Convegno
Fisica e Radioterapia

NUOVE FRONTIERE
TRA HIGH TECH
E
POST GENOMICA

Perugia, 2 Luglio 2010

Convento di S. Francesco del Monte
Monteripido

Modelli predittivi basati sul profilo genetico

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FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

PROGRAMMAPROSTATA

A truism:

"not all patients will react the same way to radiotherapy"

patients with identical tumor characteristics (location, pathology, size, stage)

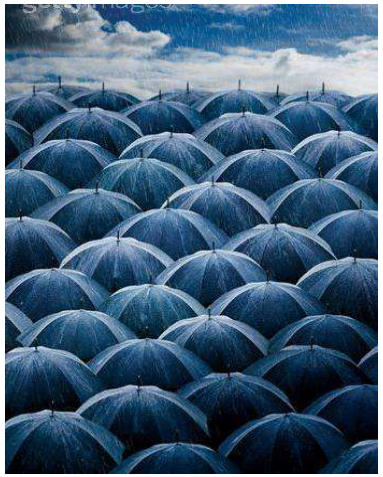
+

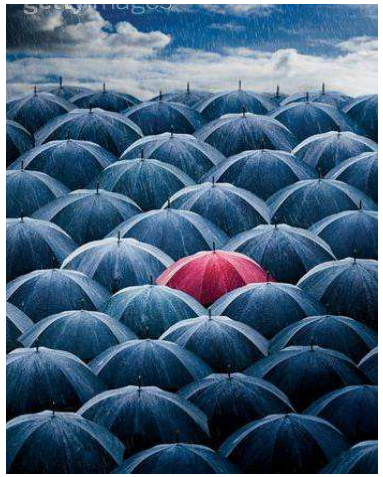
same treatment schedule

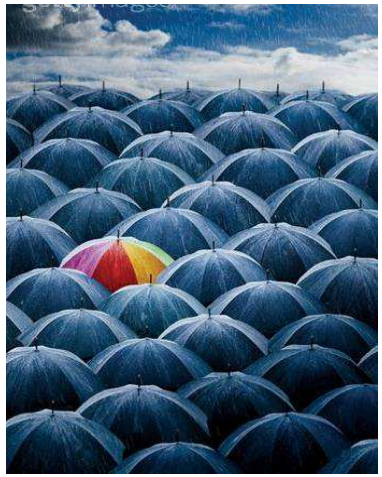
=

some will be cured and some will not

some will suffer toxicity effects and some will not







Knowing the **probable given outcome** to a given treatment **for a given patient** would certainly help!

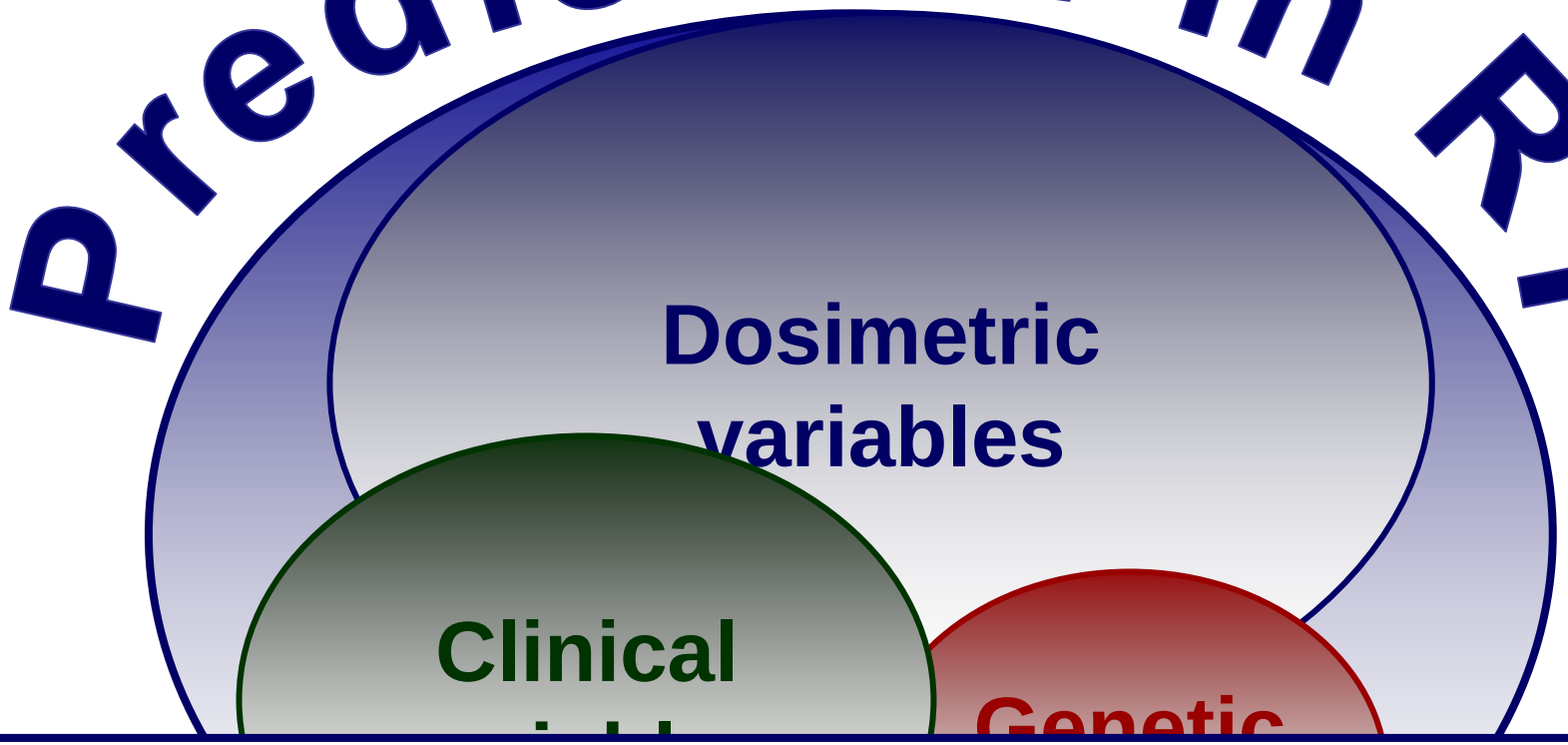
other treatments?
other doses?

avoid ineffective treatments and/or non-acceptable toxicity

- development of robust and accurate prediction techniques for RT
- such techniques will also give insights into causes of failure
- leading to the design of more effective intervention in the future

TCP NTCP

Prediction in RT



Measurement of a single parameter is unlike to succeed as a robust predictor

We have to learn how to cope with a “mass of information”
We have to develop models able to incorporate all relevant variables

Genetic variables … which one ?

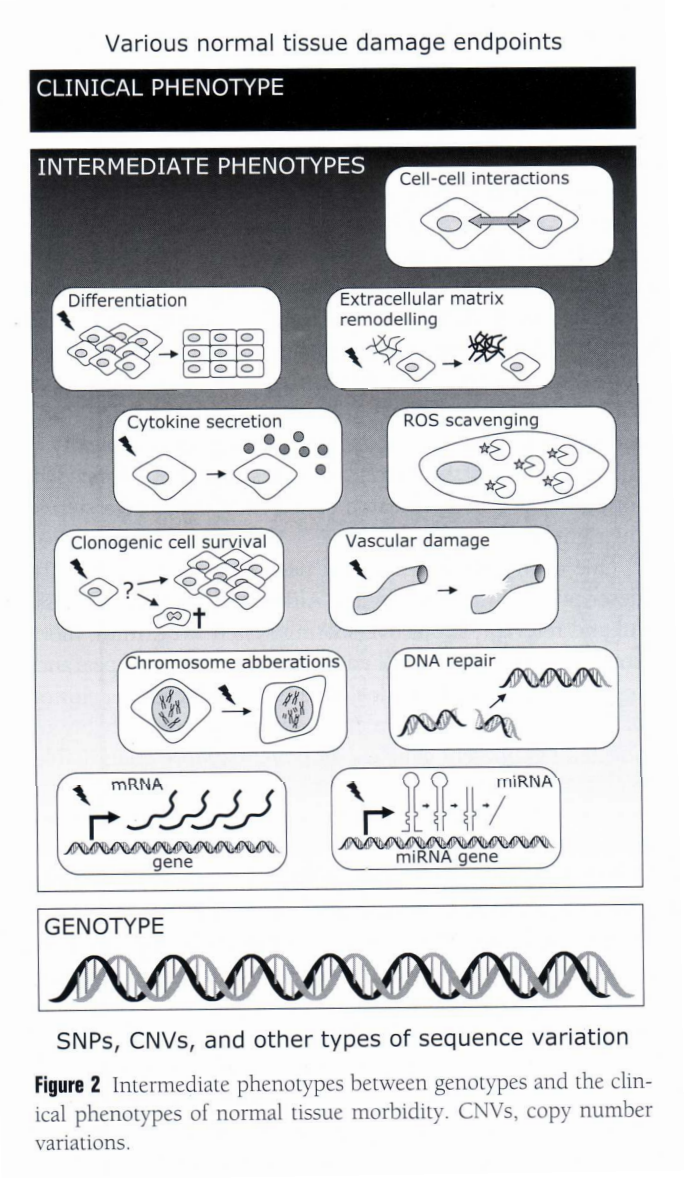


Figure 2 Intermediate phenotypes between genotypes and the clinical phenotypes of normal tissue morbidity. CNVs, copy number variations.

Alsner Seminars in Radiat Oncol 2008

Toxicity and genetic variables … genetic variants

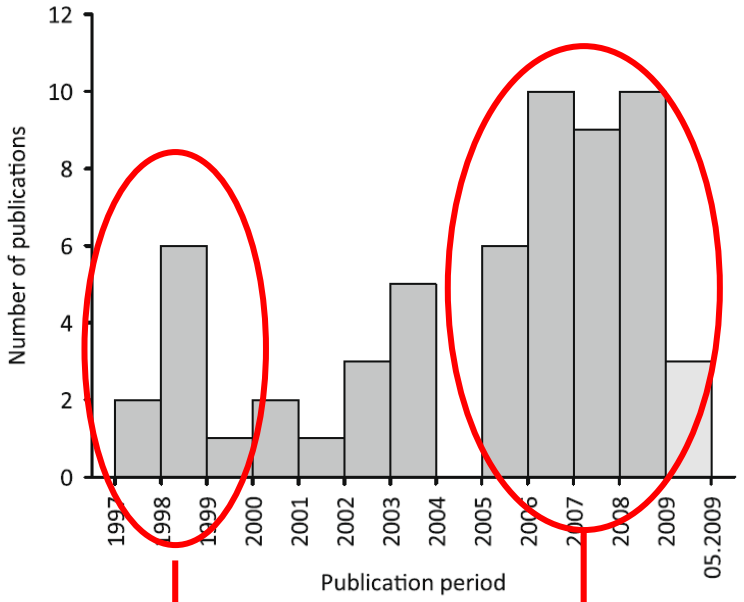


Fig. 1. Number of publications on genetic variants and normal tissue toxicity after

All studies were based on the candidate gene approach →investigate sequence alteration based on functional knowledge about the gene product

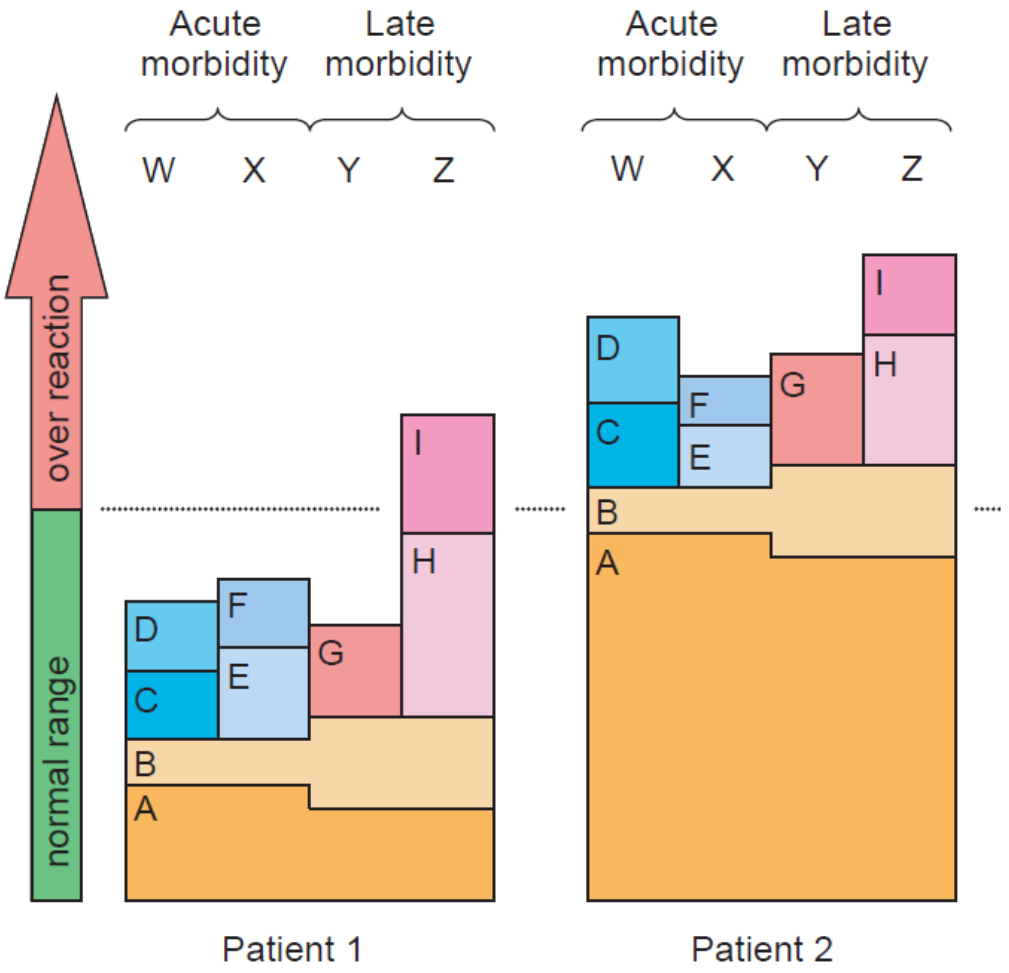
Studies include breast and prostate cancer pts and a variety of both acute and late effects

Andreassen RO 2009, review

A relatively large proportion of the studies have reported significant findings and several genetic variants have been appointed as "promising candidates": variants in ATM, TGFβ1, XRCC1 and GSTP1

Nonetheless results are often contradictory and non-replication of previous results has frequently occured

First limitation: genetic susceptibility is complex trait



Andreassen Acta Oncologica 2005, review

Second limitation: little attention to dose in OAR

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 5, pp. 1410–1416, 2007

CLINICAL INVESTIGATION **Prostate**

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

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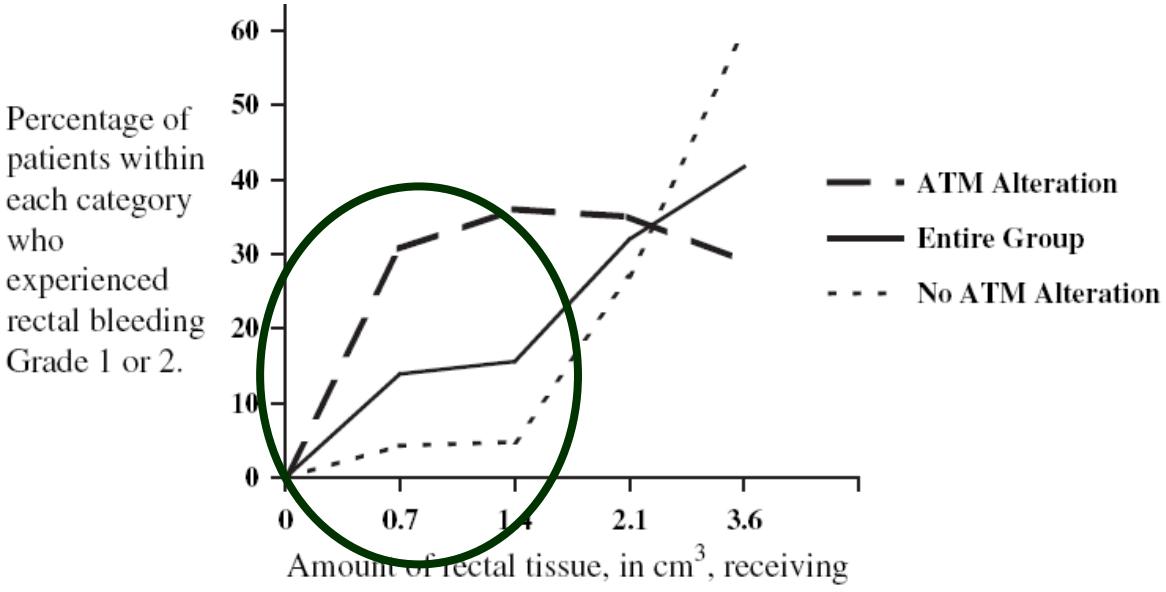
Methods and Materials: One hundred eight prostate cancer patients who underwent brachytherapy using either an ^{125}I implant, a ^{103}Pd implant, or the combination of external beam radiotherapy with a ^{103}Pd implant and had a minimum of 1 year follow-up were screened for DNA sequence variations in the 62 coding exons of the *ATM* gene using denaturing high-performance liquid chromatography. Rectal dose was reported as the volume (in cubic centimeters) of rectum receiving the brachytherapy prescription dose. The two-sided Fisher exact test was used to compare differences in proportions.

The relationship between rectal dosimetry and rectal toxicity (grade 1-2) is explicitly taken into account



"This finding supports the hypothesis that a genetically determined dose–response relationship is possible and could be used to predict the probability of side effects associated with radiotherapy and serve as a rational basis for individualized radiation dose prescriptions"

Toxicity and genetic variables … intermediate phenotype approach

Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 1150–1156, 2005

CLINICAL INVESTIGATION **Normal Tissues**

INCLUSION OF BIOLOGICAL FACTORS IN PARALLEL-ARCHITECTURE NORMAL-TISSUE COMPLICATION PROBABILITY MODEL FOR RADIATION-INDUCED LIVER DISEASE

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HSIAO-WEN CHUNG, PH.D.,* AND GWO-JEN JAN, PH.D.*

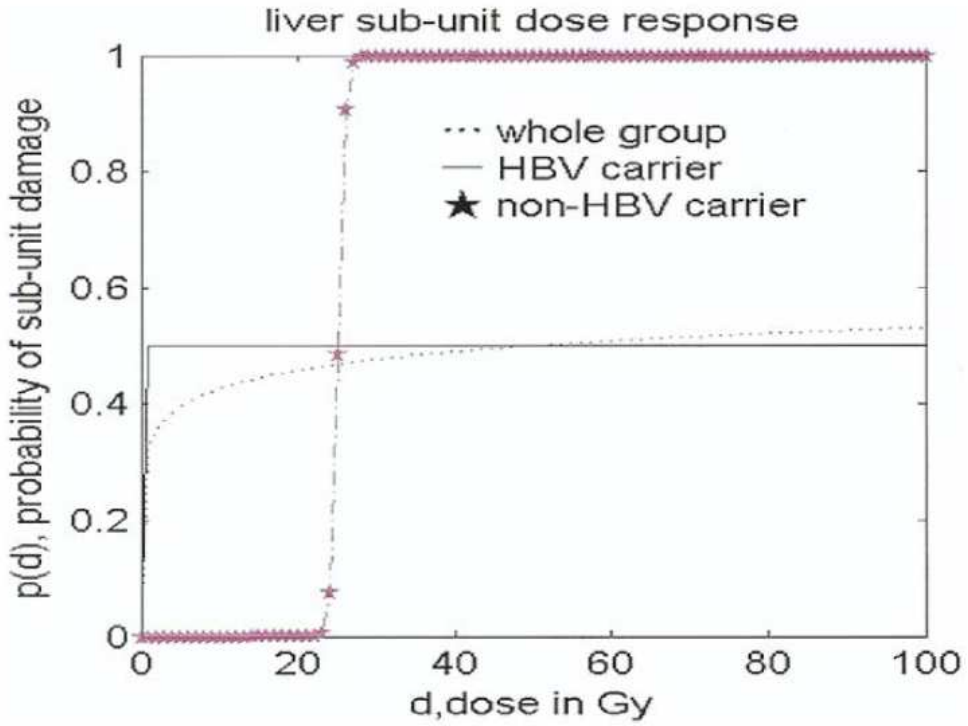

Fig. 2. The dose–response at whole volume irradiated with the best-fit model parameters in the whole group, hepatitis B virus (HBV) carrier group, and non-HBV carrier group.

Table 3. The parameters of parallel-architecture NTCP model for all patients and the subgroups

Best estimate of parameter (95% confidence interval)	v_{50}	σ	D_{50}	k
Whole group (151 patients)	0.54 (0.51–0.58)	0.14 (0.11–0.16)	50 Gy (24–110)	0.18 (0.11–0.27)
HBV carriers (76 patients)	0.53 (0.51–0.55)	0.073 (0.05–0.15)	50 Gy (0–>100)	4.56×10^{-7} (<0–0.06)
Non-HBV carriers (75 patients)	0.59 (0.52–0.63)	0.12 (0.08–0.13)	25 Gy (21–29)	59.8 (1–>100)

Abbreviation: HBV = hepatitis B virus.

Radiotherapy and Oncology 83 (2007) 261–266
www.thegreenjournal.com

Clinical radiobiology

Differential gene expression before and after ionizing radiation of subcutaneous fibroblasts identifies breast cancer patients resistant to radiation-induced fibrosis

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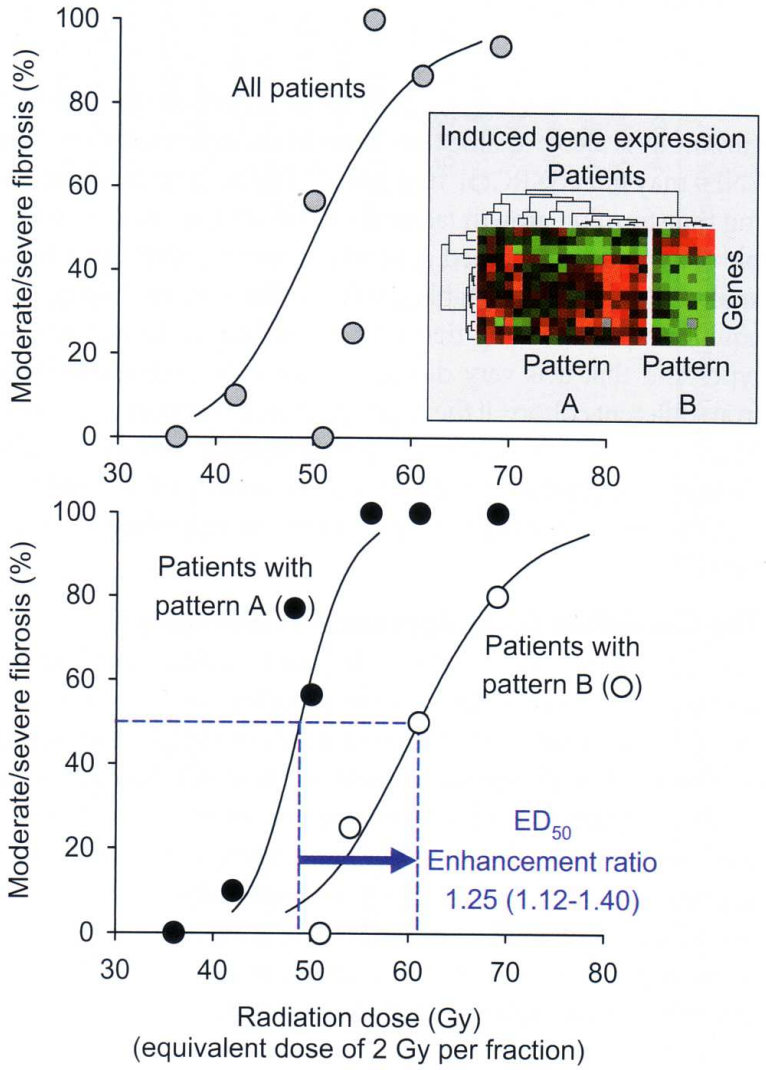
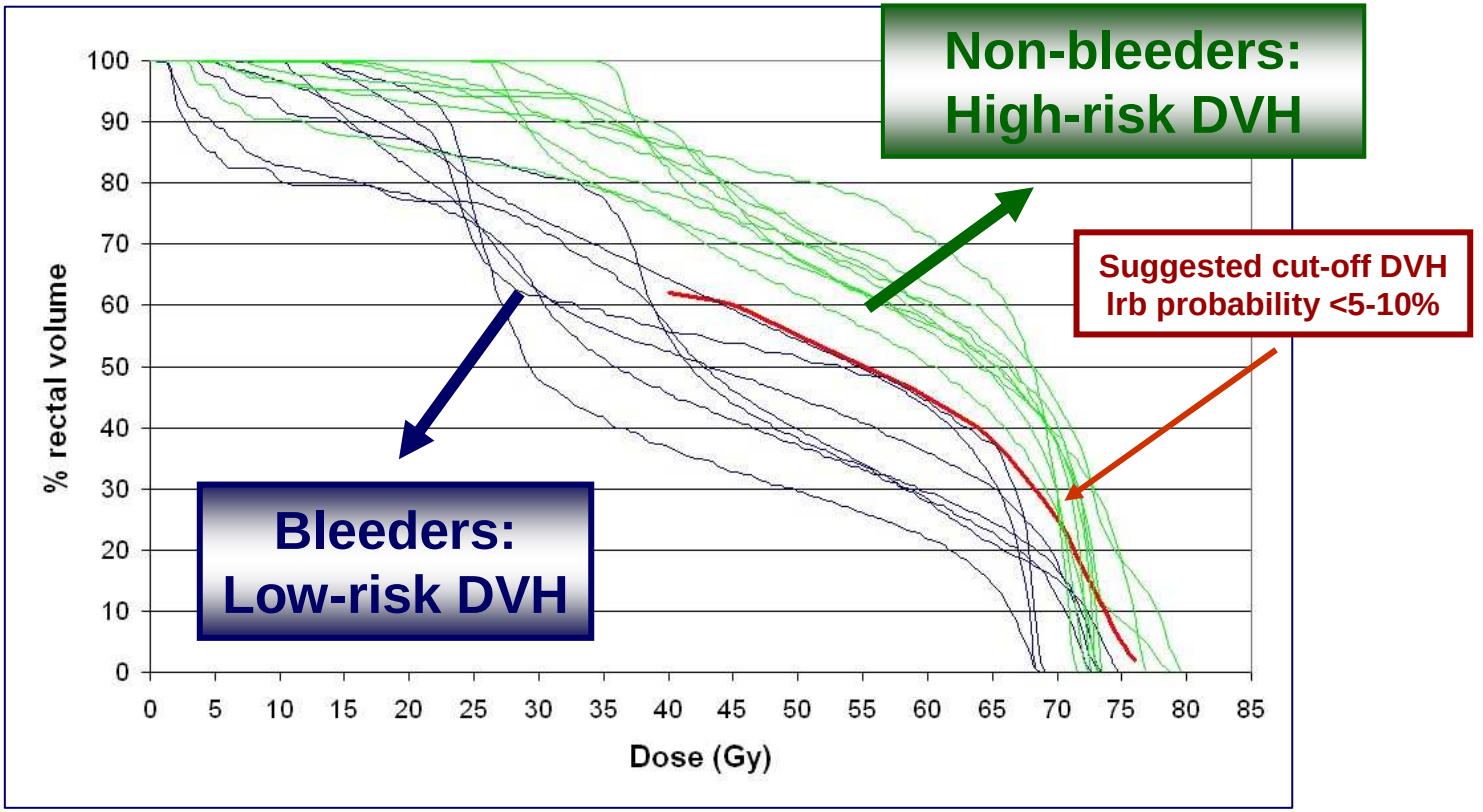
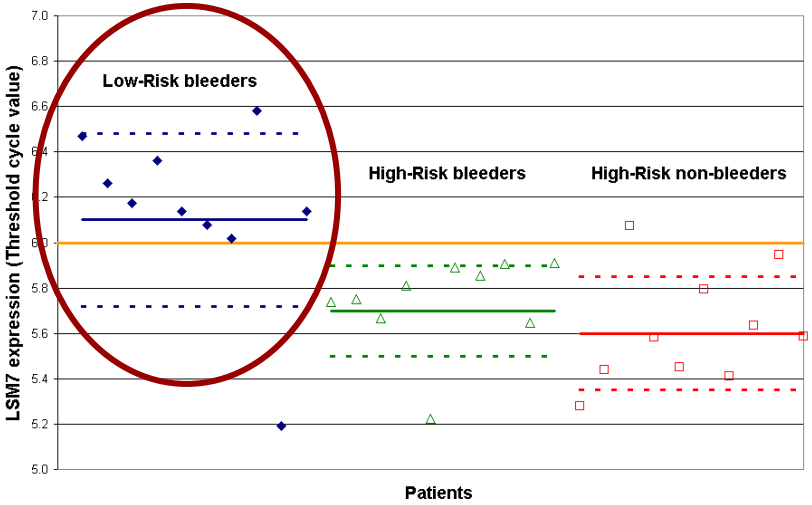
[a]*Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark,* [b]*Department of Genetics, University of Oslo, Norway*

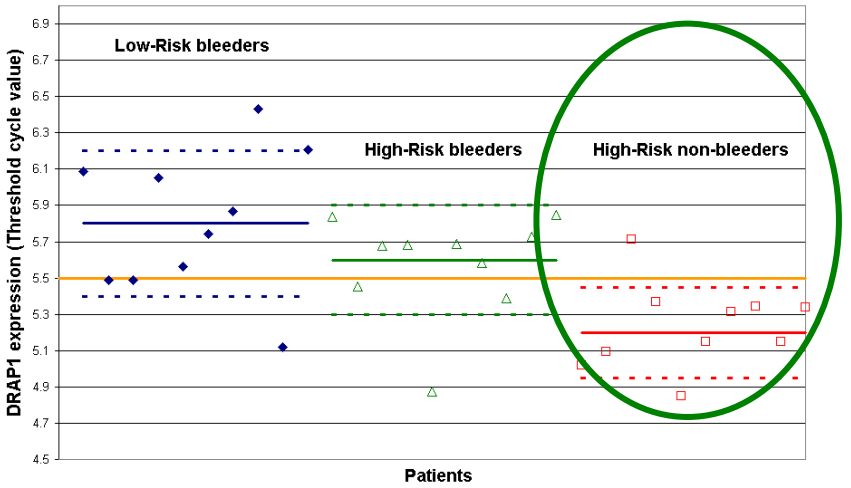


TO BLEED OR NOT TO BLEED. A PREDICTION BASED ON INDIVIDUAL GENE PROFILING COMBINED WITH DOSE–VOLUME HISTOGRAM SHAPES IN PROSTATE CANCER PATIENTS UNDERGOING THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY

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.‡§



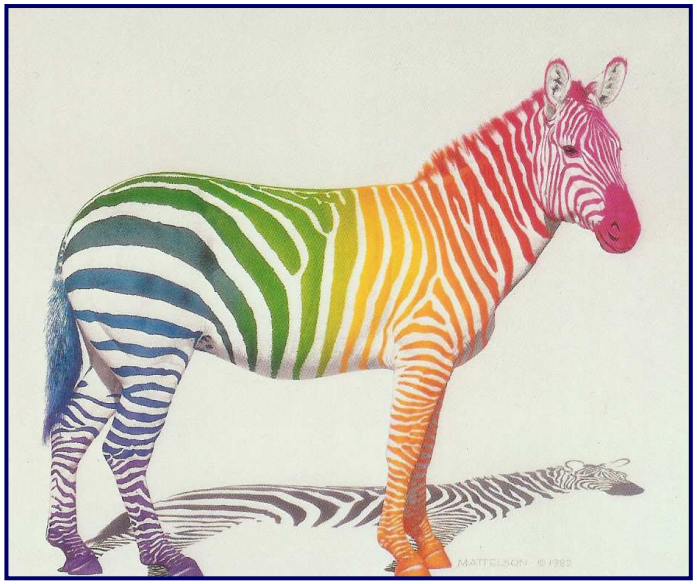


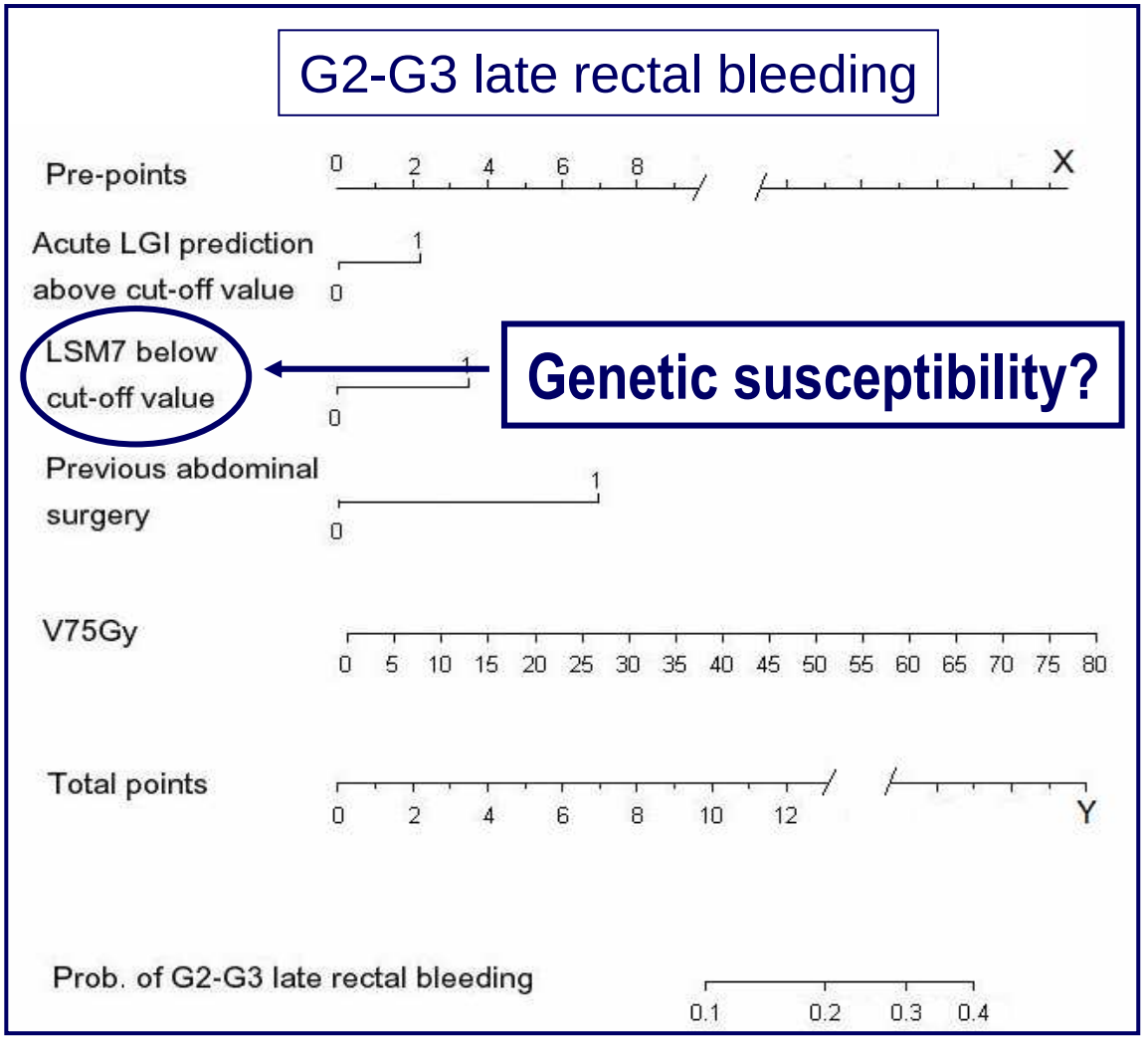


LSM7 → cut-off value = 6.0 — 9/10 pts correctly classified in Low-Risk bleeders (radiosensitive pts)

DRAP1 → cut-off value = 5.5 — 9/10 pts correctly classified in High-Risk non-bleeders (radioresistant pts)

The Future of Radio-toxicity Prediction: Including Gene Profiling in pre-treatment Nomograms ?





Predictive Models of Toxicity With External Radiotherapy for Prostate Cancer

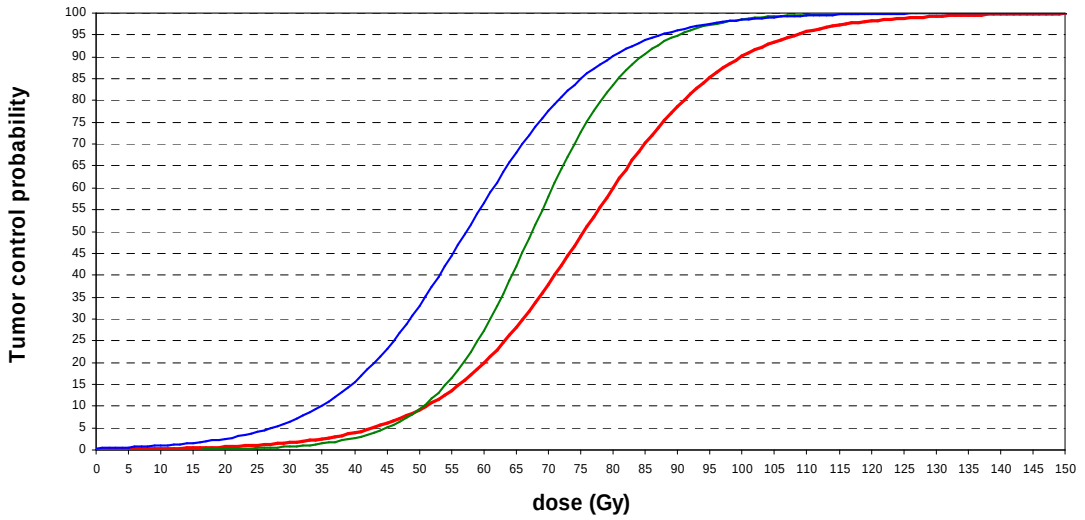
Clinical Issues*

Riccardo Valdagni, MD, PhD[1]; Tiziana Rancati, PhD[1]; and Claudio Fiorino, PhD[2]

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

Tumor Control and genetic variability

$$TCP = \frac{1}{K} \cdot \sum_{i=1}^{K} \prod_{j=1}^{M} \exp\left[-\rho_j V_t f_j \cdot \exp\left(-\alpha_i D_j \right) \right]$$



Tumor Control and genetic variability

First step was to assess intrinsic radiosensitivity, repopulating ability and hypoxia, three factors that were known to influence treatment outcome

→Studies on p53, apoptosis, DNA breaks, PTEN

These studies provided a lot of proof-of-principle data, but did not evolve in useful tools for clinical routine

→ tumor biology is very complex
measurement of a single parameter is unlikely to be a useful predictor

Use of proteomics?

DEFINITIONS:

Proteomics is the large-scale study of proteins, particularly their structures and functions.

Proteins are vital parts of living organisms, as they are the main components of the physiological metabolic pathways of cells.

The ensemble of various technologies necessary to identify and ascribe biology to proteins in vivo" (DM&D proteomics report).

Use of proteomics?

Investigate proteins that may mediate differences in response to radiotherapy:

→ Allal et al. (Proteomics 2004), identification of a small list of proteins measured in biopsy before RT and related to RT response (radioresistant)

Assess the proteomic profile of a tumor to predict present state of the disease, prognosis and response to specific therapies:

→ Yanagisawa et al. (Lancet 2003), protein mapping of 42 lung tumors, with ability to classify cancer histologies and nodal involvement with 85% accuracy, and distinguish patients with good and poor prognosis.

- development of robust and accurate prediction techniques for RT
- such techniques will also give insights into causes of failure
- leading to the design of more effective intervention in the future

… LAST MESSAGE

- Still in the stone-age!
- No genetic TCP-NTCP model is available for routine use in the clinic
- The great achievement of the recent years is the awareness that in this field a wide multidisplinary approach is needed in order to study all aspects involved in the prediction of the response to RT