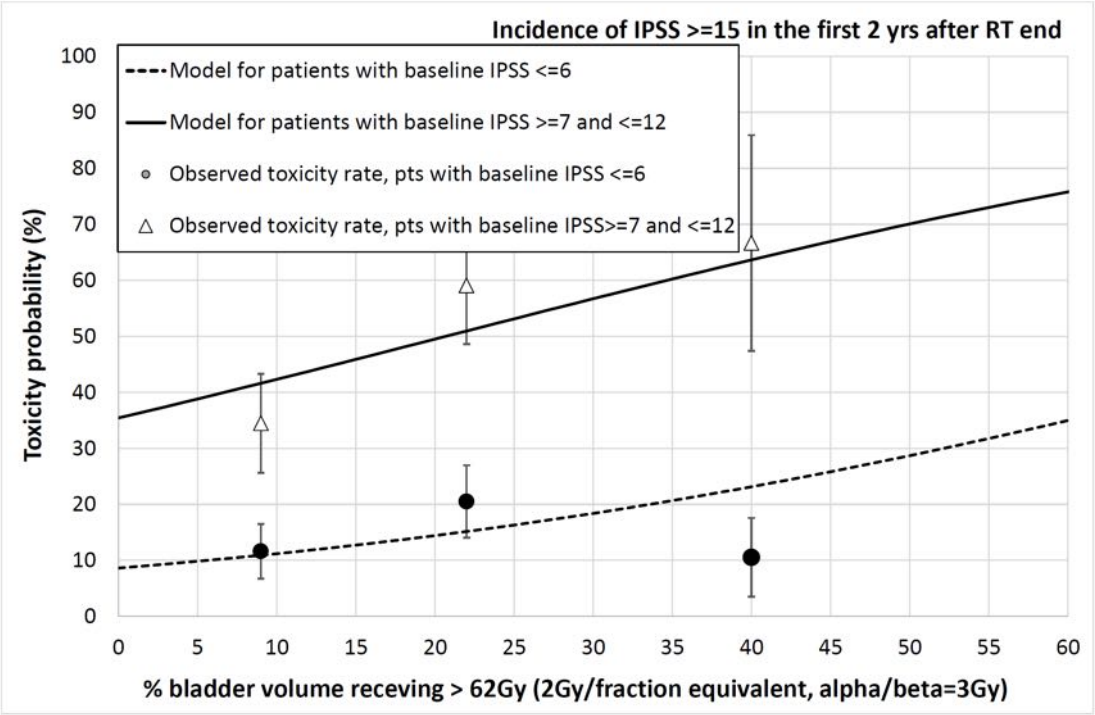


Sparing of the anterior surface of bladder in the region near the bladder base might have the potential of significantly reducing acute toxicity

Palorini et al., DUE01 Trial, IJROBP submitted

Late GU toxicity: some hints for Clinical-Dosimetric Age

Late GU toxicity as measured by IPSS
(IPSS ≥15, in patients with baseline IPSS≤12, 2 yrs fup)



Bladder dose (V62Gy) and presence of baseline symptoms are the main predictors of late GU toxicity.

Badenchini, presentazione orale AIRO 2015

Genitourinary toxicity: first steps towards the Genetic-Age

A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1

Laura Fachal[1,2], Antonio Gómez-Caamaño[3], Gillian C Barnett[4], Paula Peleteiro[3], Ana M Carballo[3], Patricia Calvo-Crespo[3], Sarah L Kerns[5], Manuel Sánchez-García[6], Ramón Lobato-Busto[6], Leila Dorling[4], Rebecca M Elliott[7], David P Dearnaley[8], Matthew R Sydes[9], Emma Hall[10], Neil G Burnet[11], Ángel Carracedo[1,2,12], Barry S Rosenstein[5], Catharine M L West[7], Alison M Dunning[4] & Ana Vega[1,2]

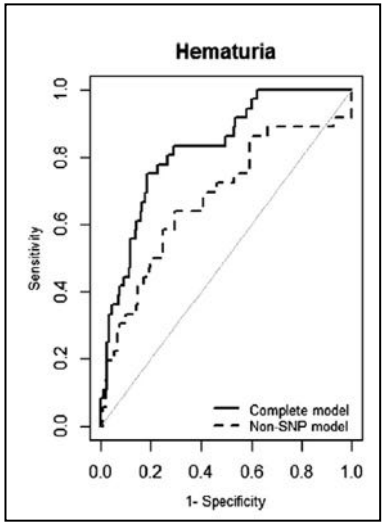
Nature Genetics 2014

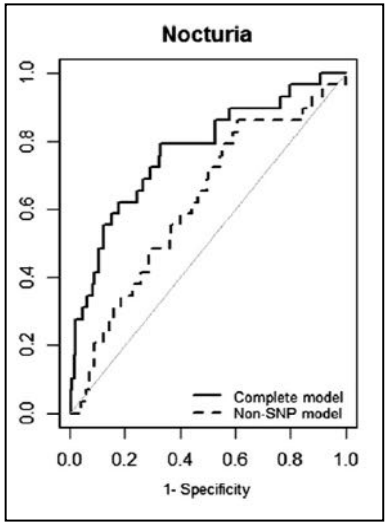
One locus comprising *TANC1* (lowest unadjusted *P* value for overall late toxicity = 6.85 × 10^{-9}, odds ratio (OR) = 6.61, 95% confidence interval (CI) = 2.23–19.63) was replicated in the second stage (lowest unadjusted *P* value for overall late toxicity = 2.08 × 10^{-4}, OR = 6.17, 95% CI = 2.25–16.95; $P_{combined}$ = 4.16 × 10^{-10}). The inclusion of the third cohort gave unadjusted $P_{combined}$ = 4.64 × 10^{-11}. These results, together with the role of *TANC1* in regenerating damaged muscle, suggest that the *TANC1* locus influences the development of late radiation-induced damage.

Integrated models for the prediction of late genitourinary complaints after high-dose intensity modulated radiotherapy for prostate cancer: Making informed decisions

Sofie De Langhe[a,*], Gert De Meerleer[b], Kim De Ruyck[a], Piet Ost[b], Valérie Fonteyne[b], Wilfried De Neve[b], Hubert Thierens[a]

Radioth Oncol 2014





V75Gy
TURP
HMGRC rs3931914
NOS1 rs2293054
PTGER2 rs708498

Minimum dose to CTV
CTV volume
NOS rs 799983
CASP8 rs 1045485
NR2F6 rs4898611

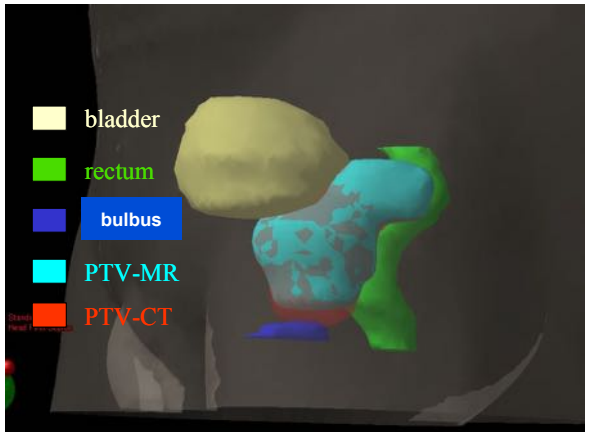
Evidence for the role of selected SNPs in determining GU tox probability

A forgotten endpoint?

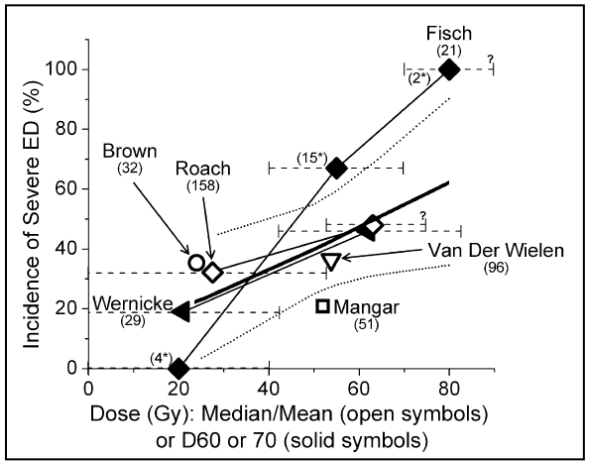
Gastro-intestinal toxicity

Genito-urinary toxicity

Erectile dysfunction

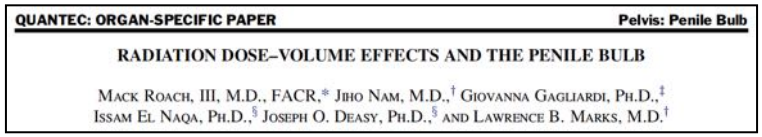


Still in the era of "chaos"!



Despite QUANTEC suggestions …

"It is prudent to limit mean dose to 95% of penile bulb <50Gy and dose to 70% < 70Gy and dose to 90% < 50Gy"



QUANTEC: ORGAN-SPECIFIC PAPER — Pelvis: Penile Bulb

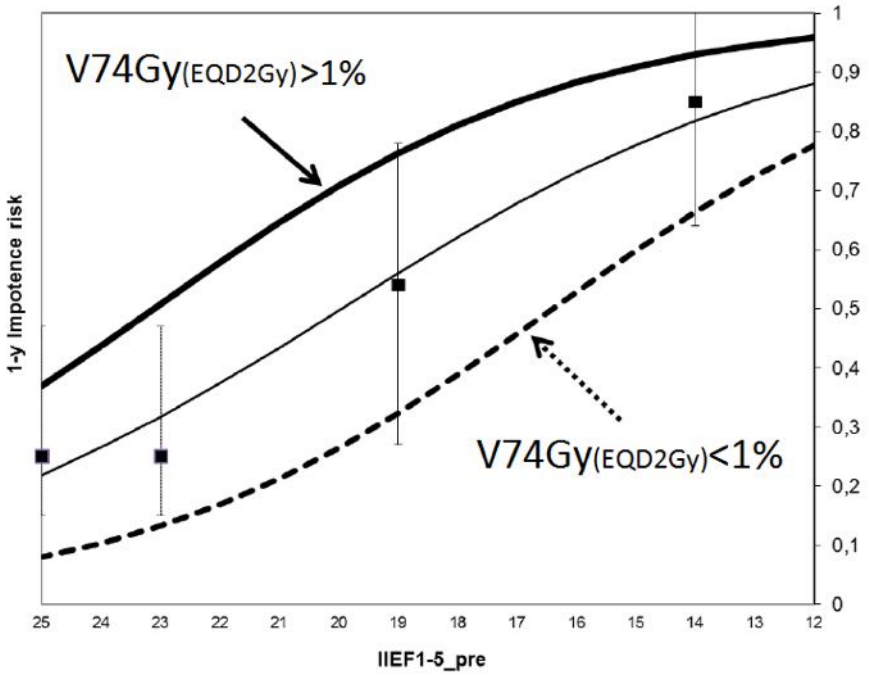
RADIATION DOSE–VOLUME EFFECTS AND THE PENILE BULB

Mack Roach, III, M.D., FACR,* Jiho Nam, M.D.,† Giovanna Gagliardi, Ph.D.,‡ Issam El Naqa, Ph.D.,§ Joseph O. Deasy, Ph.D.,§ and Lawrence B. Marks, M.D.†

… something is coming out of the fog…

In HT-naive potent men, the risk of 1-year impotence may be predicted by a 2-variable model including baseline status (as measured by IIEF1-5) and dose to the penile bulb (V74Gy(EQD2Gy)<1%)

The steep relationship with V74Gy(EQD2Gy)<1% suggests that avoiding/minimizing the overlap between PTV and PB could dramatically improve potency preservation (need of using MRI for contouring in potent men?)



First results of the DUE01 multicenter trial,
Cozzarini et al, Clinical Oncology submitted

HSR	Milan
INT	Milan
Humanitas Gavazzeni	Bergamo
Arcispedale SMN	Reggio E
Ospedale ASL 9	Ivrea
Ospedale Bellaria	Bologna
Ospedale Parini	Aosta
IRCCS	Candiolo

Erectile Dysfunction: What do we have at this point?

First results

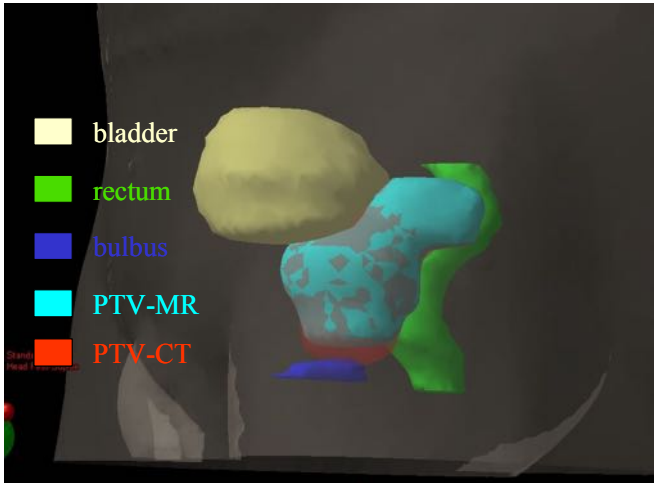
BUT

new large prospective studies are evaluating this endpoint, analyzing many factors influencing ED

Patients' factors possibly involved in ED

- ✓ **Age**
- ✓ **Smoking**
- ✓ **Alcohol**
- ✓ **Hypertension**
- ✓ **Cardiovascular diseases**
- ✓ **Diabetes**
- ✓ **Baseline potency**
- ✓ **BMI**
- ✓ **Presence of GU symptoms**
- ✓ **Use of drugs**
- ✓ **Psycho-emotional aspects regarding cancer diagnosis and treatment**

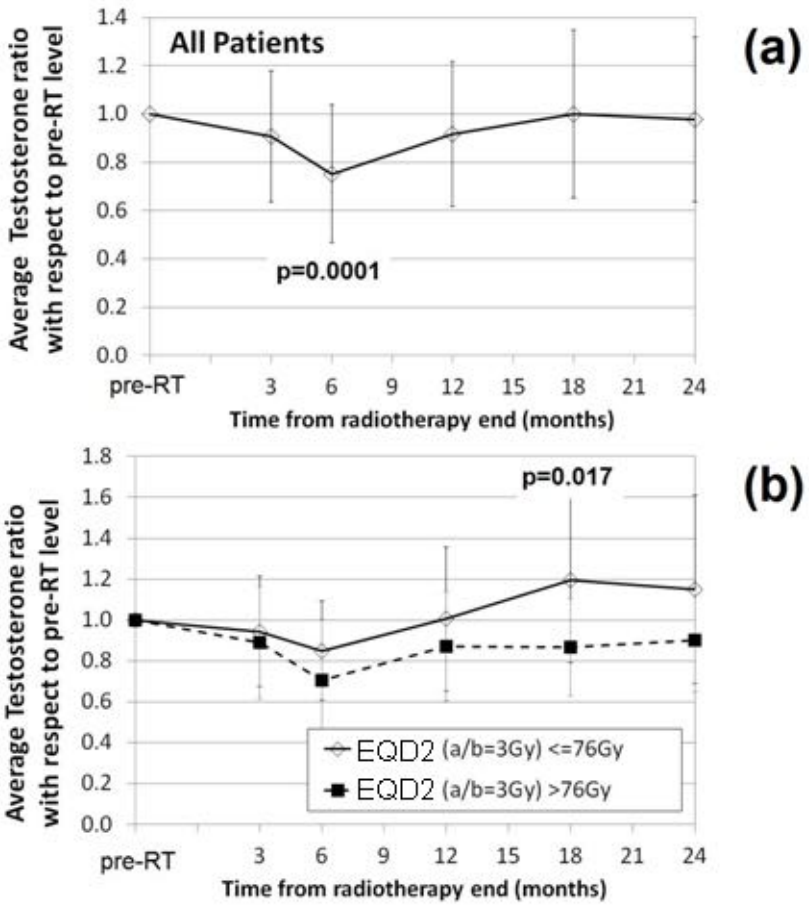
Organs at Risk



- Rectum
- Anal canal
- Small intestine
- Bladder
- Urethra
- Penile Bulb
- **Testicles**
- Bone marrow
- Second cancers

Trying to measure toxicity to testicles
What happens to testosterone levels after radical radiotherapy for prostate cancer?

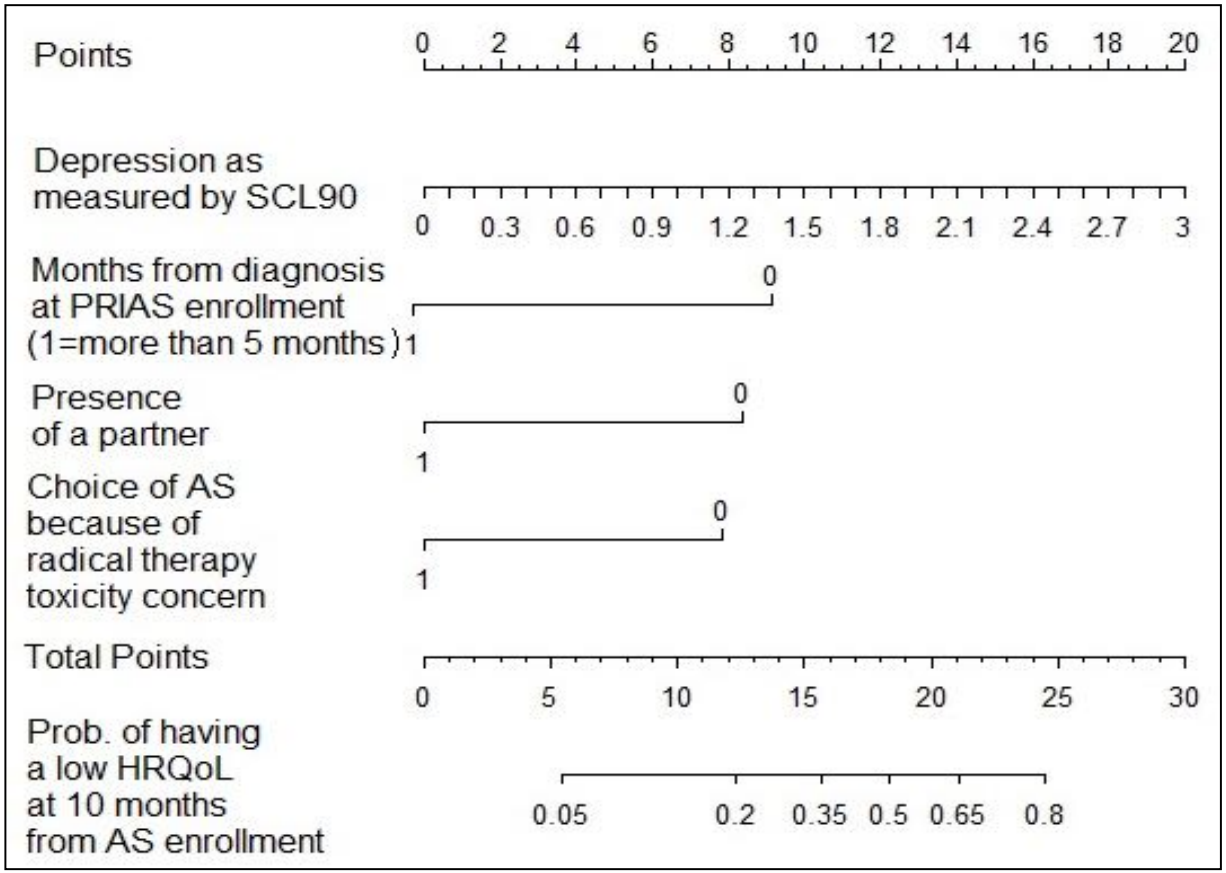
Population of patients treated with RT alone (no association with hormone therapy) and with a minimum follow-up of two years after the end of RT



- Significant testosterone decrease after prostate RT, with nadir at 6 months after RT end
- For most patients this decrease was temporary with recovery at 18-24 months
- Significant correlation with prescription dose >76Gy-equivalent, with patient exhibiting longer recovery times.
  Prescription dose is probably a surrogate of testicular dose.

First results of the DUE01 multicenter trial,
Avuzzi et al, oral communication at AIRO 2015

The next Challenge: Predicting Quality of Life after RT including psycho-emotional domains



L. Bellardita et al, QoL in Active Surveillance, Eur Urol, 2012

Paris 24-28 February 2012
27th Annual EAU Congress
13th International EAUN Meeting

Best Poster award

Factors predicting radio-induced toxicities in prostate cancer

Promoting the Age of Big Data

New frontiers in predictive modelling:
"to predict the future,
consider the present as well as the past"

Cooperberg, Eur Urol 2012

We should encourage the widespread collection of clinical/ dosimetric/genetic data on tumor control and radio-induced toxicity, ideally for all treated patients, and invest in data warehousing, data mining, and statistical analysis.

"More than 95% of clinical data are DARK MATTER.
It's time to enlighten it"

T.R. Mackie, ASTRO 2012

Conclusions

1. GI toxicity prediction reached very good levels and validation tests are ongoing
2. GU toxicity prediction is highly promising due to new prospective trials
3. ED prediction still needs a lot of work
4. Prediction of Quality of Life in the psycho-emotional domains after RT is a brand new topic
5. **Promote large cooperative groups for data building, data mining and rapid learning: are a promising way to speed up improvements in "knowledge based medicine"**

Fattori predittivi di tossicità nella radioterapia del carcinoma prostatico

Vi ringrazio per la vostra attenzione

AIROPROS 0102 trial

AIRC DUE 01 trial

HSR	Milan
INT	Milan
Humanitas Gavazzeni	Bergamo
Arcispedale SMN	Reggio E
Ospedale ASL 9	Ivrea
Ospedale Bellaria	Bologna
Ospedale Parini	Aosta
IRCCS	Candiolo

Grazie a tutto il team di lavoro degli studi italiani sulla modellizzazione della tossicità nella radioterapia del carcinoma prostatico

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

PROSTATE CANCER PROGRAM

UNIVERSITÀ DEGLI STUDI DI MILANO

Predictors of rectal tolerance in SBRT

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,† Christopher Straka, BS,* Alana Christie, MS,‡ Yair Lotan, MD,§ David Pistenmaa, MD,* Brian D. Kavanagh, MD,‖ Akash Nanda, MD, PhD,¶ Patrick Kueplian, MD,# Jeffrey Brindle, MD,** Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD,‖ Xian-Jin Xie, PhD,‡ and Robert D. Timmerman, MD*

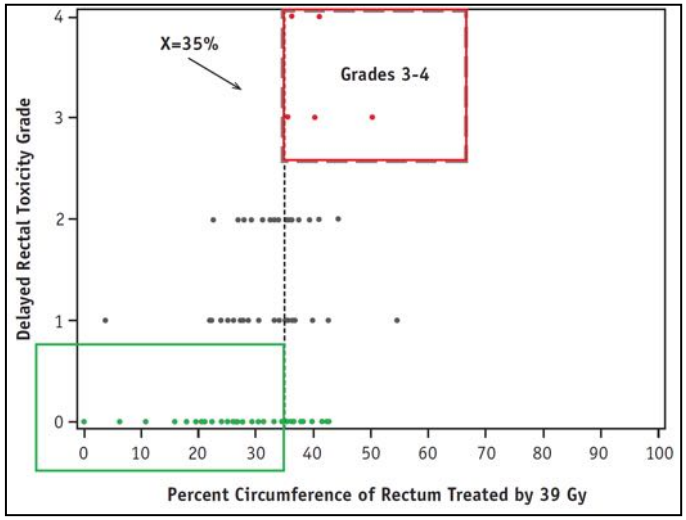
IJROBP 2014

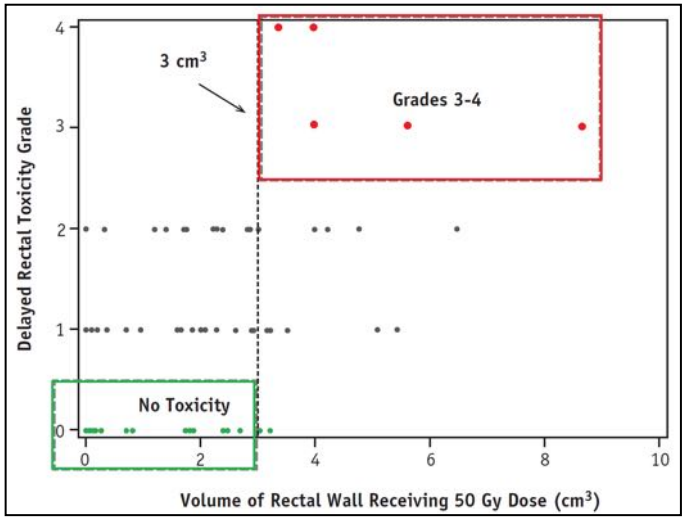
Evidenza relazione D-R con SBRT 9-9.5-10 fr:

1. Reazioni gravi sono tardive
2. G3-4: 8.2%
3. >35% circonferenza retto >39Gy
4. > 3cc >50 Gy

Table 2 Worst acute and delayed rectal toxicity in patients by radiation prescription dose level

	All patients (n=91)		45 Gy (n=15)		47.5 Gy (n=15)		50 Gy (n=61)	
Grade	Acute	Late	Acute	Late	Acute	Late	Acute	Late
0	39 (42.9)	38 (41.8)	9 (60.0)	10 (66.7)	7 (46.7)	8 (53.3)	23 (37.7)	20 (32.8)
1	33 (36.3)	27 (29.7)	6 (40.0)	4 (26.7)	4 (26.7)	2 (13.3)	23 (37.7)	21 (34.4)
2	17 (18.7)	21 (23.1)	0	1 (6.7)	4 (26.7)	5 (33.3)	13 (21.3)	15 (24.6)
3	1* (1.1)	3 (3.3)	0	0	0	0	1* (1.6)	3 (4.9)
4	1 (1.1)	2 (2.2)	0	0	0	0	1 (1.6)	2 (3.3)





EQD2Gy(50Gy)=
107Gy (α/β=5Gy)
130Gy (α/β=3Gy)

EQD2Gy(39Gy)=
70Gy (α/β=5Gy)
81Gy (α/β=3Gy)

Predictors of rectal tolerance in SBRT

Table 4 Analysis of dosimetric and clinical parameters for high-grade delayed rectal toxicity

Parameter	Odds Ratio	95% CI	*P*
Clinical			
Age	0.92	(0.80-1.06)	.2610
Race			.0756
African American vs Caucasian	15.0	(1.44-155.75)	
All other vs Caucasian	8.1	(0.46-142.93)	
Gleason score			.9427
3+4 vs 3+3	1.3	(0.18-9.92)	
4+3 vs 3+3	1.5	(0.12-17.41)	
Diabetes	3.5	(0.54-23.3)	.1888
Baseline EPIC bowel symptom score	1.05	(0.86-1.28)	.6558
Smoking history*	N/A	N/A	.8043
Androgen deprivation therapy*	N/A	N/A	.5793
Dosimetric			
PTV volume, cm^3	1.03	(0.99-1.07)	.1248
Max PTV length, cm	2.12	(0.56-8.05)	.2695
Max PTV width, cm	5.28	(0.50-55.62)	.1664
Rectal wall volume, cm^3	1.03	(0.96-1.11)	.3466
Max point dose on rectum	1.01	(0.997-1.01)	.1981
% Circumference of rectum treated by 24 Gy	1.1	(1.01-1.2)	.0265
% Circumference of rectum treated by 39 Gy	1.18	(1.01-1.38)	.0374
Volume of rectal wall receiving specified dose, cm^3			
35 Gy	1.72	(1.13-2.62)	.0115
37.5 Gy	1.84	(1.15-2.92)	.0103
40 Gy	1.95	(1.18-3.22)	.0095
42.5 Gy	2.40	(1.21-4.77)	.0122
45 Gy	2.17	(1.19-3.97)	.0117
47.5 Gy	2.25	(1.19-4.24)	.0124
50 Gy	2.67	(1.25-5.71)	.0113
Volume of anterior rectal wall receiving specified dose, cm^3			
35 Gy	2.17	(1.12-4.19)	.0212
37.5 Gy	2.20	(1.15-4.19)	.0165
40 Gy	2.21	(1.18-4.13)	.0134
42.5 Gy	2.18	(1.19-3.98)	.0115
45 Gy	2.20	(1.19-4.08)	.0119
47.5 Gy	2.31	(1.20-4.45)	.0122
50 Gy	3.29	(1.37-7.91)	.0077

Only dosimetric predictors