



INSTITUT ONCOLÒGIC TEKNON



Hôpitaux
Universitaires
Genève

«Optimizing prostate cancer irradiation: from technology to fractionation»

Raymond Miralbell

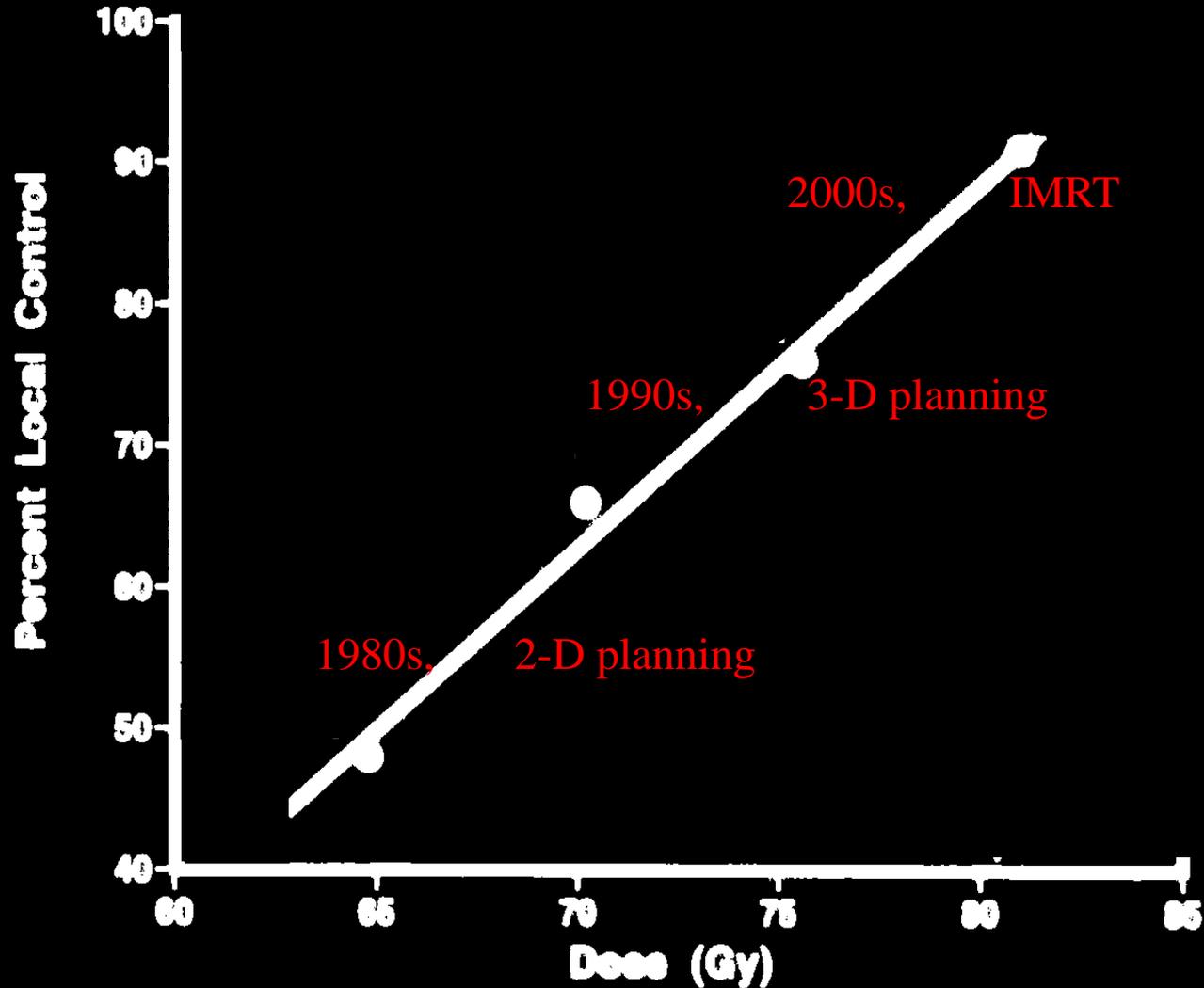
Service de Radio-Oncologie, HUG, Geneva

Institut Oncològic Teknon, Barcelona

“ICTR –PHE 2016”

Centre International de Conferences de Genève, 17.02.2016

Local control vs. dose: the influence of «physics, technology, and imaging»

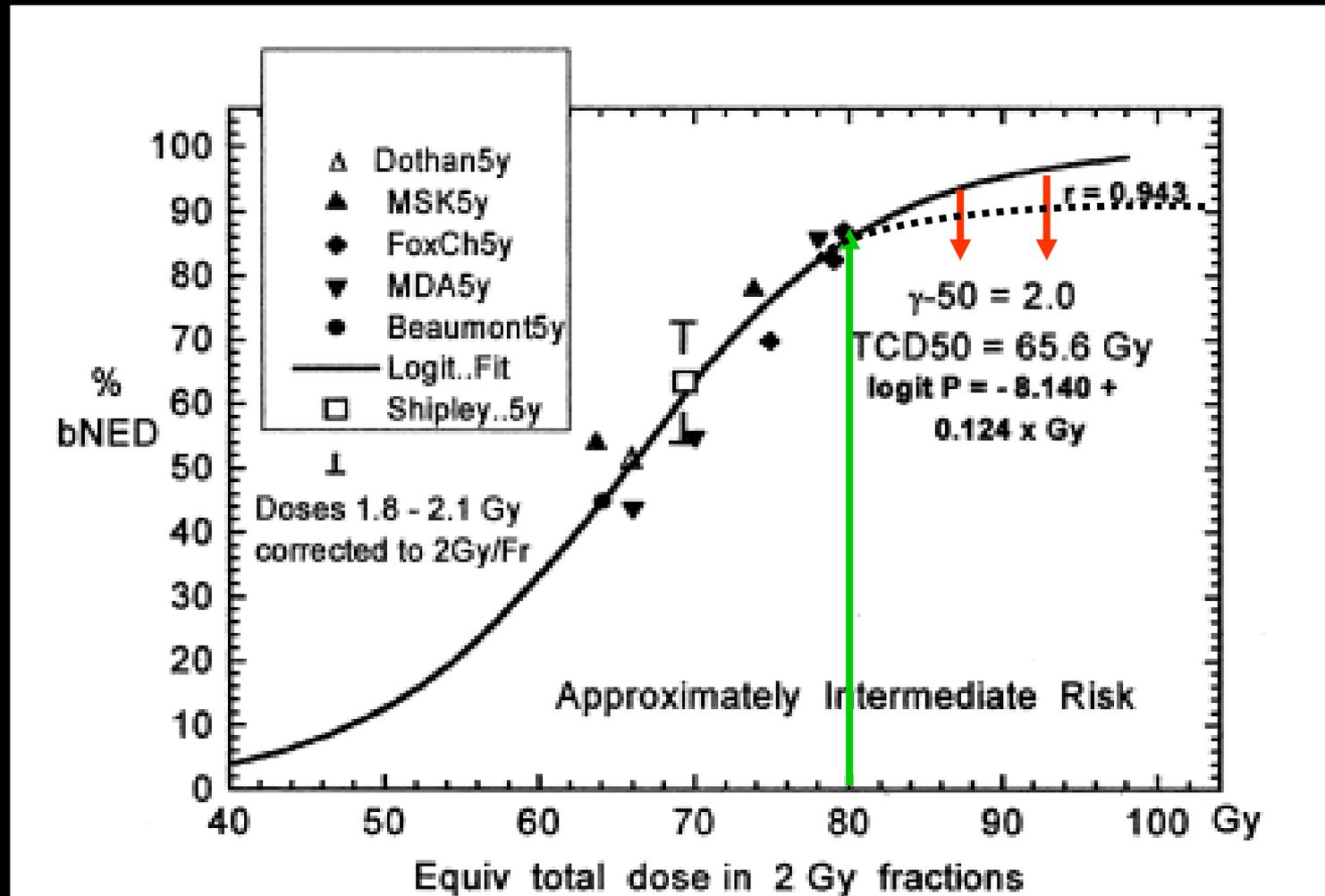


Increasing the dose (up to 80 Gy) with standard 3D-CRT...

Better bDFS figures, but higher
risk of late effects.

Pollack, Zietman, Sathya, Dearnaley, & Al-Mangami

Is there a dose limit for dose escalation?



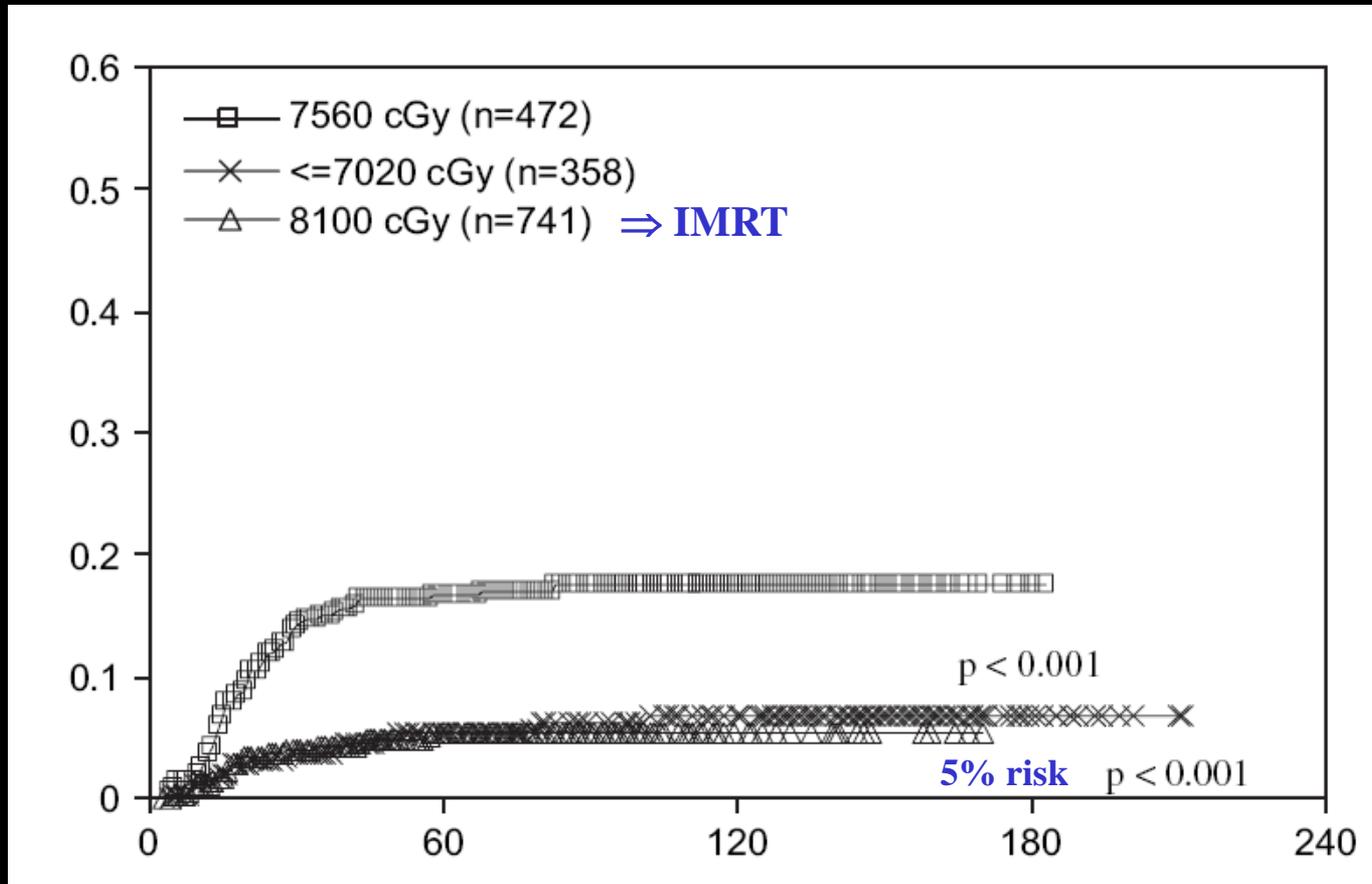
**Dose escalation with intensity
modulated RT (IMRT)?**

INCIDENCE OF LATE RECTAL AND URINARY TOXICITIES AFTER THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY AND INTENSITY-MODULATED RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

MICHAEL J. ZELEFSKY, M.D.,* EMILY J. LEVIN, B.A.,* MARGIE HUNT, M.S.,† YOSHIYA YAMADA, M.D.,* ALISON M. SHIPPY, B.A.,* ANDREW JACKSON, PH.D.,† AND HOWARD I. AMOLS, PH.D.†

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 4, pp. 1124–1129, 2008

Grade ≥ 2 late rectal toxicity in 1575 patients treated with RT

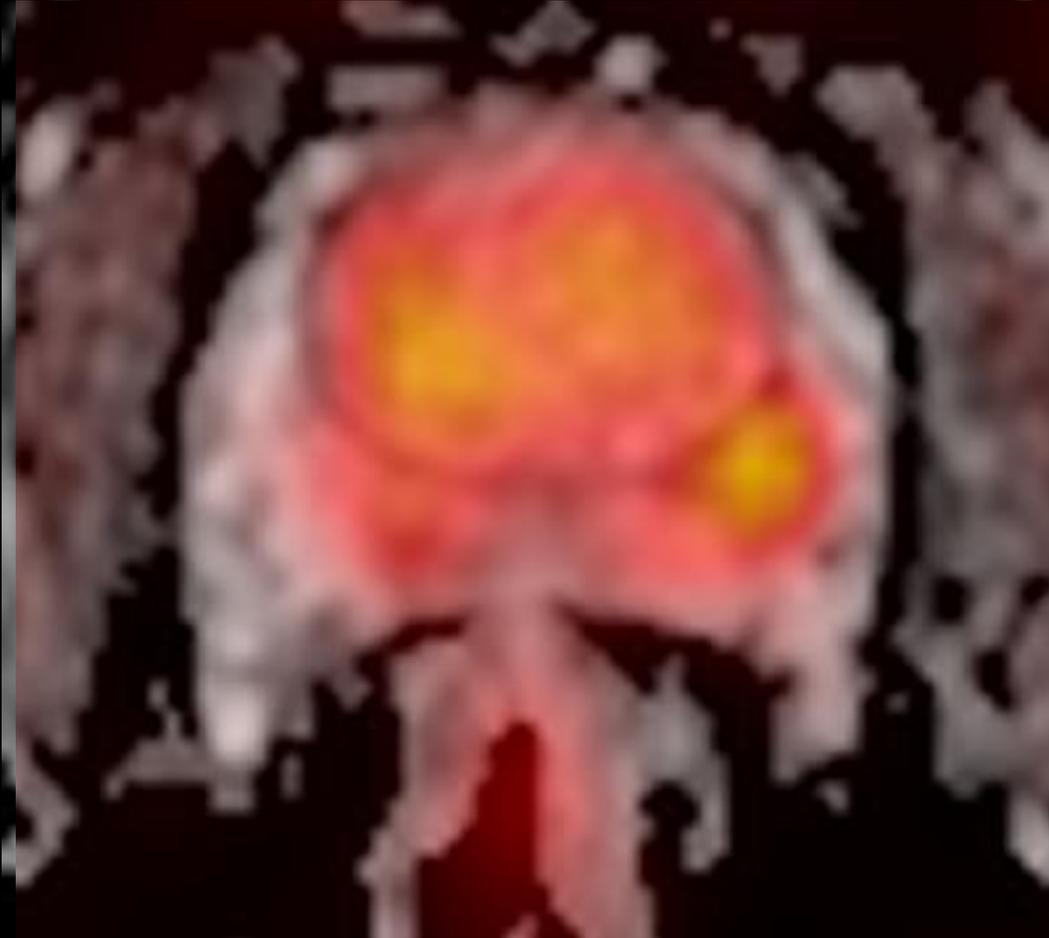


Images helping to plan



Chen et al, Cancer 2000

PET-MRI (multiparametric)



Tools helping to treat right

Image guided radiotherapy (IGRT)

«*view and shoot*» the target with daily corrections of the beam according to the random motion of the internal organs (i.e. «*catch of the day*»)

**Treatment set-up and organ
motion uncertainties:
endorectal balloons**

QLRAD[®] - endorectal balloon

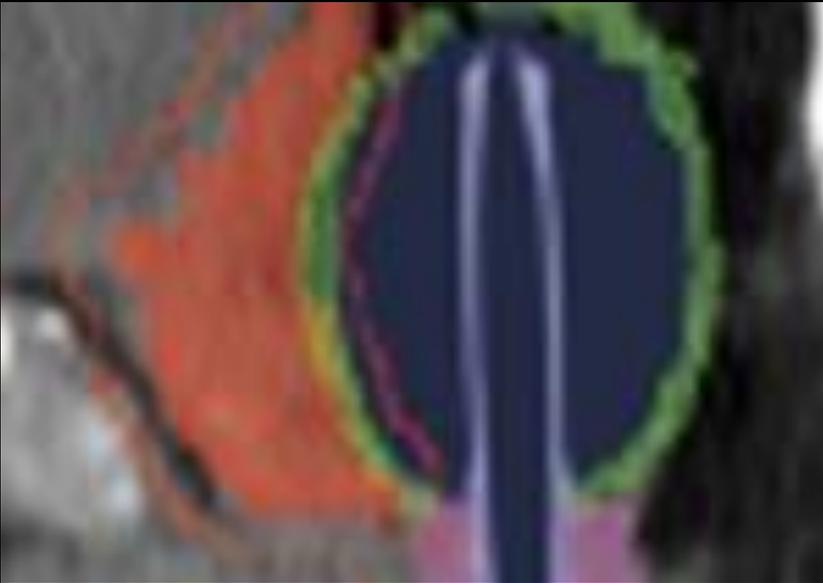


Sparing the Rectal Wall and Anal Wall during External Beam Radiation (3D-CRT and IMRT) of the Pelvic Region ***



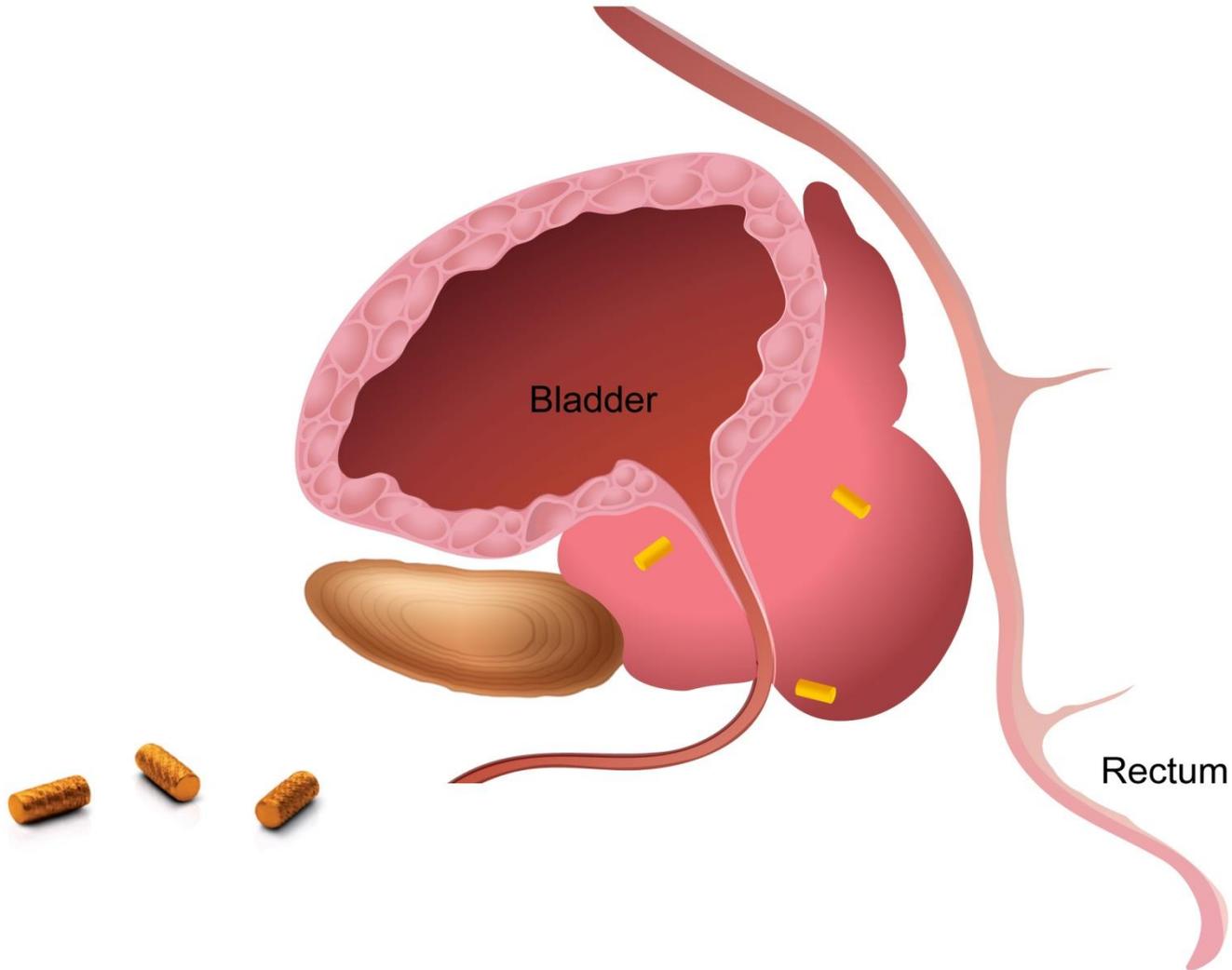
100 cc inflated balloon

Endorectal balloon (QLRAD[®])



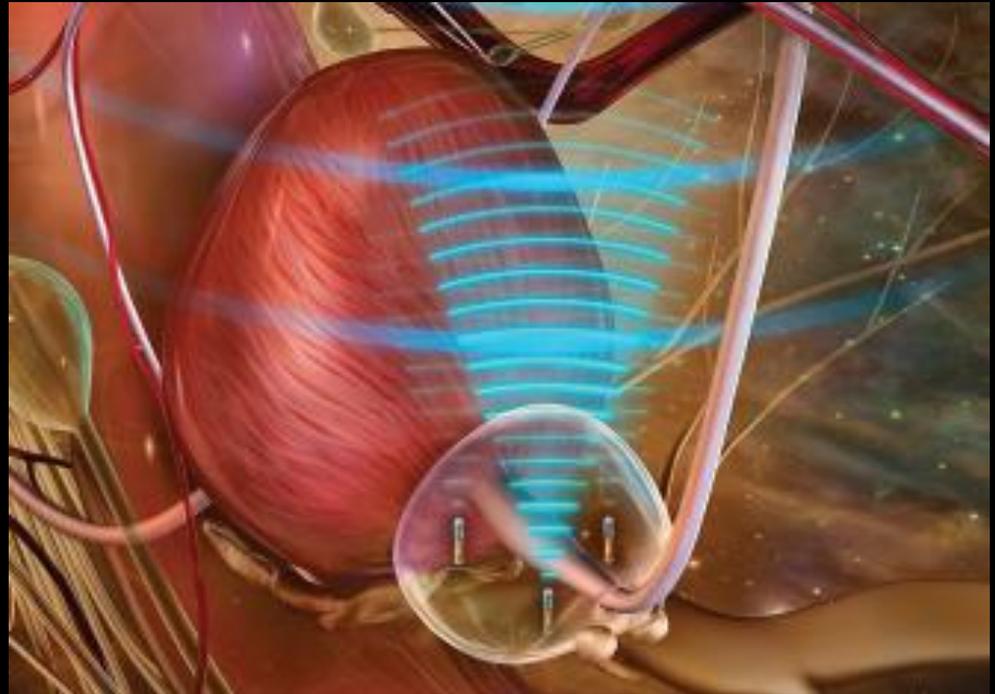
**Treatment set-up and organ
motion uncertainties:
fiducial markers**

Image guided radiotherapy (IGRT)



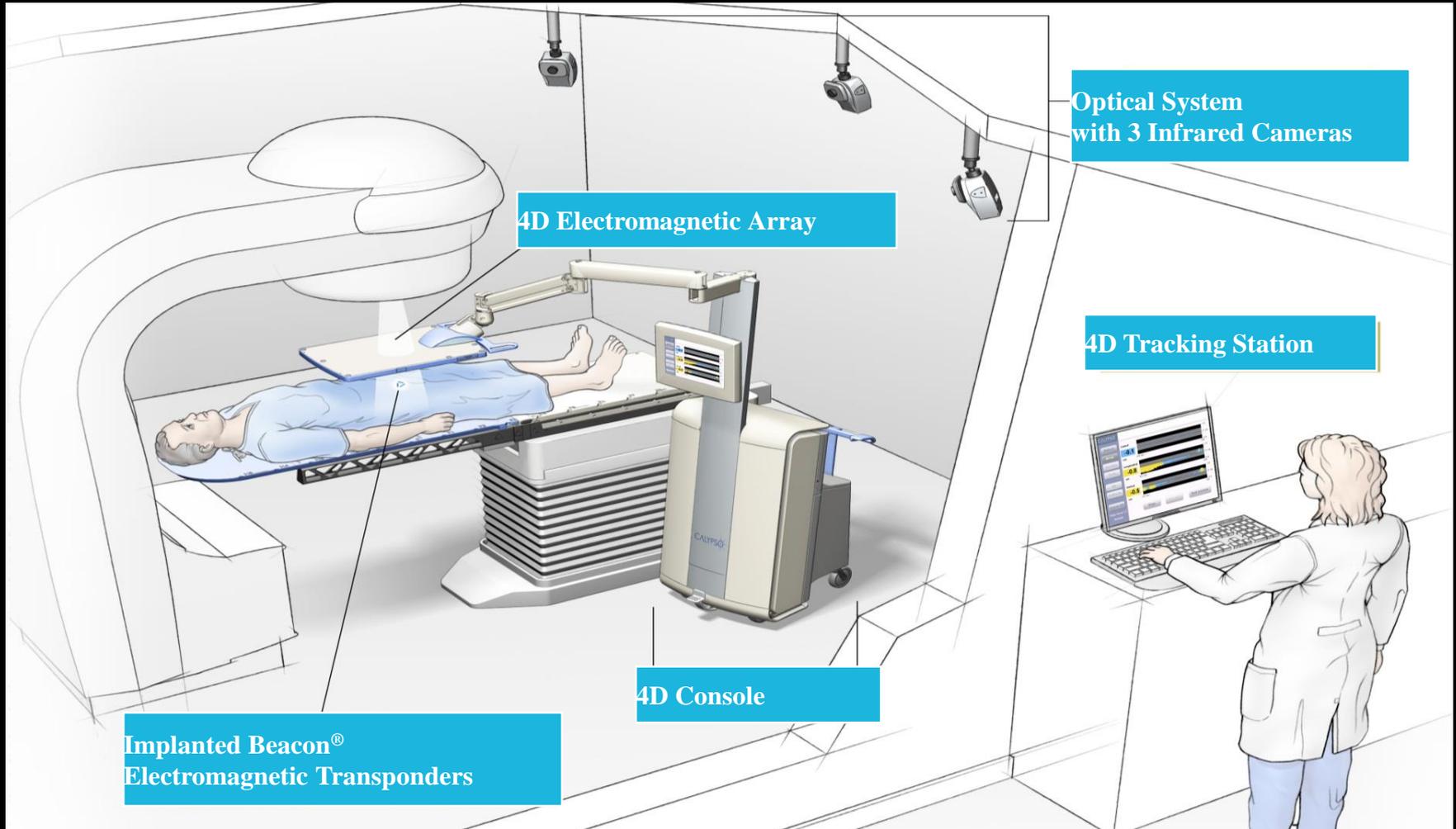
GPS seeds for treatment monitoring & repositioning

CALYPSO®

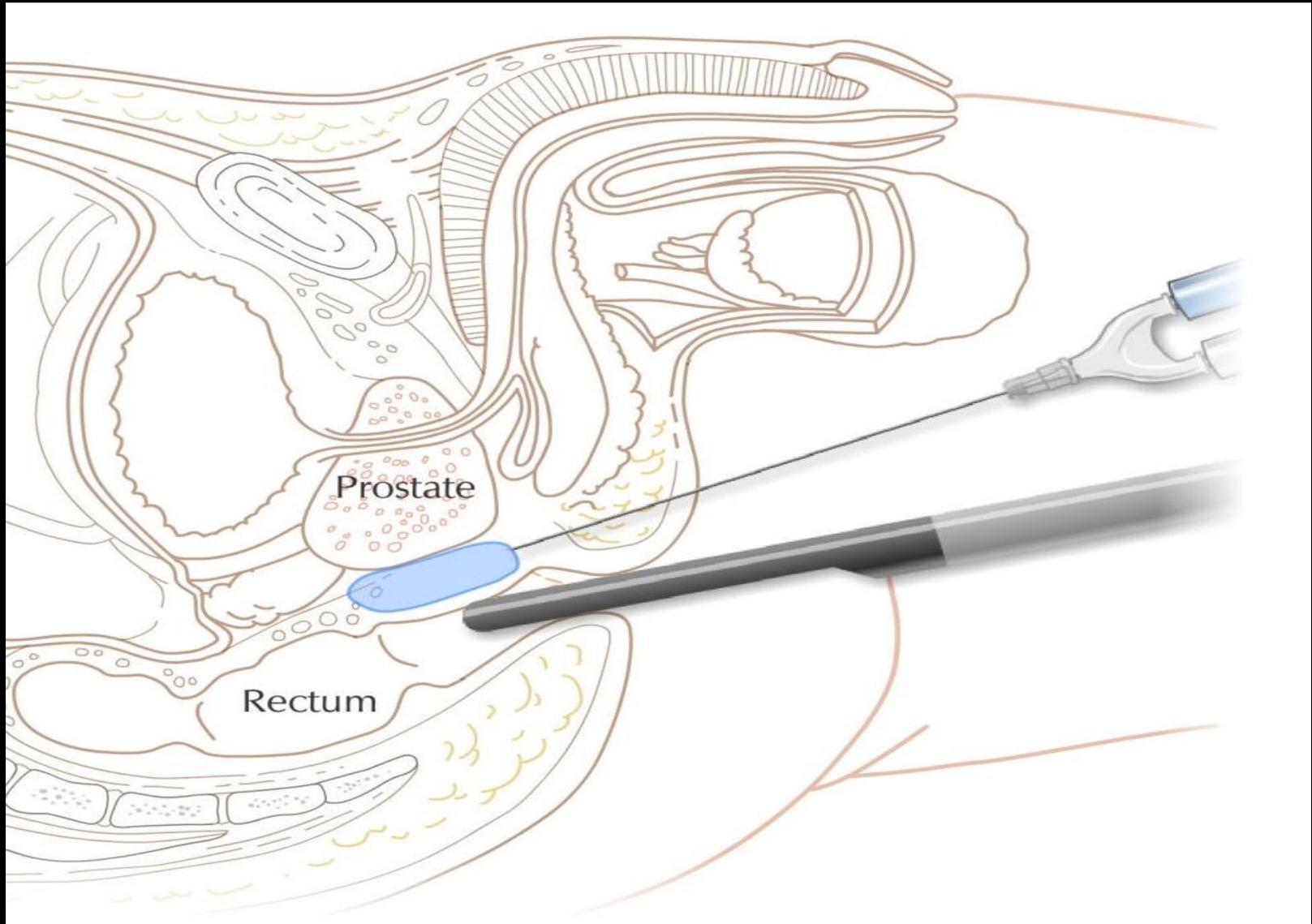




CALYPSO® SYSTEM PLATFORM

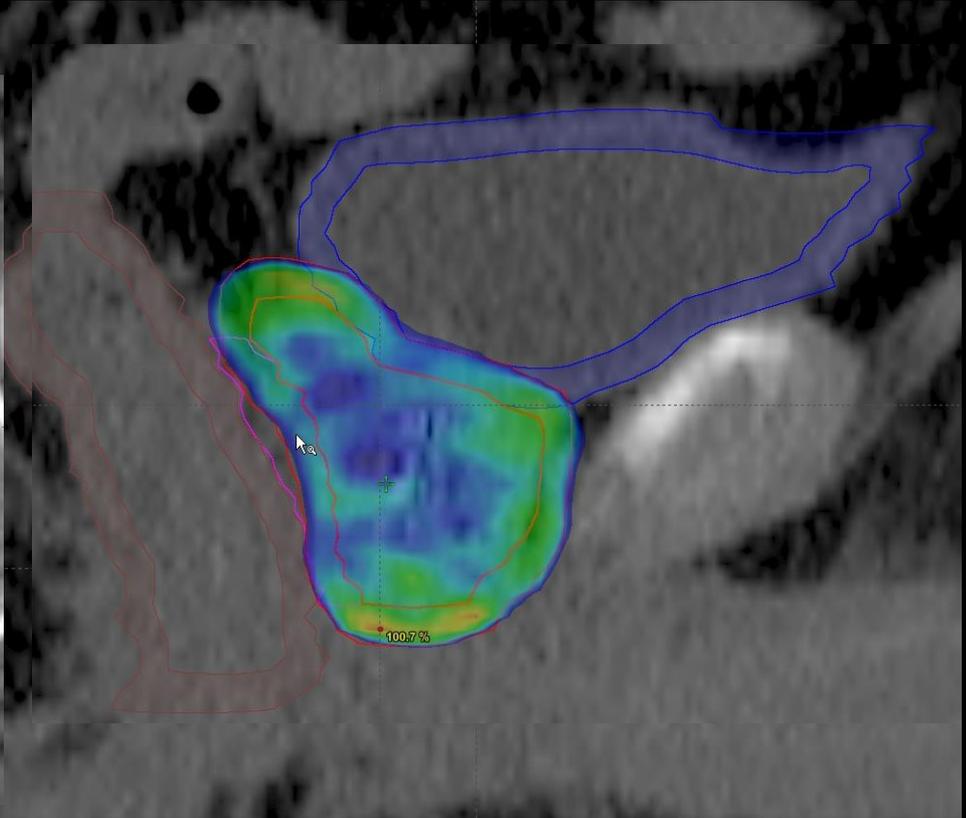
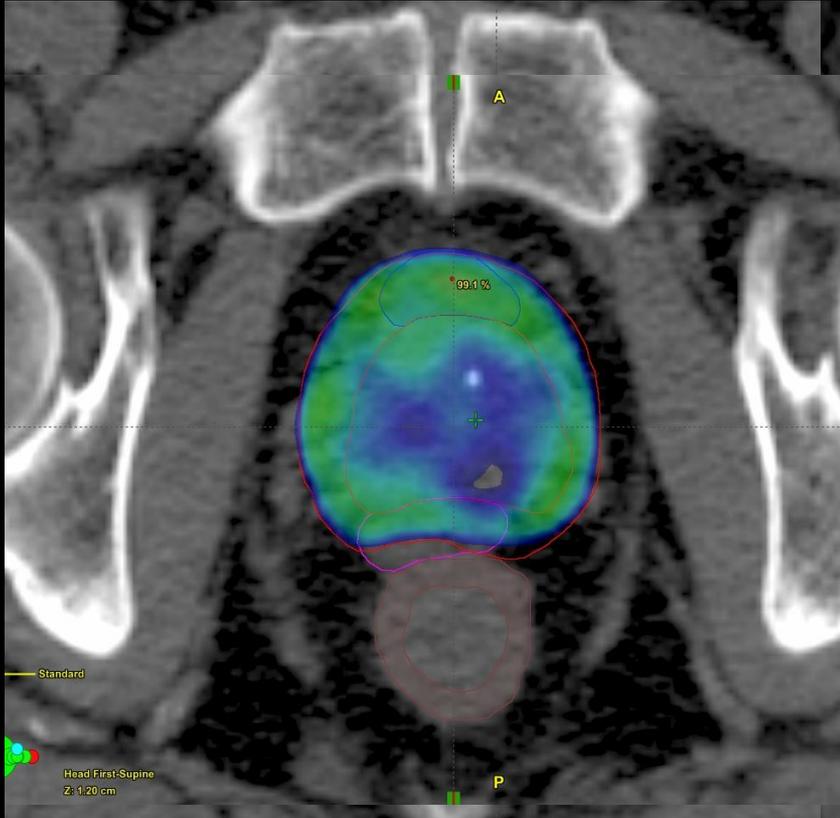


Spacer transperineal implant

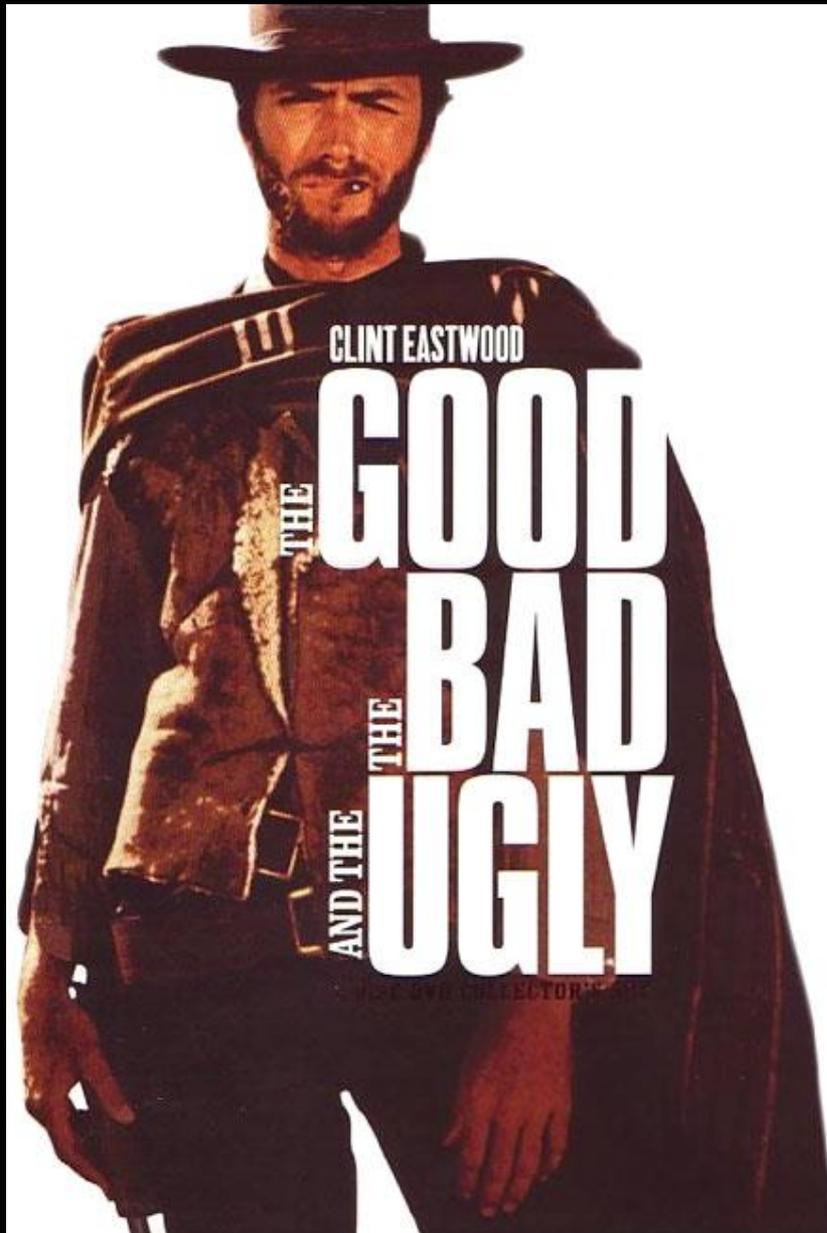


Reabsorbable spacer between the rectum and the prostate

- **Hyaluronic acid (RESTYLANE®)**
- **Hydrogel (AUGMENIX®)**
- **Biodegradable balloon (BIOPROTECT®)**



Hypofractionation: translational radiobiology



**The LQ model
(the good?)**

**Overall
treatment time
(the bad?)**

**Treatment
fraction time
(the ugly?)**



ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. e17–e24, 2012
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0360-3016/\$ - see front matter

doi:10.1016/j.ijrobp.2010.10.075

CLINICAL INVESTIGATION

Genitourinary Cancer

**DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM
RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL
INSTITUTIONAL DATASETS: $\alpha/\beta = 1.4$ (0.9–2.2) GY**

RAYMOND MIRALBELL, M.D.,^{*†} STEPHEN A. ROBERTS, PH.D.,[‡] EDUARDO ZUBIZARRETA, M.D.,[§]
AND JOLYON H. HENDRY, PH.D.^{||}

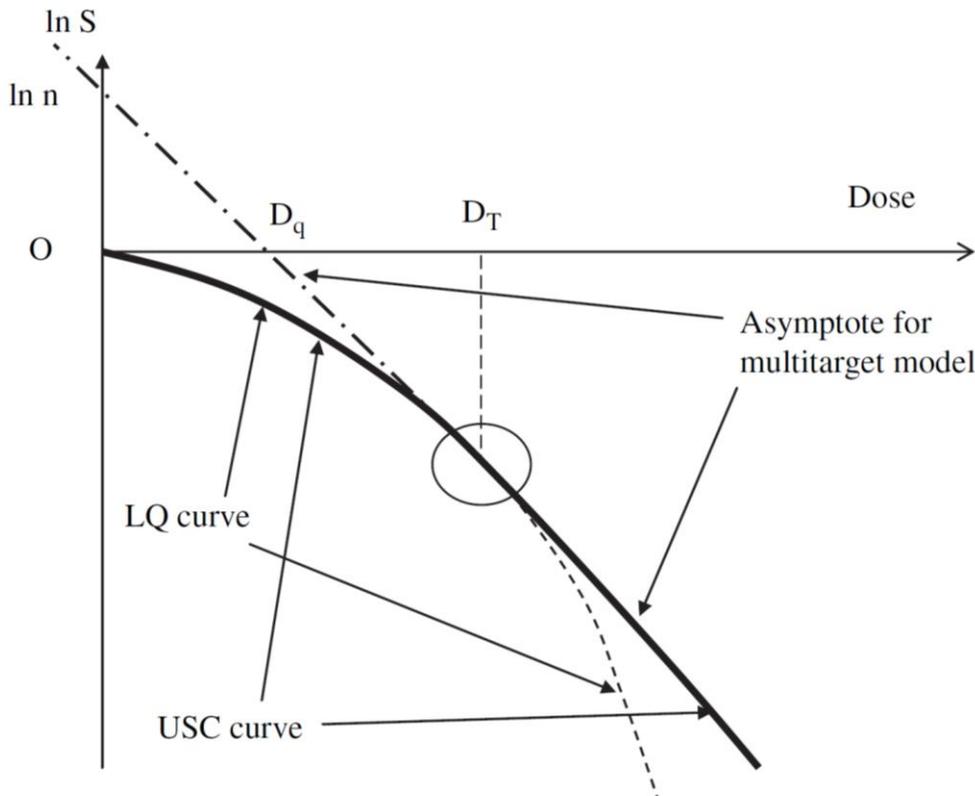
^{*}University Hospital, Geneva, Switzerland; [†]Institut Oncològic Teknon, Barcelona, Spain, [‡]Health Sciences—Methodology, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom; [§]International Atomic Energy Agency, Vienna, Austria; and ^{||}Adlington, Macclesfield, United Kingdom

UNIVERSAL SURVIVAL CURVE AND SINGLE FRACTION EQUIVALENT DOSE: USEFUL TOOLS IN UNDERSTANDING POTENCY OF ABLATIVE RADIOTHERAPY

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 847–852, 2008

CLINT PARK, M.D. M.S., LECH PAPIEZ, PH.D., SHICHUAN ZHANG, M.D., PH.D.,
MICHAEL STORY, PH.D., AND ROBERT D. TIMMERMAN, M.D.

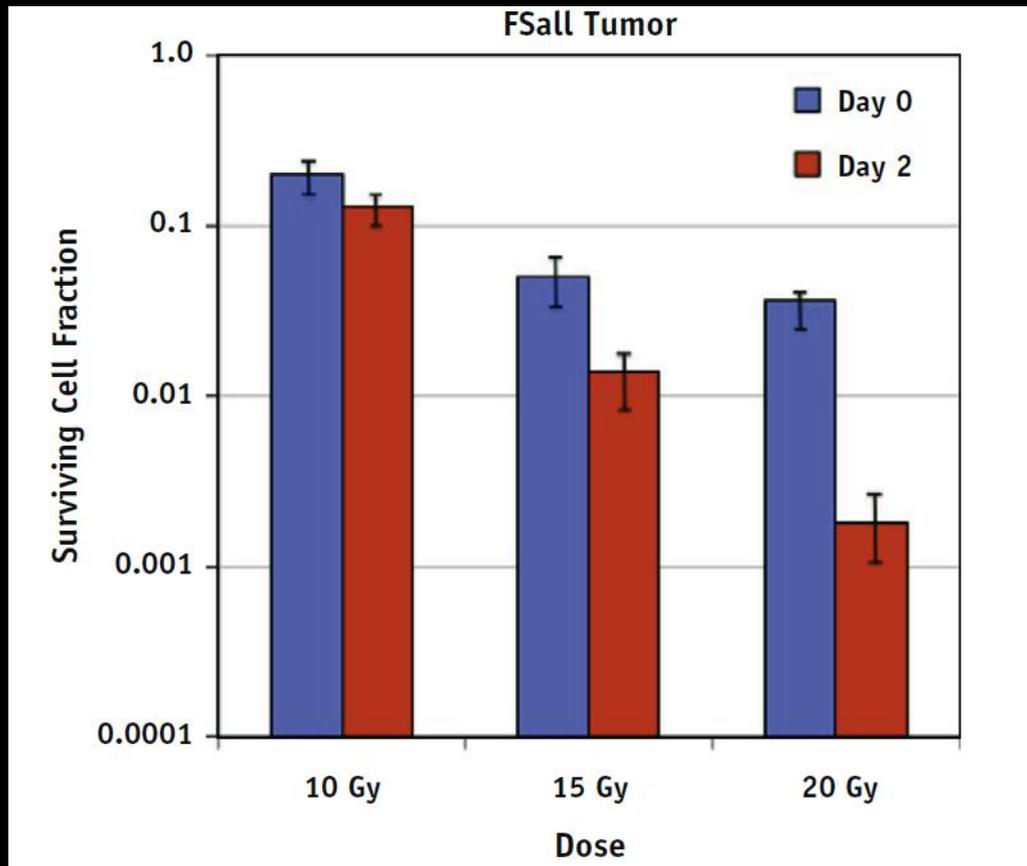
$$\ln S = \begin{cases} -(\alpha \cdot d + \beta \cdot d^2) & \text{if } d \leq D_T \text{ (LQ model)} \\ -\frac{1}{D_0} d + \frac{D_q}{D_0} & \text{if } d \geq D_T \text{ (MT model)} \end{cases}$$



Universal survival curve (USC) and D_T , transition between dose range at which **linear quadratic (LQ)** model is valid and dose range at which **multitarget model (MT)** is valid

Is Indirect Cell Death Involved in Response of Tumors to Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy?

Int J Radiation Oncol Biol Phys, Vol. 89, No. 4, pp. 924–925, 2014



Irradiation with high doses per fraction induces indirect death in tumor cells likely due to radiation-induced vascular damage

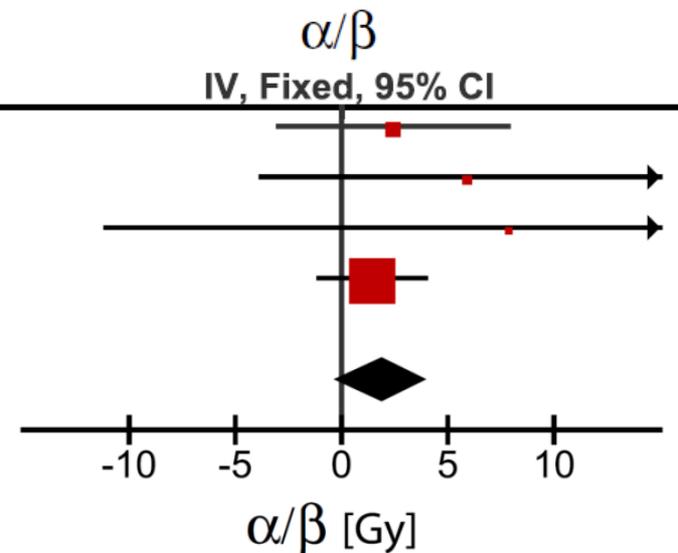
The proliferation factor

Meta-analysis of the Alpha/Beta Ratio for Prostate Cancer in the Presence of an Overall Time Factor: Bad News, Good News, or No News?

Ivan R. Vogelius, PhD,* and Søren M. Bentzen, PhD, DSc†

Int J Radiation Oncol Biol Phys, Vol. 85, No. 1, pp. 89–94, 2013

	α/β IV, Fixed, 95% CI
Leborgne 2011	2.44 [-2.98, 7.85]
Lukka 2005	5.91 [-3.79, 15.61]
Valdagni 2005	7.86 [-11.10, 26.82]
Yeoh 2011	1.46 [-1.06, 3.97]
Total (95% CI)	1.93 [-0.27, 4.14]
Heterogeneity:	$P = 0.75$; $I^2 = 0\%$



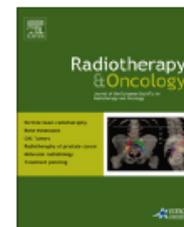
HDR-BT and the LQ model



Contents lists available at [ScienceDirect](#)

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Prostate brachytherapy

A modelled comparison of prostate cancer control rates after high-dose-rate brachytherapy (3145 multicentre patients) combined with, or in contrast to, external-beam radiotherapy

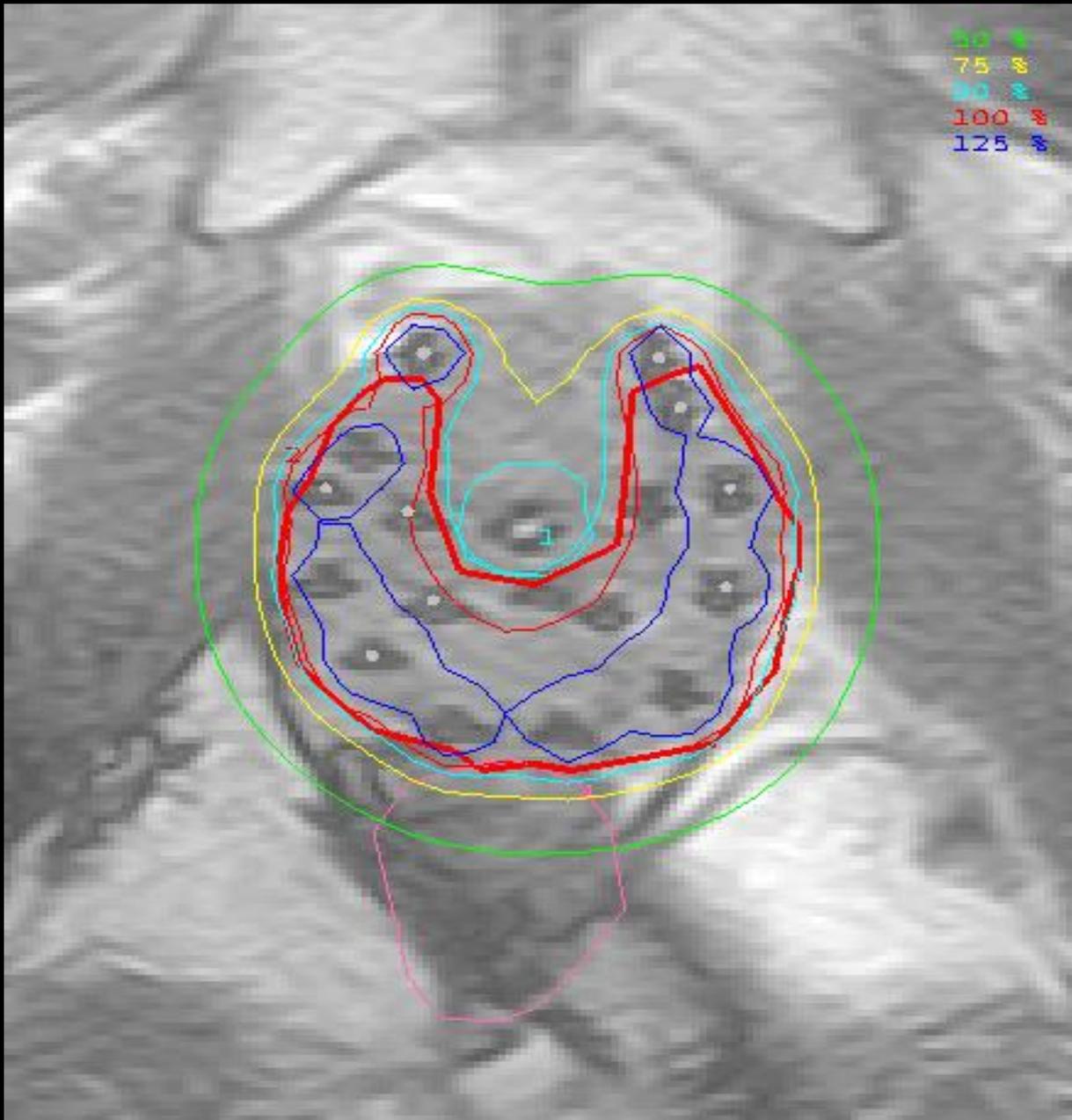


Stephen A. Roberts^{a,*}, Raymond Miralbell^{b,c}, Eduardo H. Zubizarreta^d, Jack F. Fowler^e, Jolyon H. Hendry^f

^a Centre for Biostatistics, Institute of Population Health, Manchester Academic Health Sciences Centre, University of Manchester, United Kingdom; ^b University Hospital, Geneva, Switzerland; ^c Institut Oncològic Teknon, Barcelona, Spain; ^d International Atomic Energy Agency, Vienna, Austria; ^e 150 Lambeth Road, London SE1 7DF; and ^f Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, United Kingdom

Results

$\alpha/\beta = 95\%$ CI: $-\infty, \infty$!!



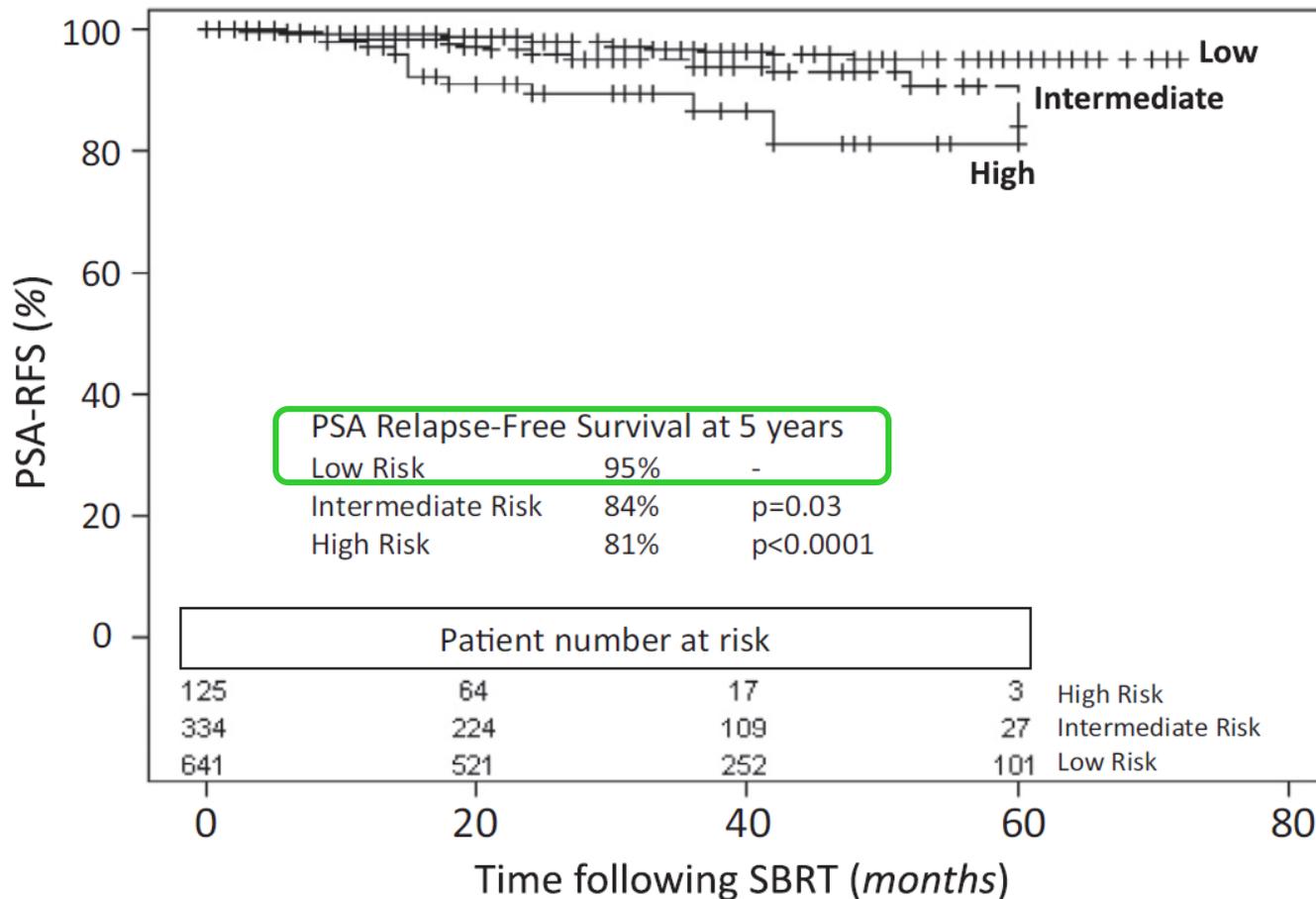
Even a small underdosage of the target may have a negative influence on outcome (especially true for low α/β tumors).

SBRT? What else...



Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆

Christopher R. King^{a,*}, Debra Freeman^b, Irving Kaplan^c, Donald Fuller^d, Giampaolo Bolzicco^e, Sean Collins^f, Robert Meier^g, Jason Wang^a, Patrick Kupelian^a, Michael Steinberg^a, Alan Katz^a *Radiotherapy and Oncology xxx (2013)*



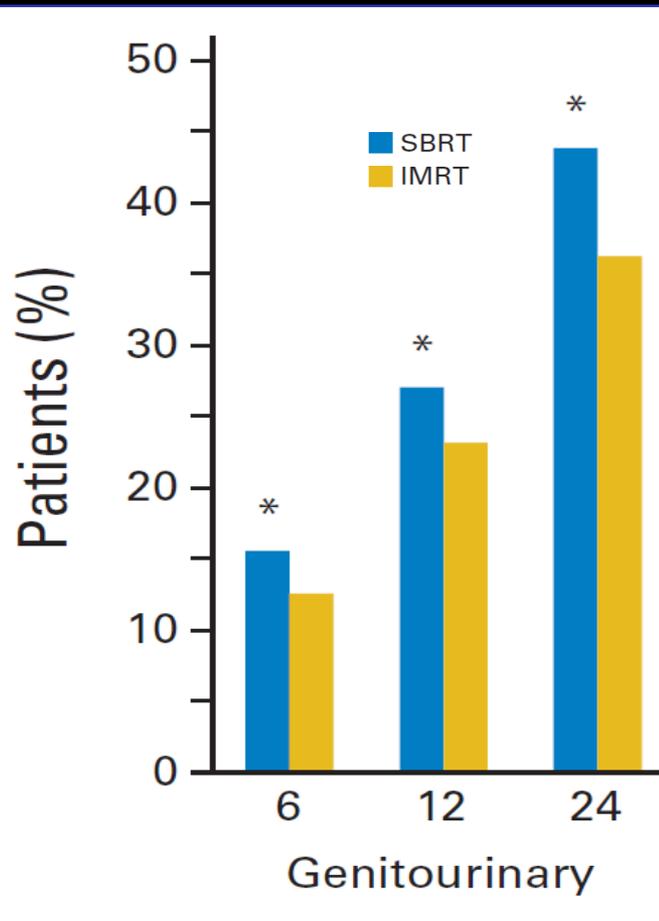
Reimbursement in Switzerland (*Tarmed*): EBRT + HDR-BT vs. IMRT vs. SBRT

- EBRT (45 Gy) + HDR-BT (3 x 7 Gy): **18'184 CHF**
- IMRT (42 x 2 Gy = 84 Gy): **22'687 CHF**
- SBRT (5 x 7.25 Gy): **13'544 CHF**

Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross

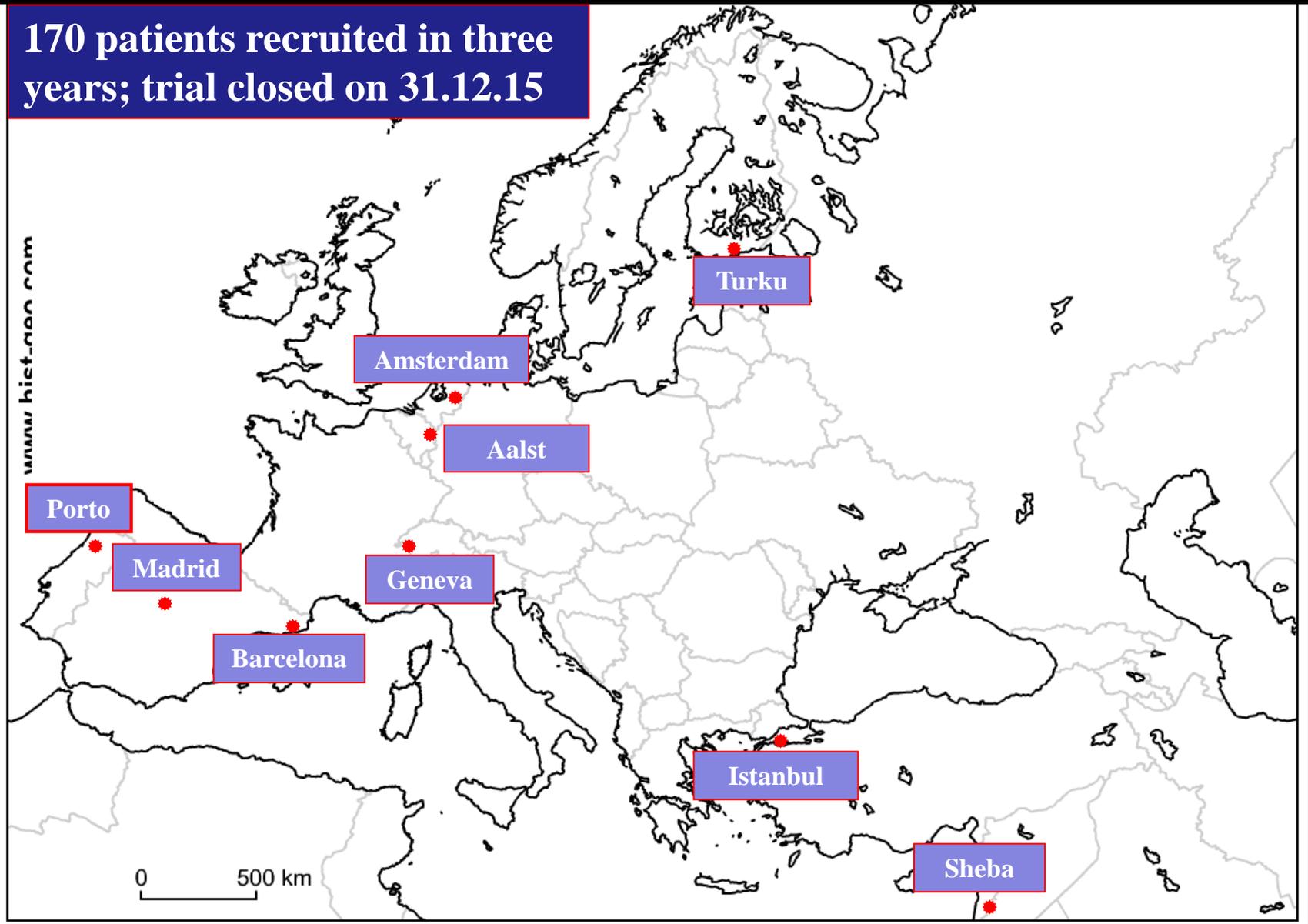
J Clin Oncol 32:1195-1201. © 2014

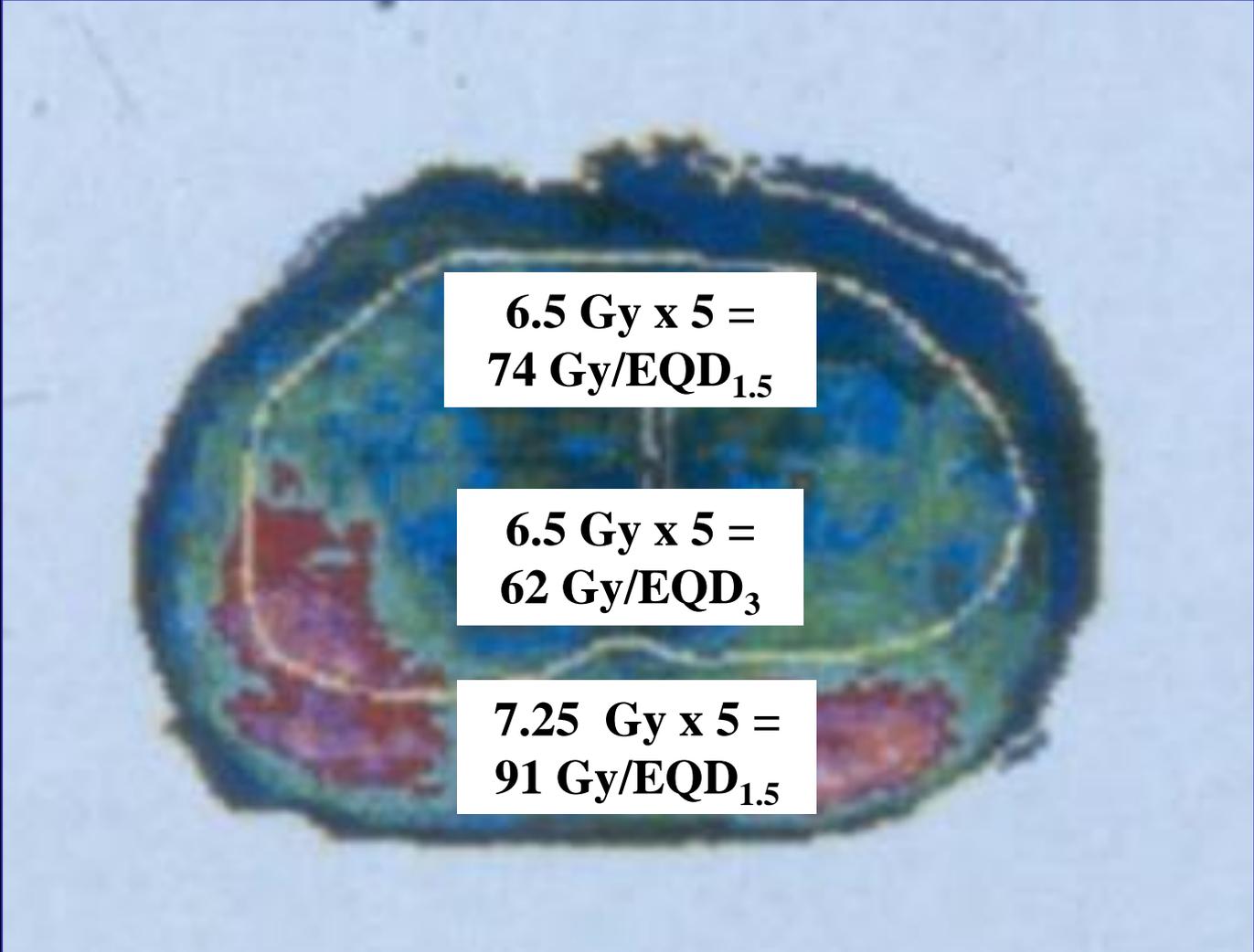


A significantly () increased GU toxicity (mostly urethral-related) with less expensive SBRT (696 pts) was observed compared with standard IMRT (1392 pts) in a national sample of Medicare beneficiaries.*

The Novalis Circle Prostate SBRT Trial

170 patients recruited in three years; trial closed on 31.12.15





**6.5 Gy x 5 =
74 Gy/EQD_{1.5}**

**6.5 Gy x 5 =
62 Gy/EQD₃**

**7.25 Gy x 5 =
91 Gy/EQD_{1.5}**

Summary of the *Novalis circle* trial



NOVALISCIRCLE

Randomization

cT1c-T3a, GS ≤ 7,
Roach index for N+ ≤ 20%;
IPSS < 19; WHO 0-1

7.25 Gy x 5 fx
(9 days, every other day)

7.25 Gy x 5 fx
(28 days, once a week)

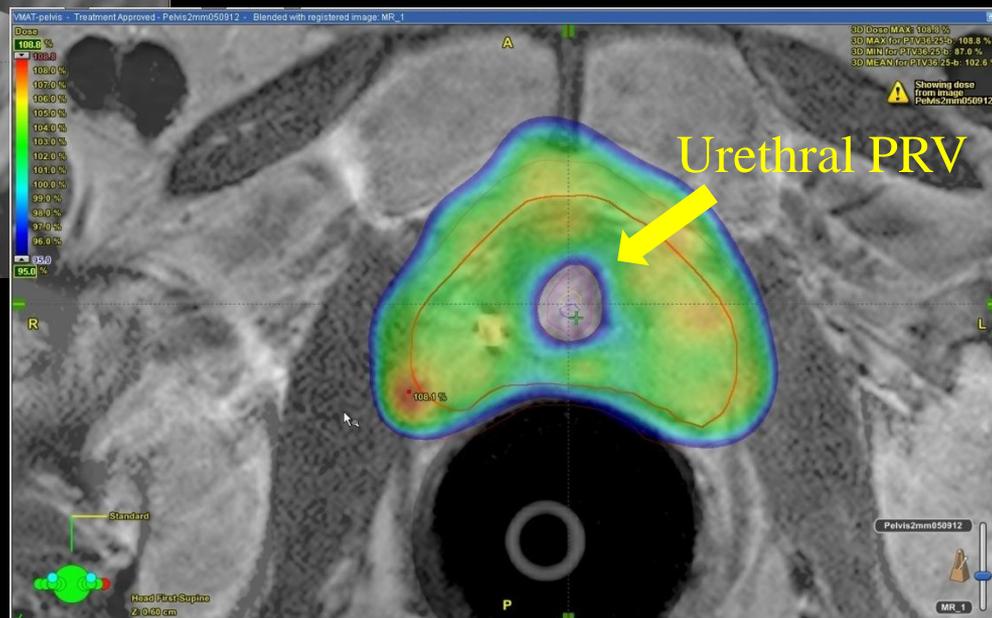
ADT 6 mo if risk factors

(2 mo neoadjuvant + 4 mo concomitant/adjuvant)

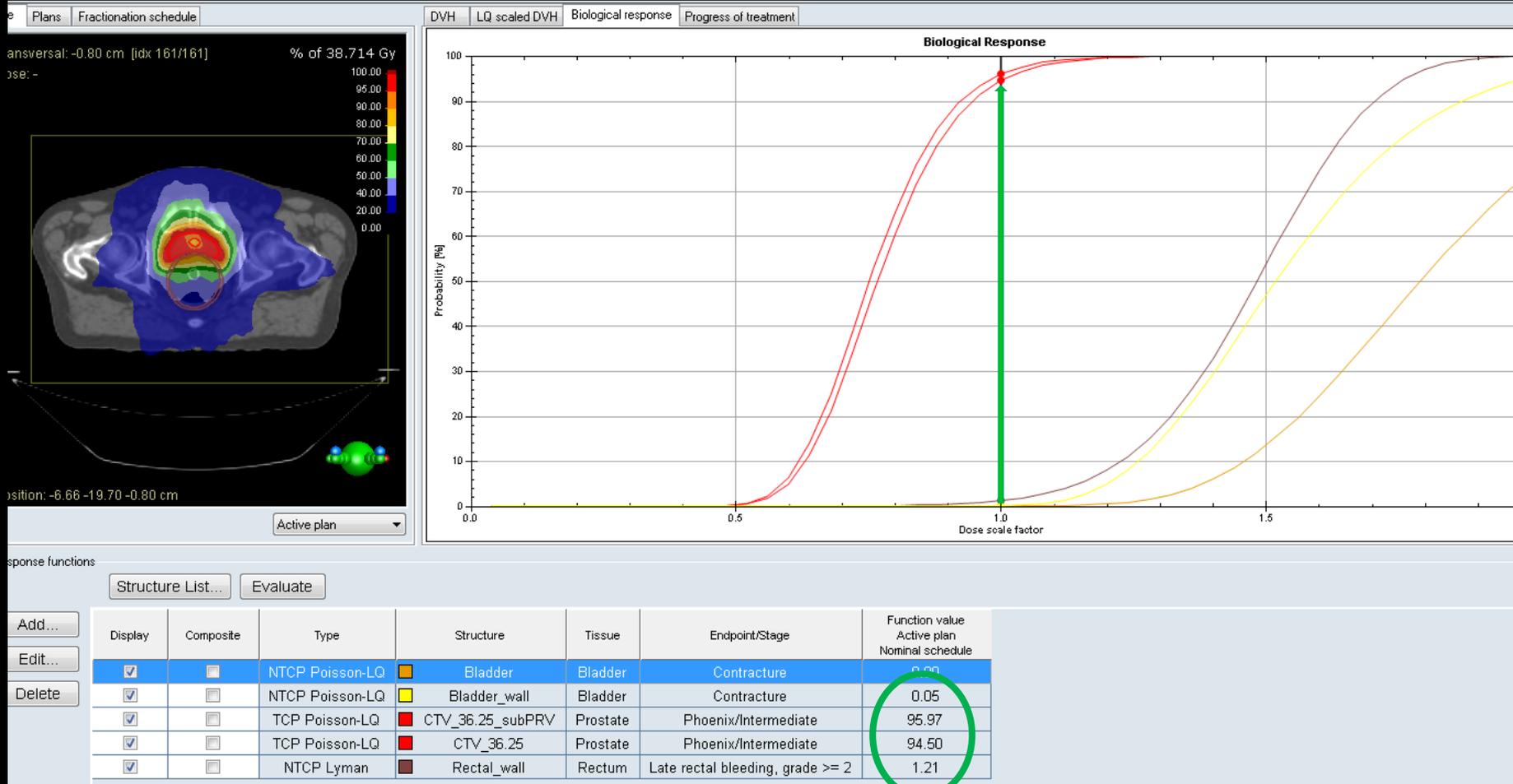
Dose distribution



PTV = CTV + 5mm,
except posteriorly (3mm)



Novalis Circle SBRT Trial: TCP & NTCP



IPSS and QoL

Paired t-test (restricted to 32 complete observations) comparing the average of the total IPSS score after the 5th fraction and at week 12 with the respective baseline

	<i>Baseline</i>		<i>After 5th fraction</i>		<i>Week 12</i>	
	A	B	A	B	A	B
Average	7.5	8.1	14.0	12.7	7.5	8.9
N	32	32	32	32	32	32
p-value	-	-	<0.001	<0.001	0.807	0.377

IPSS scores: mild: 1-7; moderate: 8-19; severe: 20-35

Conclusions

- Dose escalation with hypofractionated IGRT techniques is a promising option to treat prostate cancer with RT.
- Available clinical evidence is consistent with a low α/β value for prostate cancer cells (dose/fraction $\approx 2.5 - 4$ Gy).
- Cure after HDR-BT +/- EBRT may be limited by dose inhomogeneity and geographical misses.
- Extreme HF (SBRT, dose/fraction ≥ 7 Gy) with 5 (or less) fractions is still a clinical (though very exciting!) research matter.

The α/β frontliners



J. Fowler



S. Roberts



J.H. Hendry



E. Zubizarreta



R. Miralbell