Congresso Inter-regionale
AIRO Lombardia e AIRO Piemonte-Liguria-Valle d'Aosta

L'innovazione tecnologica in radioterapia:
nuovi standard clinici e problematiche gestionali

Innovazioni tecnologiche e declinazioni cliniche: dove puntare le nostre risorse? Il caso del cancro della prostata

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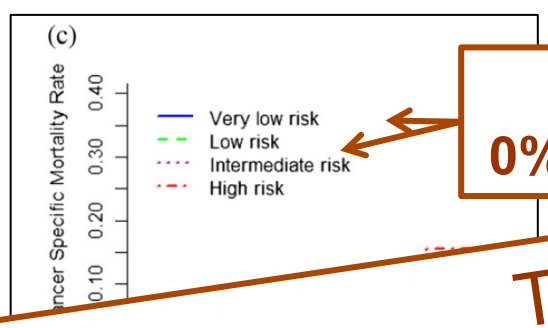
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

PROSTATE CANCER PROGRAM

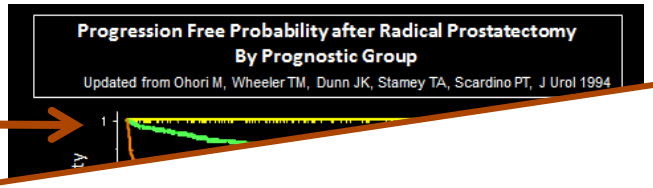
Outline

1. Investire nel cercare ridurre o eliminare le aree di "*incertezza clinica*"
2. Investire nel cercare di migliorare e ottimizzare le distribuzioni di dose
3. Investire nel cercare di ridurre o eliminare le *"incertezze legate al paziente"*
4. Investire nel cercare di migliorare le modalità di raccolta e di analisi delle conoscenze acquisite

1. Invest in reducing clinical uncertainties



PCM:
0% at 10yr



Take Home Message

In very low and in most, if not all, low risk prostate cancer, Radiation Dose should be

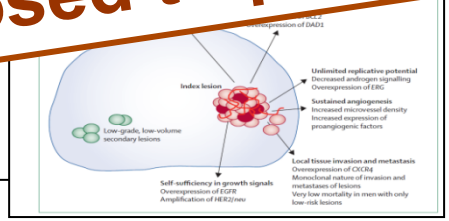
Zero Gy

and Active Surveillance proposed to patients

...ncers bear the

...Manit Arya, Alex Freeman, Mark Emberton

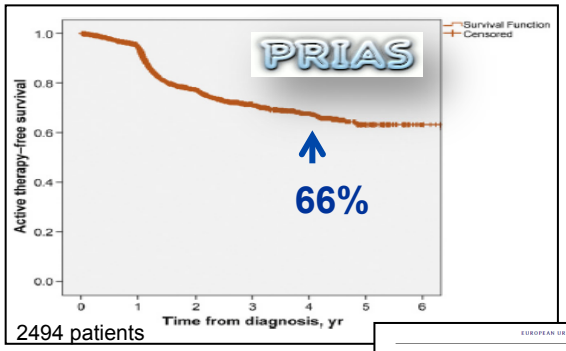
Lancet Oncology 2012

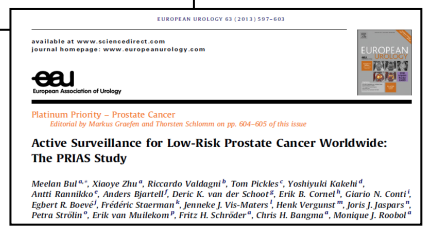


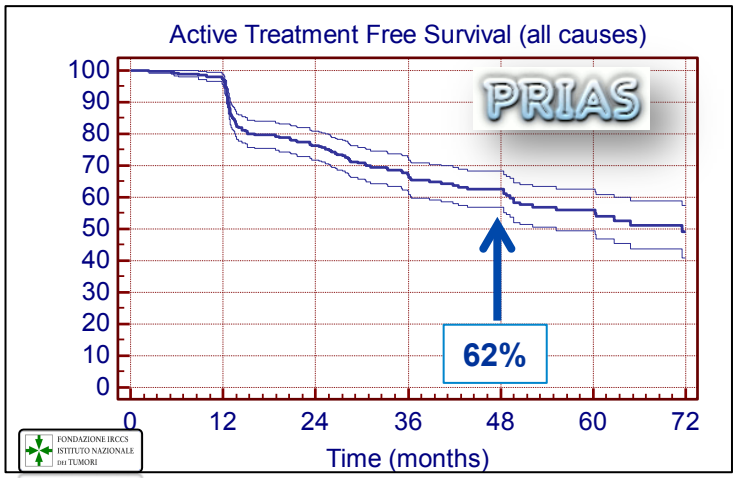
*Is it really a **certainty***
that we should deliver Radiation to all patients with very low and low risk prostate cancer?

1. Invest in reducing clinical uncertainties

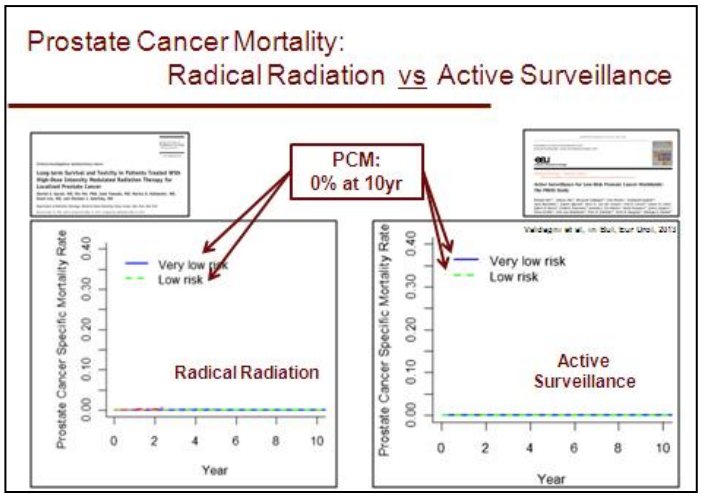
Where do we put our resources?
Active Surveillance and research of biomarkers to identify indolent/aggressive tumours?







Valdagni et al, nov 2014, unpublished



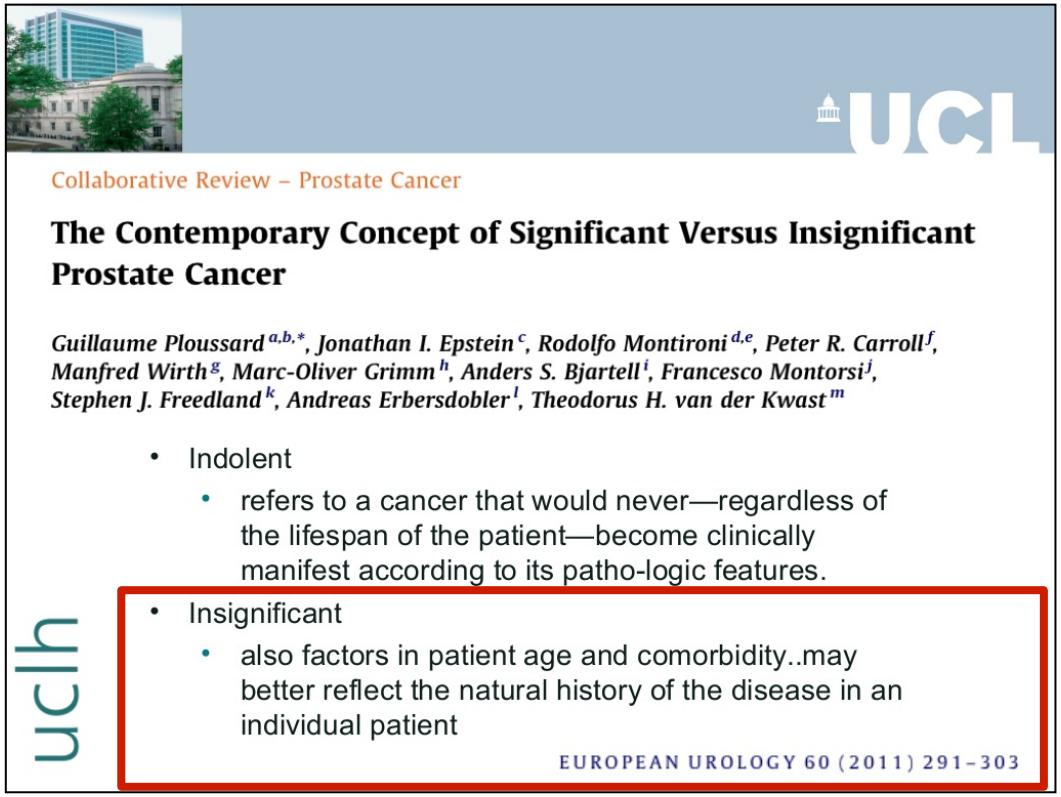
Better selection of AS candidates avoiding early drop out

1.A. Clinical Appropriateness of Radiation Therapy: Which patients should be treated?

Zero Gy: going even further …
Prostate Cancer ***Patients*** **and Life Expectancy** ?

Redefining insignificant cancer?

Grade and Volume,
+
Patient's Factors



C. Moore, 2° ESO Inside Track Conference, Amsterdam Febr. 2014

1. Invest in reducing clinical uncertainties

"Men with the highest Charlson scores should consider conservative management of low-risk and intermediate-risk tumors (selected HR), given their exceedingly high risk of death from other causes and low risk of prostate cancer."

*Is it really a **certainty** that we should treat all patients with low, intermediate and high risk prostate cancer? Or ...*

Take Home Message

Patients with **highest Charlson score** should not be considered for radical treatment but for **conservative management**

...consider conservative management of low-risk and intermediate-risk tumors, given their exceedingly high risk of death from other causes and low risk of prostate cancer mortality. *Cancer* **2011;117:4642–50.** © *2011 American Cancer Society.*

KEYWORDS: prostatic neoplasms, comorbidity, outcome assessment, prostate.

The first decision facing a man with a new diagnosis of clinically localized prostate cancer is whether to pursue aggressive treatment. Level I evidence shows that significant survival benefits do not develop until 8 to 10 years after treatment.[1] Because definitive local therapy risks morbidities that may significantly affect quality of life,[2-5] it is widely accepted that most men whose comorbidity gives them a low probability of long-term survival should not be aggressively treated. As such, the American Urological Association and National Comprehensive Cancer Network treatment guidelines recommend using life expectancy to help triage patients with clinically localized disease between aggressive and nonaggressive management.[6,7]

Despite the recognized role of life expectancy in medical decision making for men with prostate cancer, the determination of who is too ill to benefit from aggressive treatment remains ill-defined. This is largely because of the absence of a widely accepted method of assessing prognosis that incorporates an individual's health status. The American Urological Association suggests that clinicians use life tables to estimate prognosis, but because life tables are population-based, they fail to account for the individual's health; they overestimate 10-year life expectancy by as much as 22% in men undergoing prostatectomy.[8] The National Comprehensive Cancer Network guidelines recommend adjusting life table estimates for the individual by adding or subtracting 50% of projected years based on whether the patient is in the highest or lowest quartile of health. Yet the National Comprehensive Cancer Network guidelines offer no method for categorizing patients as such.[7]

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See editorial on pages 4576-8, this issue.

DOI: 10.1002/cncr.26104, **Received:** August 19, 2010; **Revised:** November 26, 2010; **Accepted:** December 6, 2010, **Published online** April 8, 2011 in Wiley Online Library (wileyonlinelibrary.com)

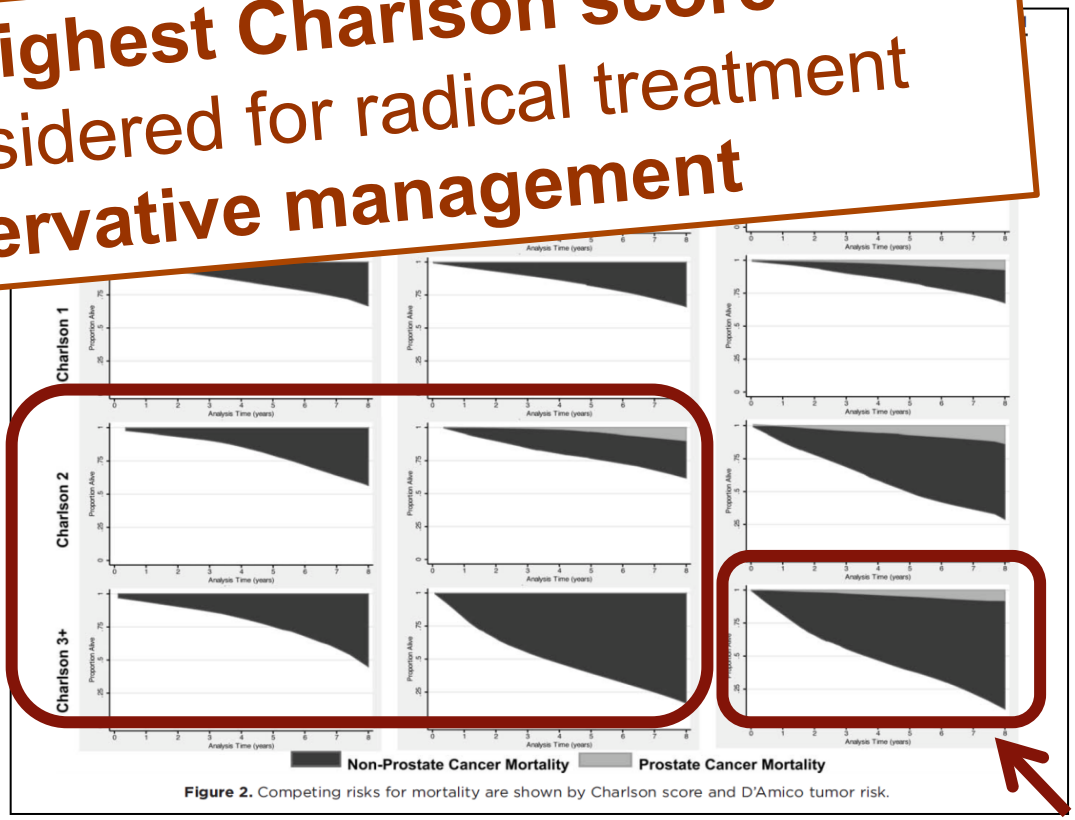


Figure 2. Competing risks for mortality are shown by Charlson score and D'Amico tumor risk.

1. Invest in reducing clinical uncertainties

Once an indication for radiation therapy is defined:

1.B Selecting (and identifying) the appropriate targets: (e.g. *whole pelvic RT: Yes? ↔ No?)*

1.C Selecting total dose (and fractionation) as a function of risk class (e.g. overcoming the practice of *equally escalated dose for all risk classes; over-dose?)*

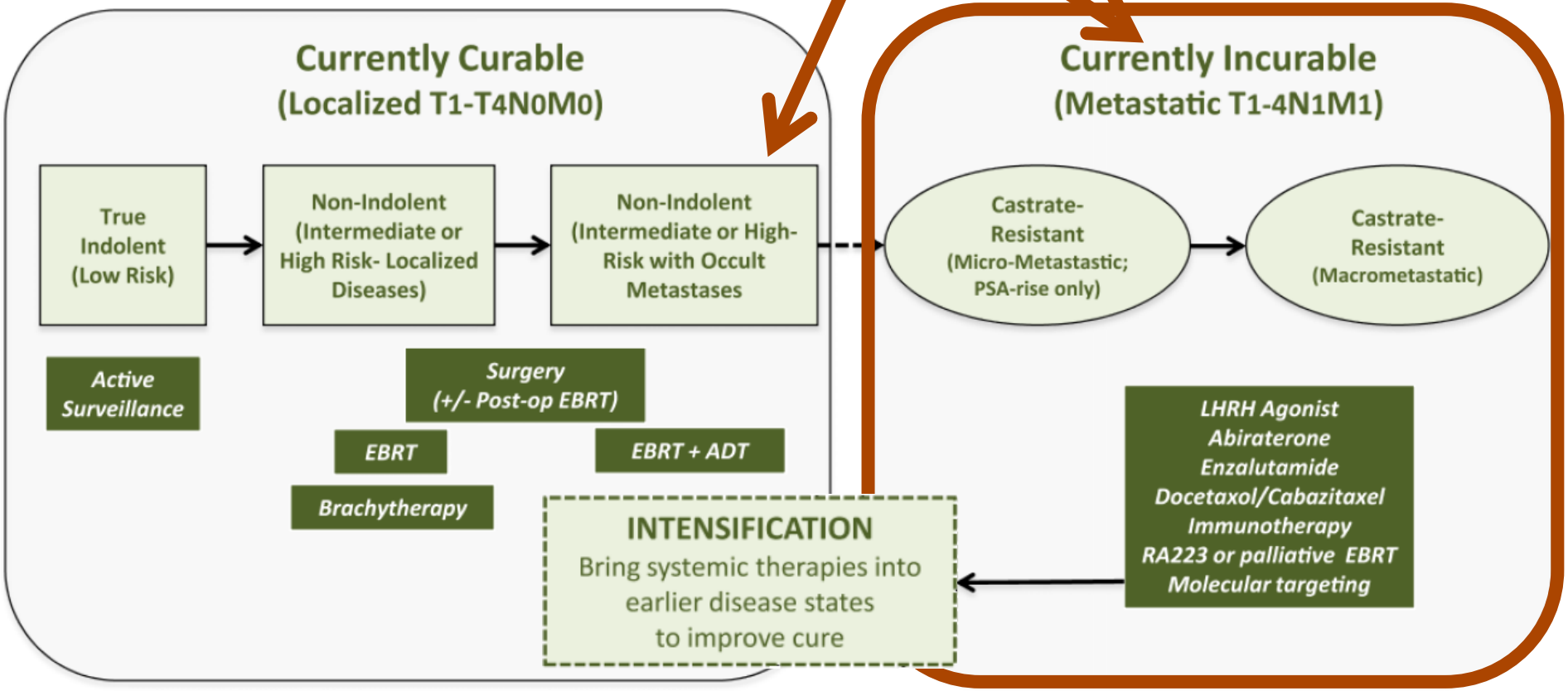
Clinicians often disregard these factors as potential sources of clinical uncertainty and assume that (limited investments):

- ✓all tumors involve the *whole* prostate in the same way
- ✓that prostate cancer cells are equally and uniformly radiosensitive
- ✓and that all pts need the same total dose

1. Invest in reducing clinical uncertainties

1.D Invest in prostate cancer biology, improving tumor characterization thus optimizing prescribed doses (dose levels, dose targets) and adjuvant therapies

Bristow, Br J Radiol 2014

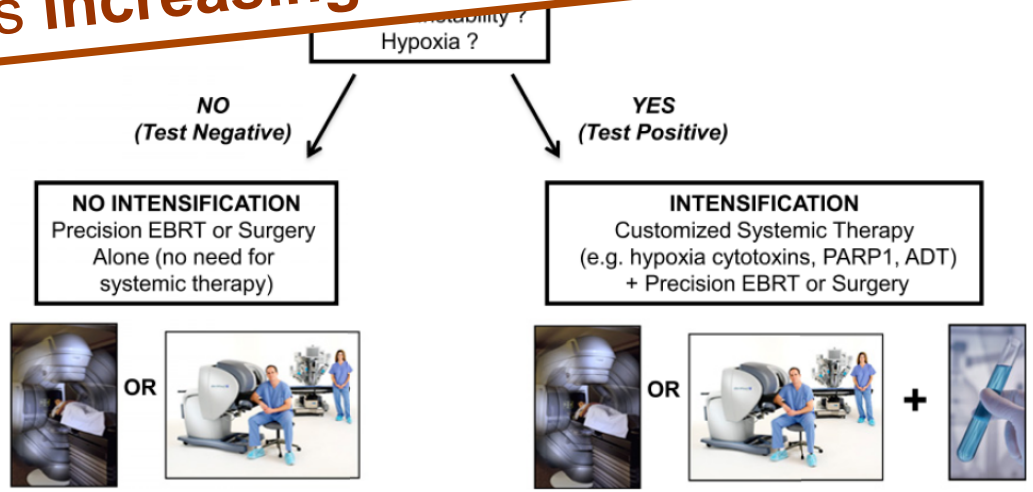


1. Invest in reducing clinical uncertainties

1.D improve treatment individualization: combine pre-treatment genomic tests (DNA or RNA indices) and/or assays for cancer metabolism to define pt-specific CaP characteristics and select pts to be treated with intensified prot

Take Home Message

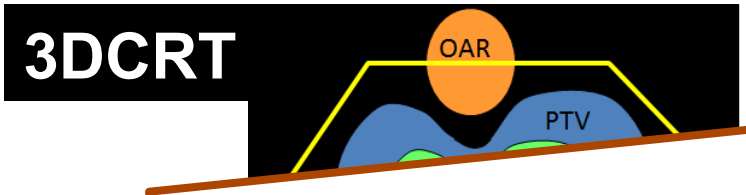
Invest (economic) resources in better identifying tumor targets, tumor cell radiosensitivity, cancer metabolism, agressiveness and proliferation capability, thus **increasing treatment personalization**

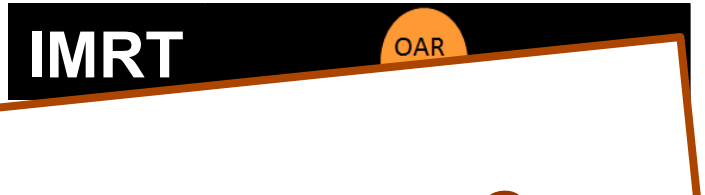


2. Invest in improving dose distributions

2. Invest in new technologies

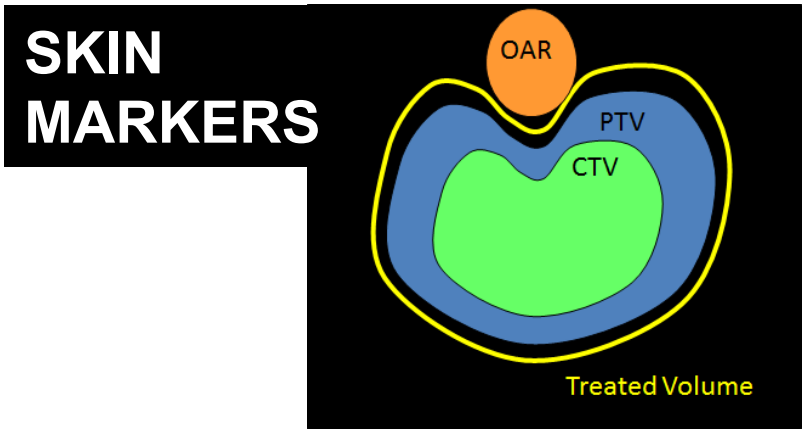
A. IMRT → improving dose conformity

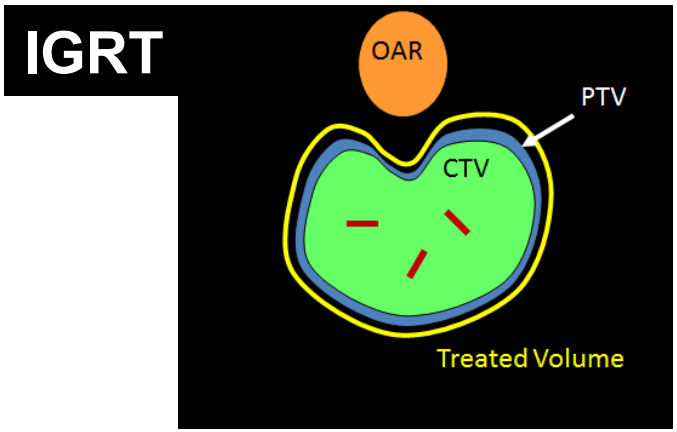




Which is the clinical impact?

B. IGRT → reducing PTV-CTV margins





2. Invest in improving dose distributions

Better shaping of dose distributions
plus reduced PTV

↓

Reduced normal tissue volumes in the high-dose region and improved the target localization

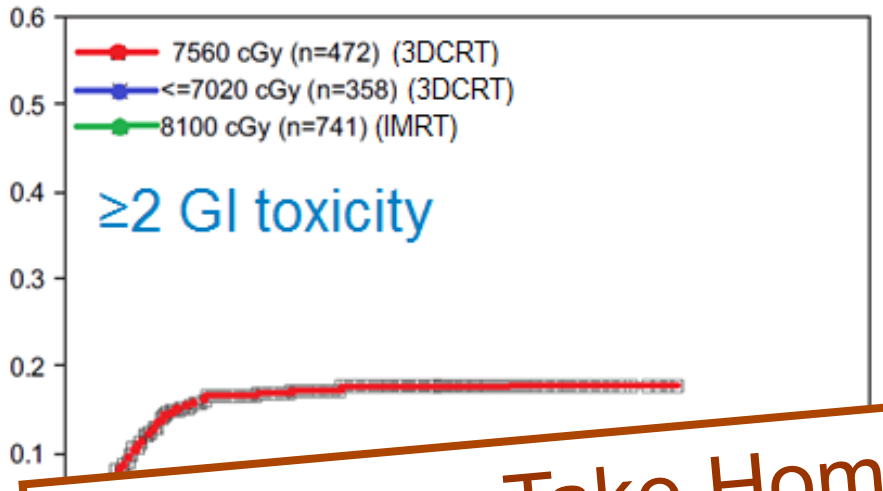
↓

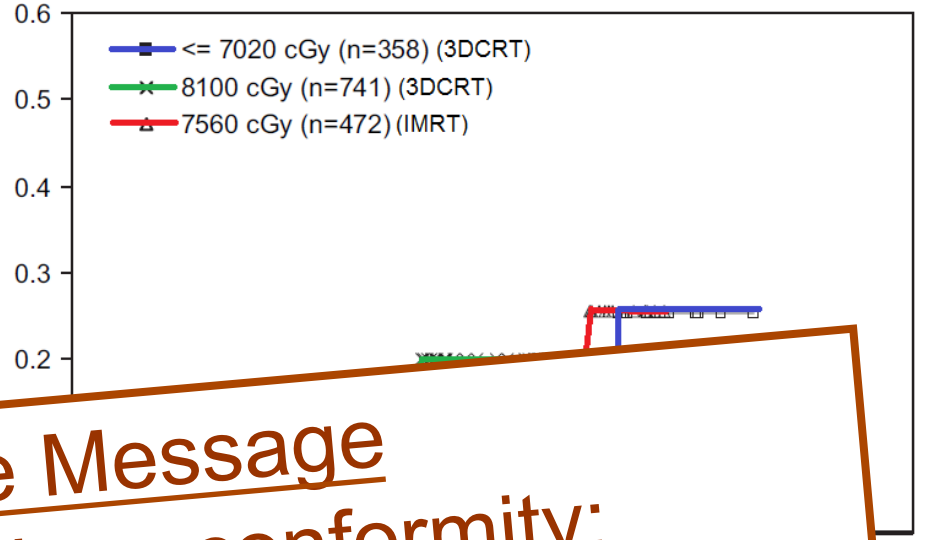
Are also toxicity rates reduced?

WARNING!
Technology is often self-referential ...

Improved Dosimetry = Improved Clinical Outcome?

2. Invest in improving dose distributions: IMRT





Take Home Message

IMRT improved dose conformity:

GI toxicities reduced

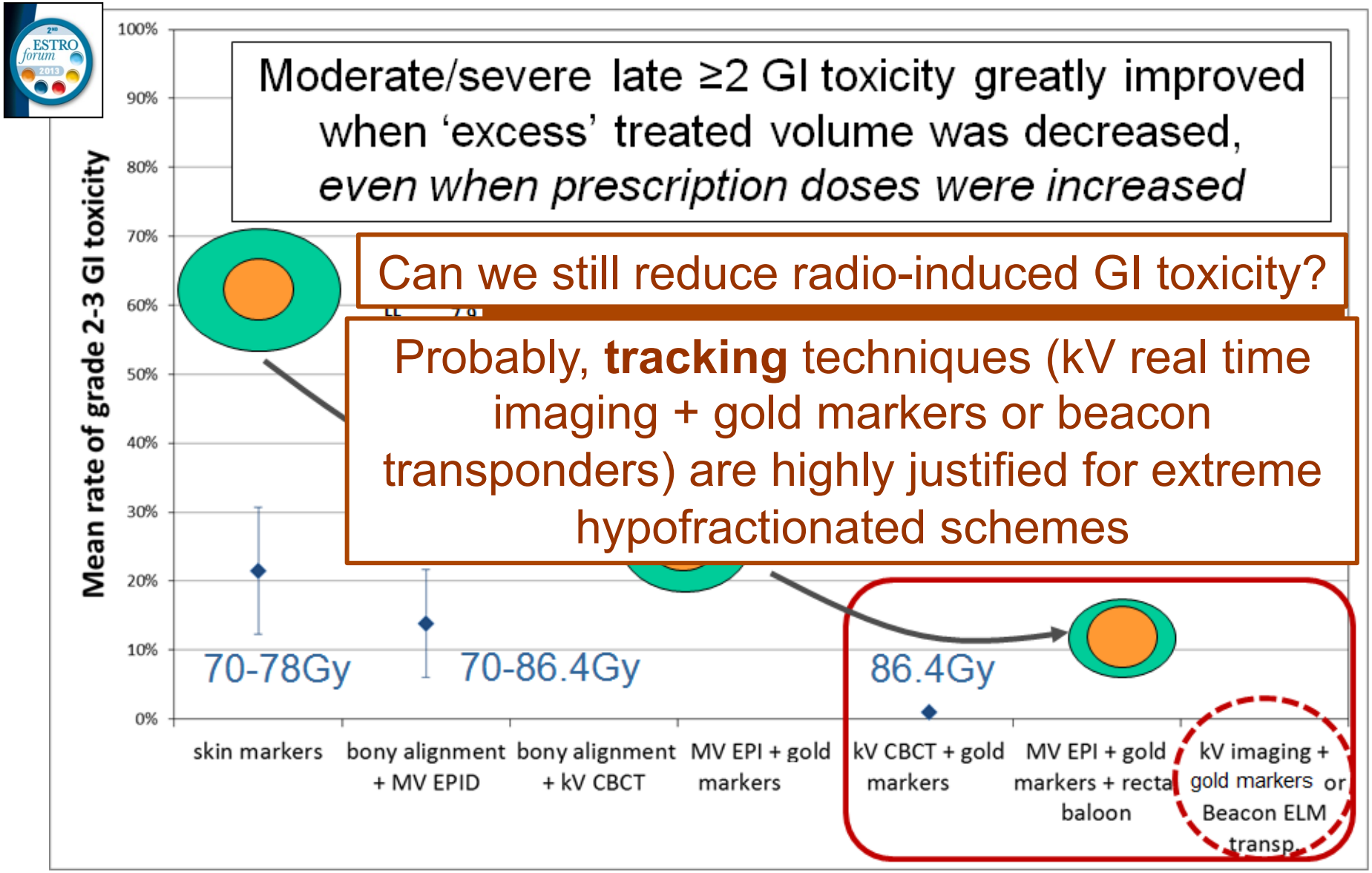
failing in reducing GU toxicity

is better than with 3DCRT (≈7 fold)

with IMRT is worse than with 3DCRT

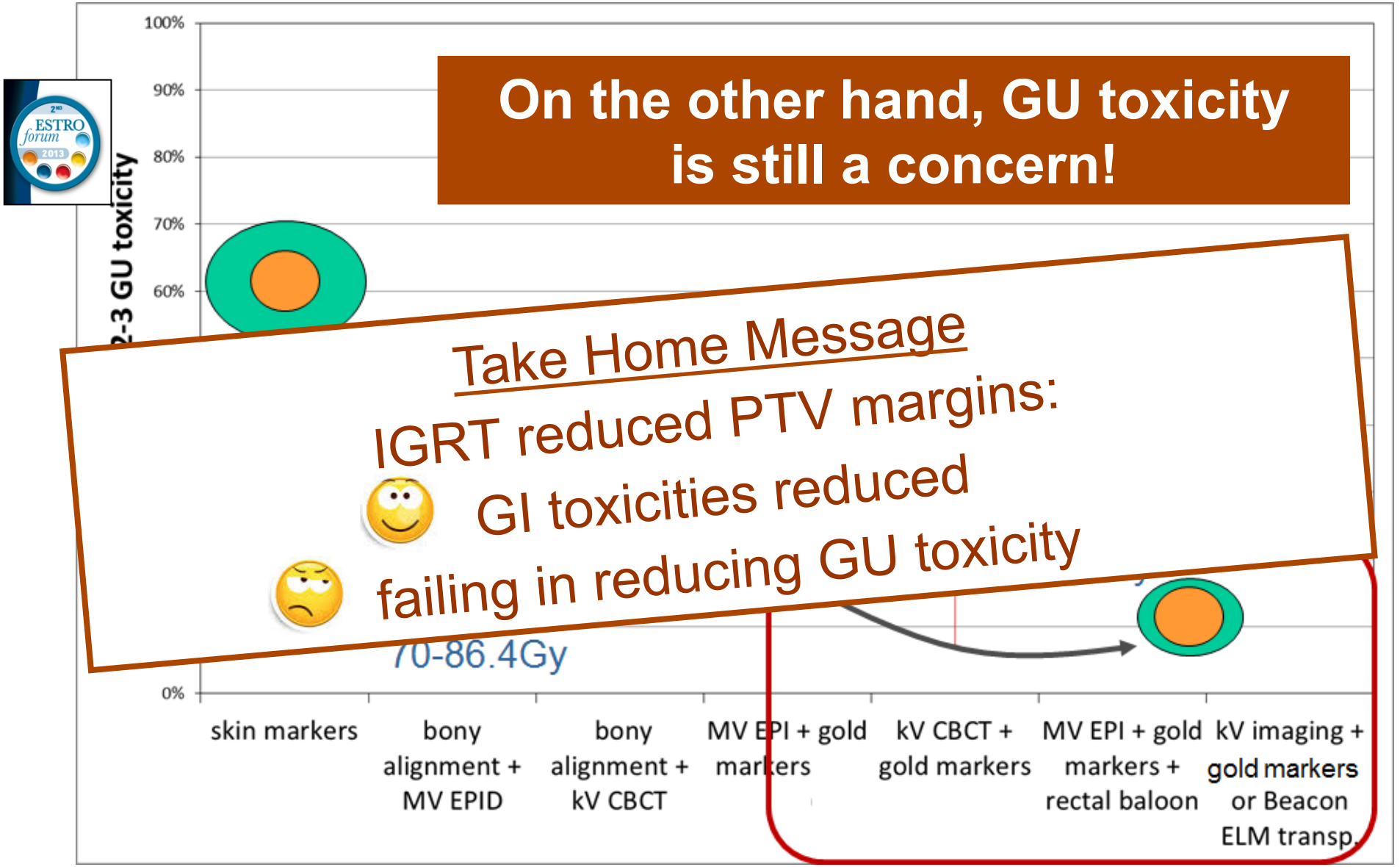
(Valdagni & Rancati, *Nature Review in Urology, 2013)*

2. Invest in improving dose distributions: IGRT



R. Valdagni, ESTRO 2013

2. Invest in improving dose distributions: IGRT



R. Valdagni, ESTRO 2013

2. Invest in improving dose distributions

Do we need to invest further
in “extreme” new technologies?
In which cases?

… some considerations on prostate motion

What is the impact of prostate motion in the definition of CTV → PTV margins?

Analysis of intrafraction motion on 10 patients undergoing radical radiotherapy after transrectal implantation of Beacon transponders

↓

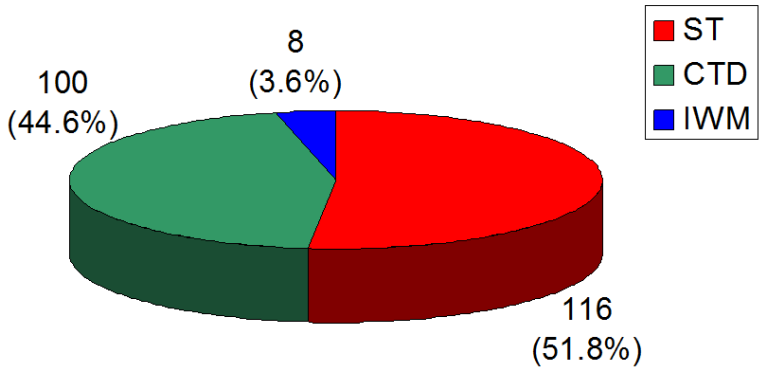
Analysis of transponder signals recorded over:

224 patient sessions

Carrara, Giandini, Pignoli, unpublished, 2014

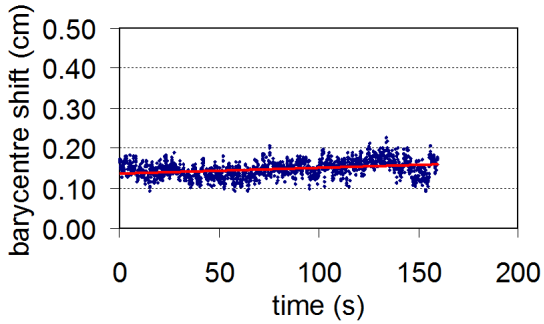
Evaluation of prostate motions

224 RT fractions were categorized in 3 different systematic motion patterns:

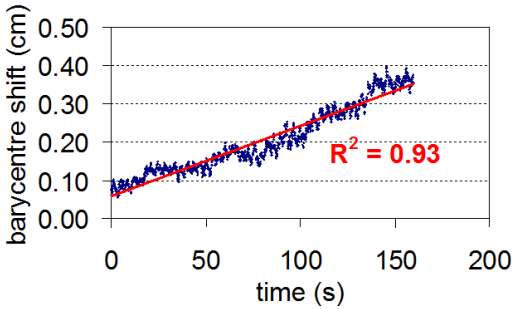


Occurrence frequencies of the different motion patterns

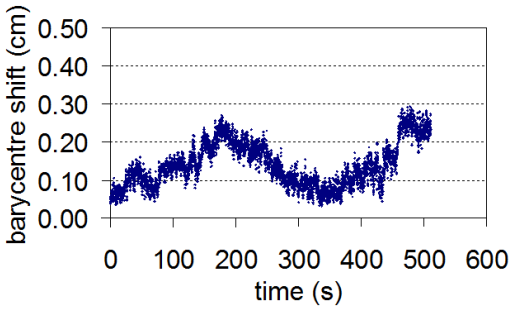
stable target at baseline (ST)



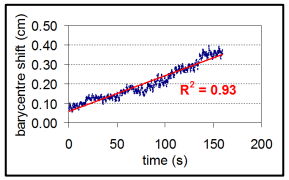
continuous target drift (CTD)



irregular wave motion (IWM)



Modeling continuous target drifts



Linear regression of the drift motion of the prostate barycentre

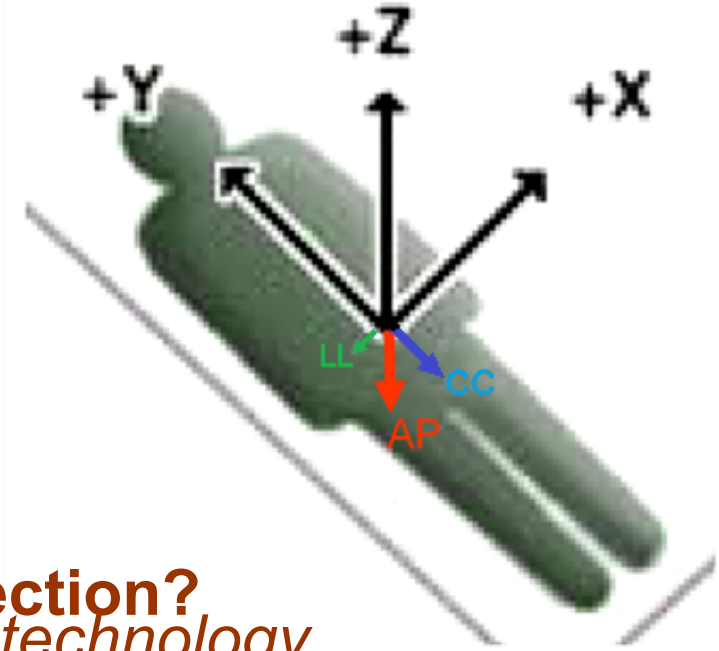
$$D(t) = v_D * t + p$$

D(t) →**barycentre position at time t**

v_D →**drift velocity**

p →**starting position for barycentre**

	mean	median
v_D (mm/s)	8 10^{-3}	6.4 10^{-3}
p (mm)	0.93	0.80



Is there a predominant motion direction?

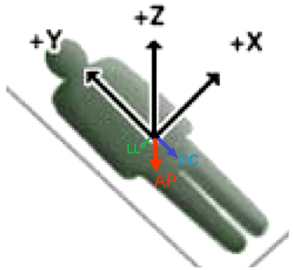
Example: prostate SBRT with VMAT technology

Duration from patient localization to end of treatment: ***6 min***

Prostate moves most times in AP direction, towards the posterior surface of the patient

→ *Mean shift of the prostate from the nominal position:*

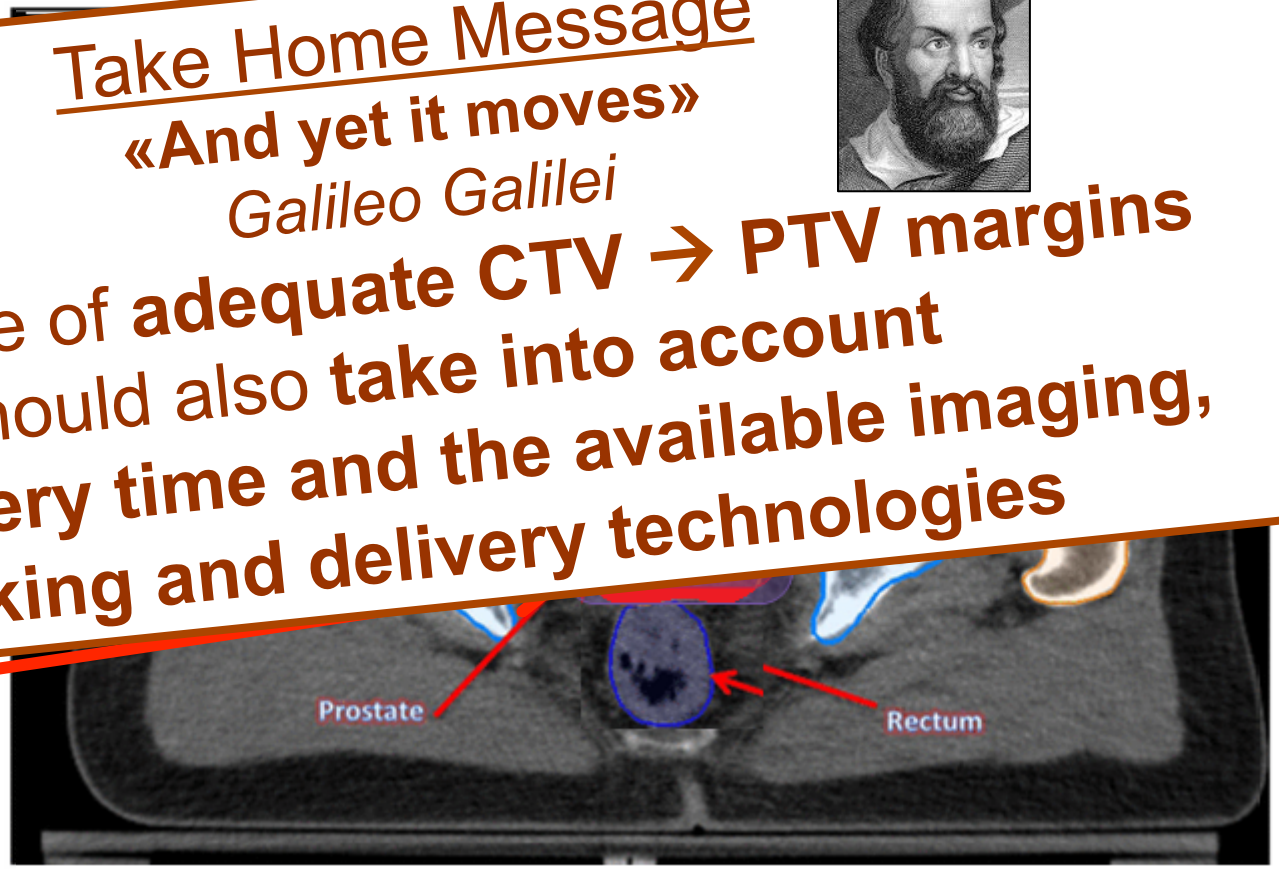
*8 10^{-3} * 360 + 0.93 =* ***3.8 mm*** *(2.1 mm @ 2Gy/fr)*



AP is the predominant motion direction.
What does this involve?

PLANNED DOSE

outside high dose region



Take Home Message

«And yet it moves»

Galileo Galilei

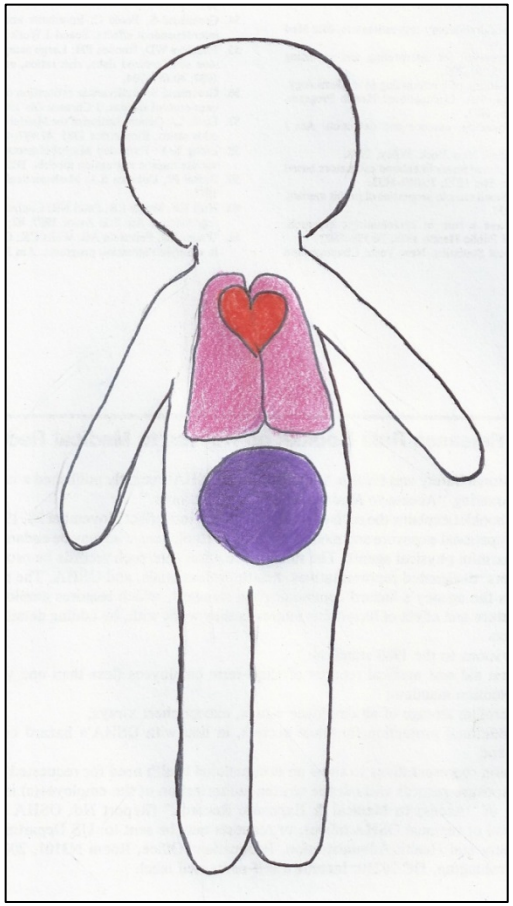
The choice of **adequate CTV → PTV margins**
should also **take into account**
the delivery time and the available imaging,
tracking and delivery technologies

3. Invest in reducing patient-related uncertainties

Gaining deeper knowledge of **clinical/molecular/ genetic risk factors** influencing individual radiosensitivity and acting as dose-response modifiers

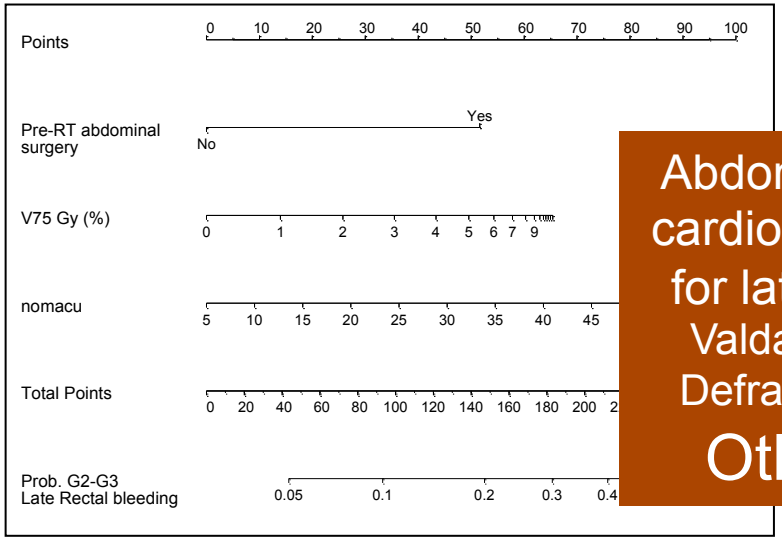
Patient's characteristics acting as dose response modifiers

- ✓ age
- ✓ previous clinical history
- ✓ comorbidities/drugs
- ✓ genetics



3. Invest in reducing patient-related uncertainties

There is growing awareness that pts harboring specific clinical factors have a greater risk of exhibiting GI/GU tox

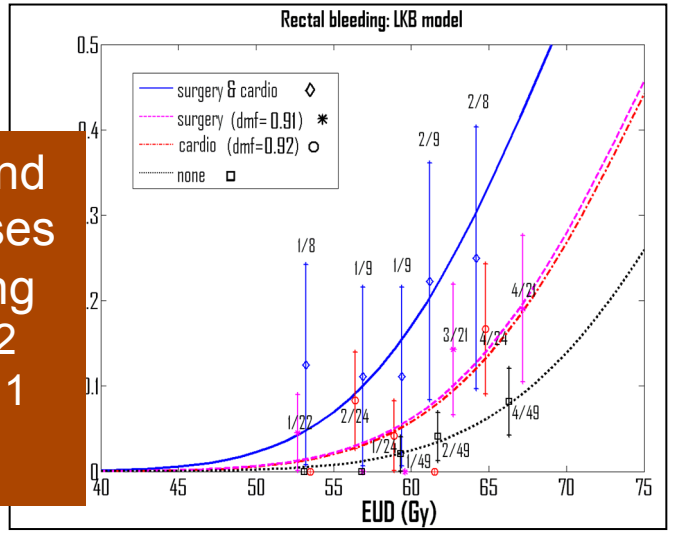


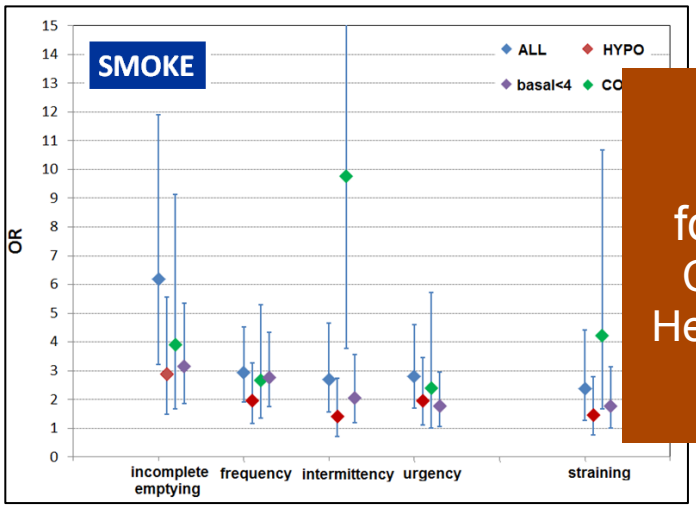
Abdominal surgery and cardiovascular diseases for late rectal bleeding

Valdagni IJROBP 2012

Defraene, IJROBP 2011

Other factors?



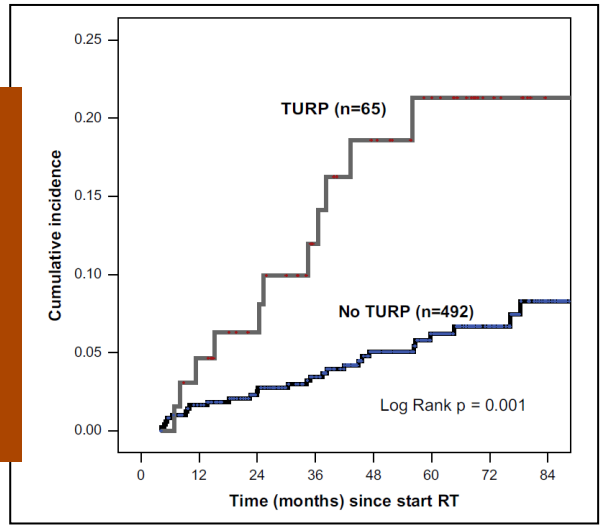


Smoke, TURP, baseline situation for acute urinary toxicity

Cozzarini, R&O submitted

Heemsbergen, IJROBP 2010

Other factors?



3. Invest in reducing patient-related uncertainties

Use of genetic profiles could help in better discriminating patients at high risk of exhibiting toxicity.
Lot of clinical research still to be done!

Take Home Message

Invest in prospective observational trials:

- to develop integrated models of radio-induced toxicity
- to validate present knowledge on clinical/genetic risk factors enhancing patient's radiosensitivity

Be aware of pts needing a more sophisticated treatment

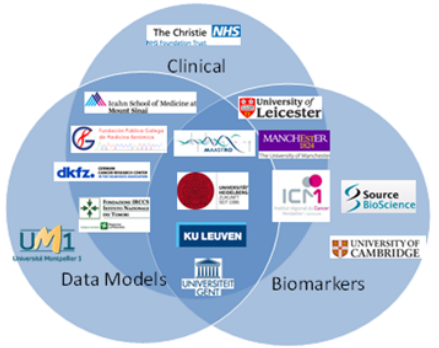
Recent positive studi

REQUITE

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

grant agreement no 601826

1100 Pca prospectively collected pts in 2 yrs (open: April 2014)

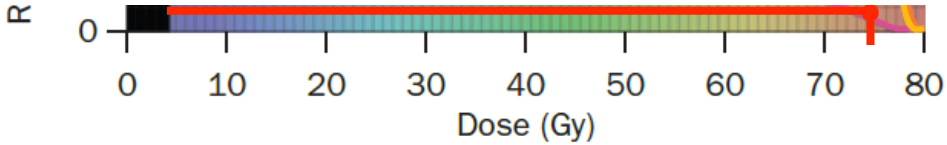


4. Invest in improving the way of accumulating and analysing knowledge

4.A e.g. Improving methods used to analyse dose distributions

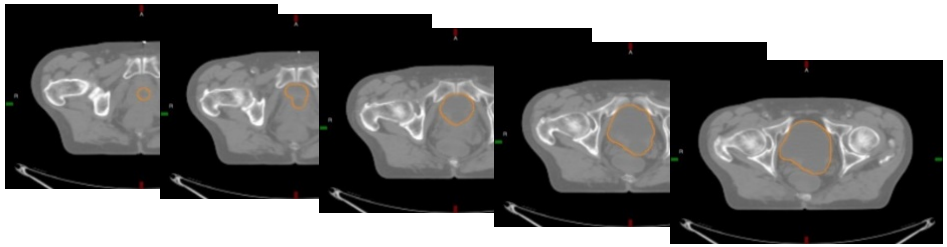
In this moment 3D dose distributions are

- thus trying to overcome the simplification due to DVHs
- re-gaining consideration of the still neglected 3D dose distributions
- going beyond the naïve idea that OaRs are uniformly sensitive to radiation

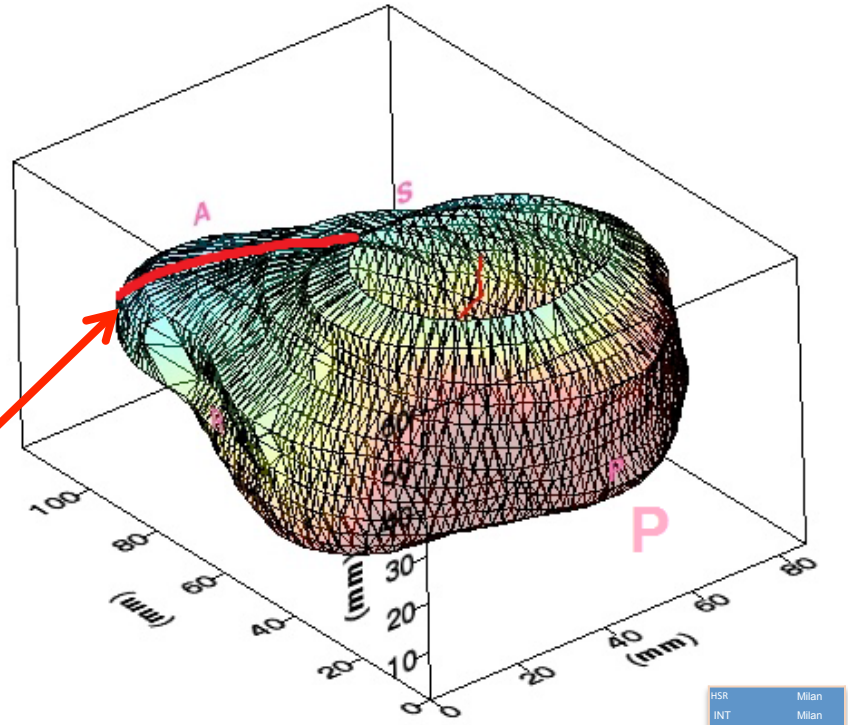


4.A Improving methods used to analyse dose distributions

Example: Correlation between acute GU tox and bladder dose-maps



Use contours of CT slices to reconstruct 3D bladder surface with its dose distribution



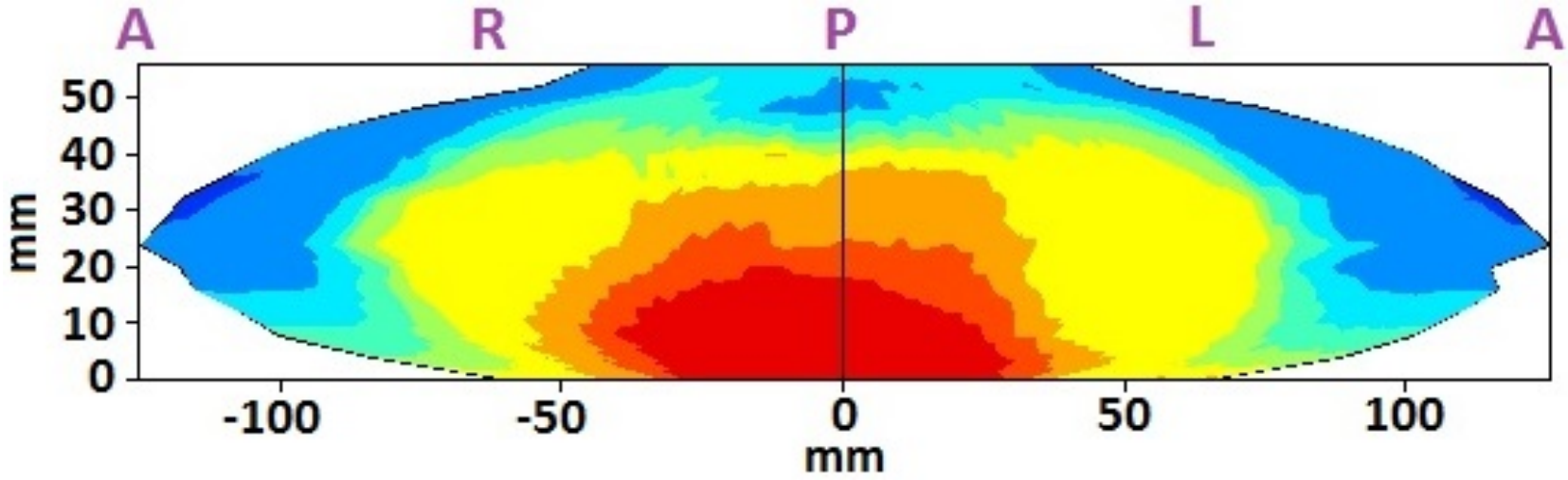
Cut the surface anteriorly

Palorini et al, DUE-01 multicenter trial, *2014*

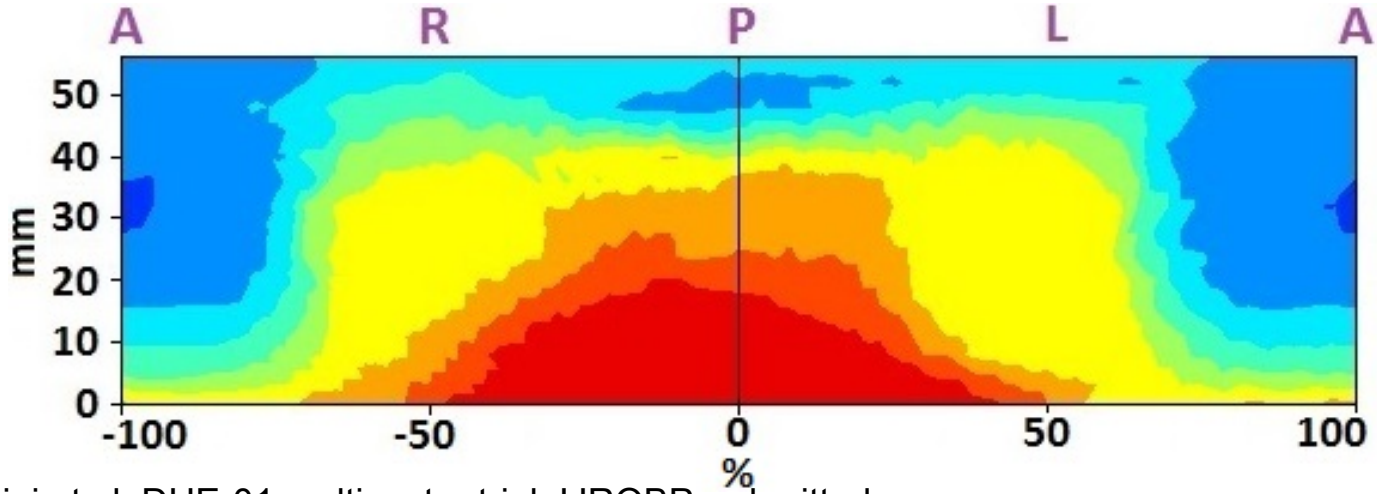
HSR	Milan
INT	Milan
Gavazzeni - Bg	Bergamo
Arcispedale SMN	Reggio E
Ospedale ASL 9	Ivrea
Ospedale Bellaria	Bologna
Ospedale Parini	Aosta
IRCCS	Candiolo

Example: Correlation between acute GU tox and bladder dose-maps

Open the surface: obtain a DOSE SURFACE MAP (DSM)



Normalise the map in the axial direction



HSR	Milan
INT	Milan
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Ospedale Parini	Aosta
IRCCS	Candiolo

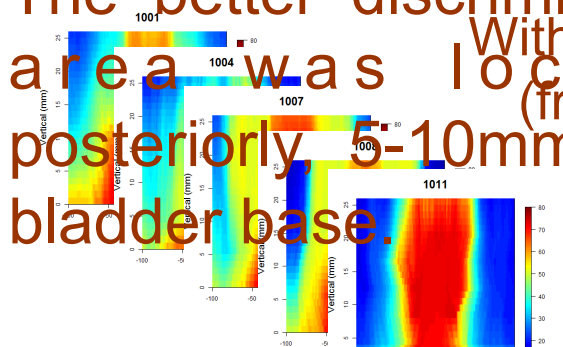
Palorini et al, DUE-01 multicenter trial, IJROBP, submitted

Example: Correlation between acute GU tox and bladder dose-maps

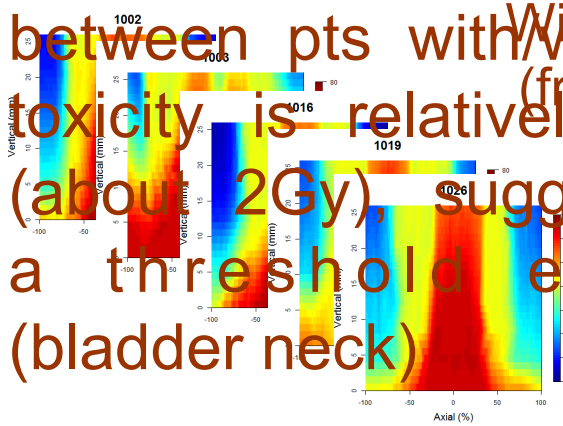
Now DSMs of patients with and without GU toxicities can be compared to highlight **where they are significantly different** i.e. if some regions of the bladder surface are particularly radiosensitive.

The better discriminating area was located posteriorly, 5-10mm from bladder base.

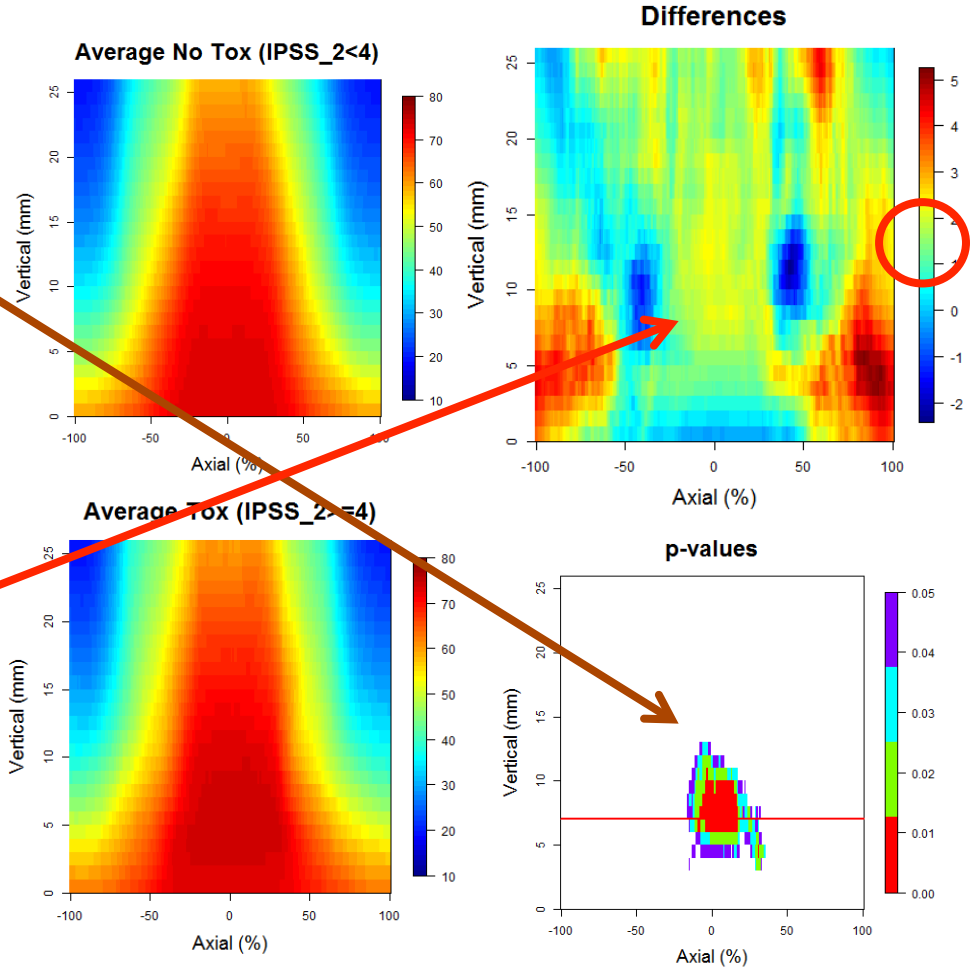
The dose difference between pts with/without toxicity is relatively low (about 2Gy), suggesting a threshold effect (bladder neck).



Without Toxicity (frequency)



With Toxicity (frequency)



Palorini,et al, DUE01 trial, IJROBP submitted

4. Invest in improving the way of accumulating and analysing knowledge

4.B Improving methods used to analyse data and develop user-friendly tools

- Use advanced (non linear) statistical techniques
- Translate statistical results into tools to be used in clinical practice (user friendly tools)

- Multivariable Logistic Analysis
- Artificial Neural Networks
- Fuzzy Logic

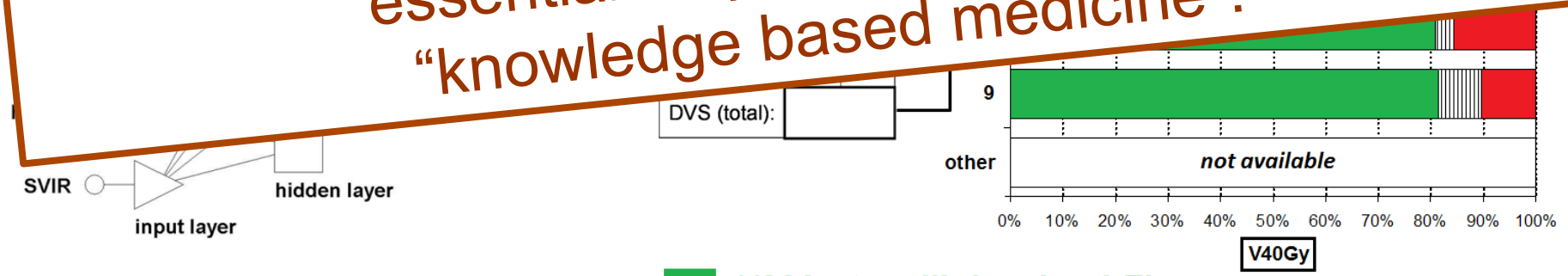
✓ Non user-friendly
✓ Statistician related
✓ Scantly useful in physicians' and patients' decision making

4.B Improving methods used to analyse data and develop user-friendly tools

Example: application of ANN to late fecal incontinence prediction, with development of a graphic tool to made ANN results available to clinicians

Take Home Message

Data analysis, data mining, model development are essential steps in the process of "knowledge based medicine".



1/200 pts will develop LFI

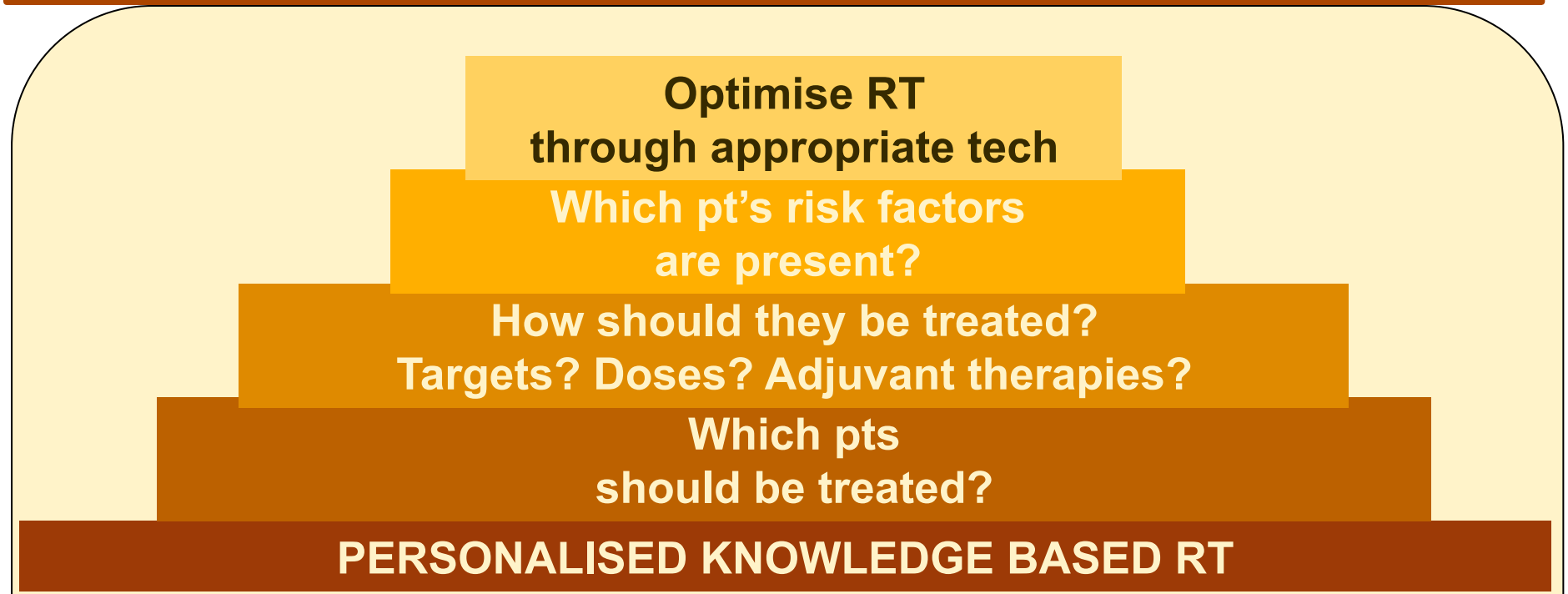
1/10 pts wil develop LFI

GREY REGION=there is not the possibility to accurately predict LFI

Carrara et al, AIRO0201, PRO submitted

SUMMARY

From "technology-based" Radiation Therapy
to
personalised "knowledge-based" Radiation Therapy



Collect and analyse data in efficient way
"consider the present to learn for the future"

"The great thing in the world is not so much where we stand, as in what direction we are moving." O.W. Holmes

Last … but not least…

In every economic balance, we should not forget to take into account **investments for professionals' that have to be trainend to accurately manage our more sophisticated techniques**

"Progress is man's ability to complicate simplicity." Thor-Heyerdahl

Congresso Inter-regionale
AIRO Lombardia e AIRO Piemonte-Liguria-Valle d'Aosta

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“Il controllo della tossicità in radioterapia: l’importanza dell’approccio multiprofessionale”

8 Maggio 2015

Aula Magna

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