

Proton Therapy for Prostate Cancer



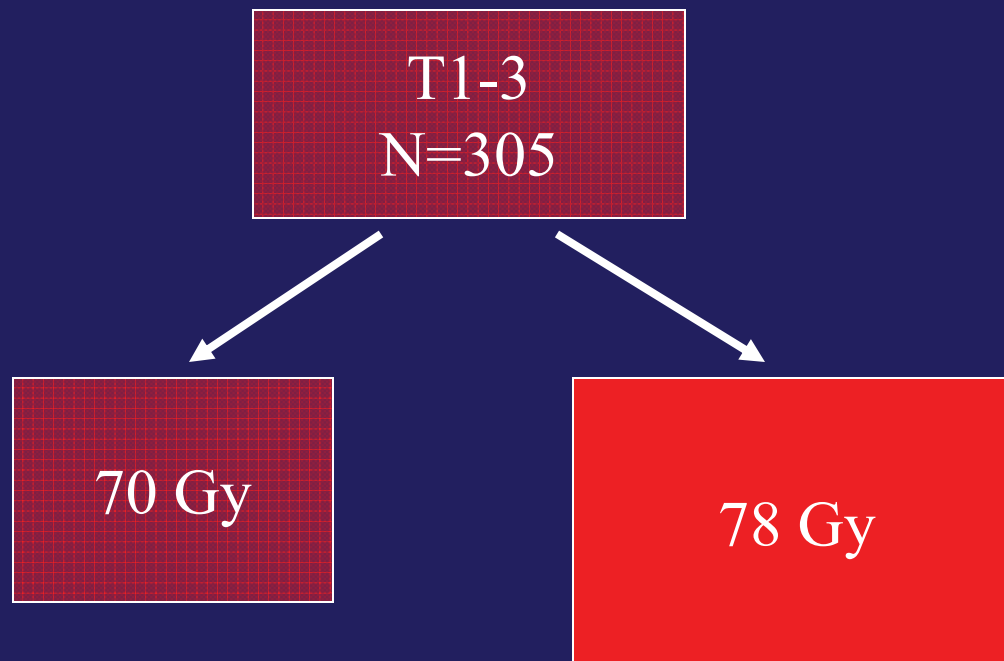
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Randomized studies showing benefit to higher dose

- MDACC randomized study of 70 vs. 78 Gy
 - Clinical benefit preferentially for 78 Gy including low risk
 - FFF
 - No difference in DM or OS
 - [JCO 18, 2000] [Updated IJROBP 2008]
- Proton randomized study LLUMC & MGH
 - 70.2 Gy vs. 79.2 Gy (1.8Gy fxn)
 - Proton boost first 19.8 vs. 28.8 CGE followed by photon 50.4 Gy
 - PSA control benefit in all patients including **low risk**

[JAMA 294:1233-39, 2005]

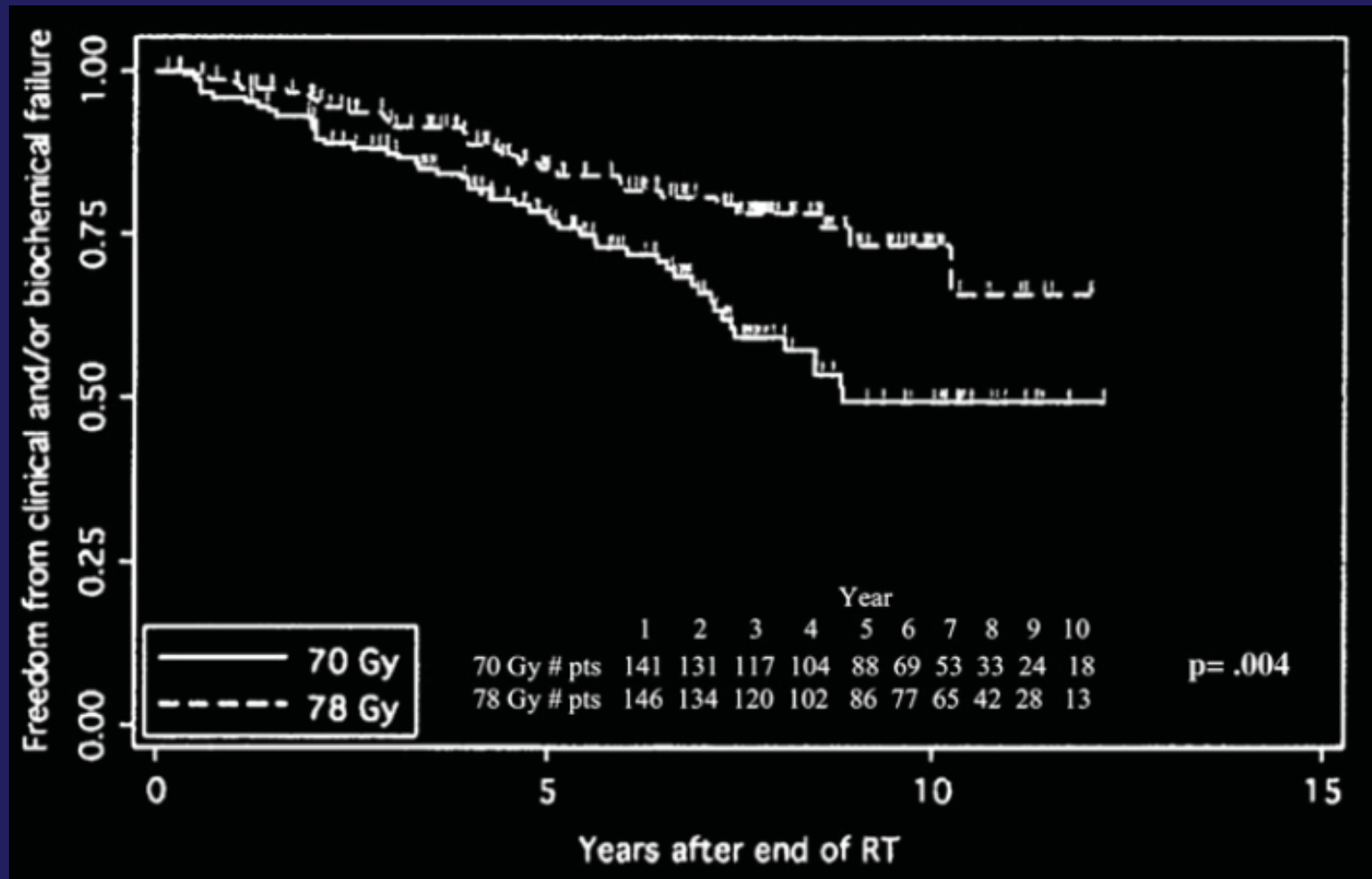
MDACC RANDOMIZED Dose-escalation Study



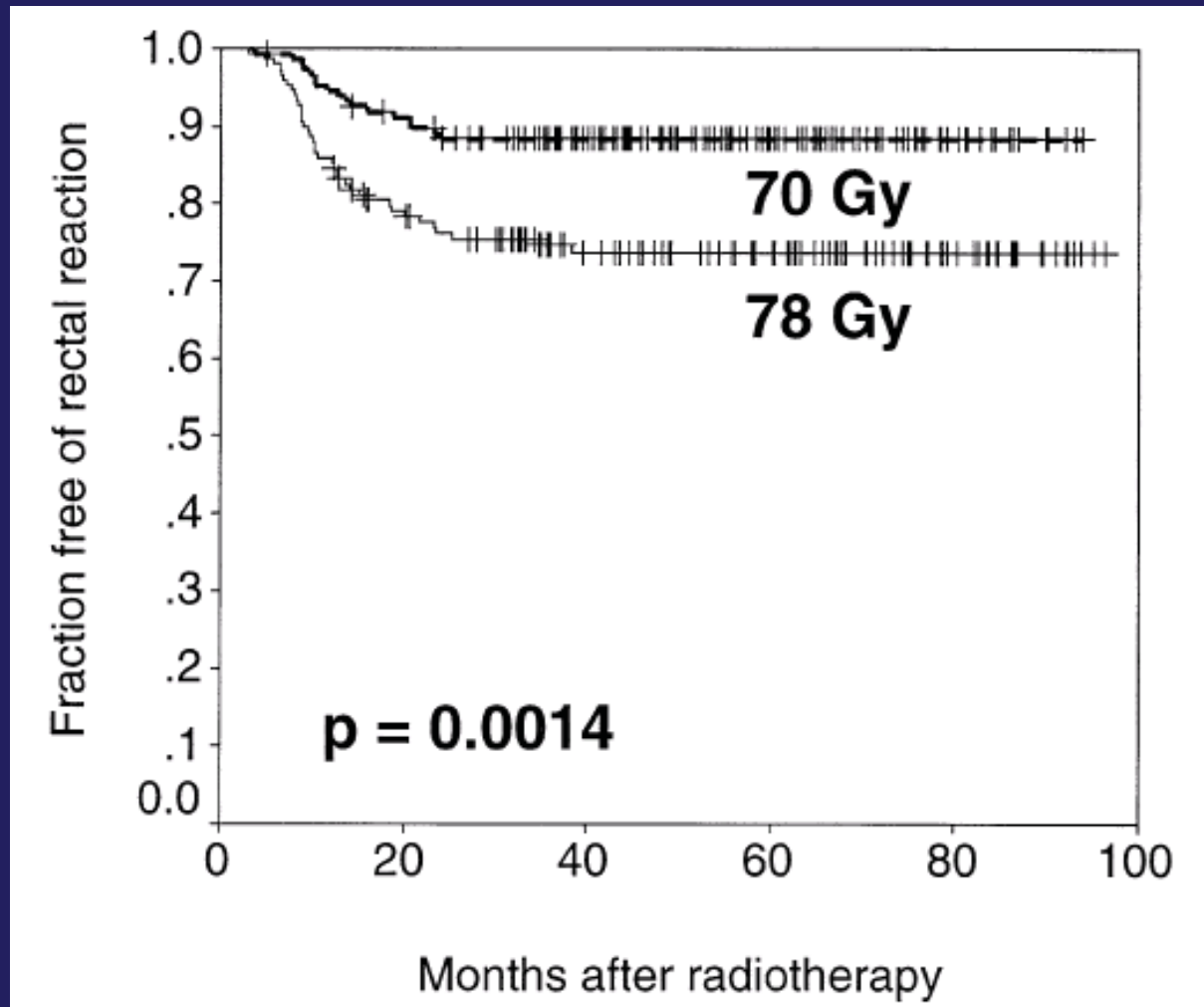
Significant difference in favor of 78 Gy
(Especially for pretreatment PSA >10)

[JCO 18, 2000 & IJROBP 54, 2002]

MDACC 78 vs 70 Gy: Freedom from failure

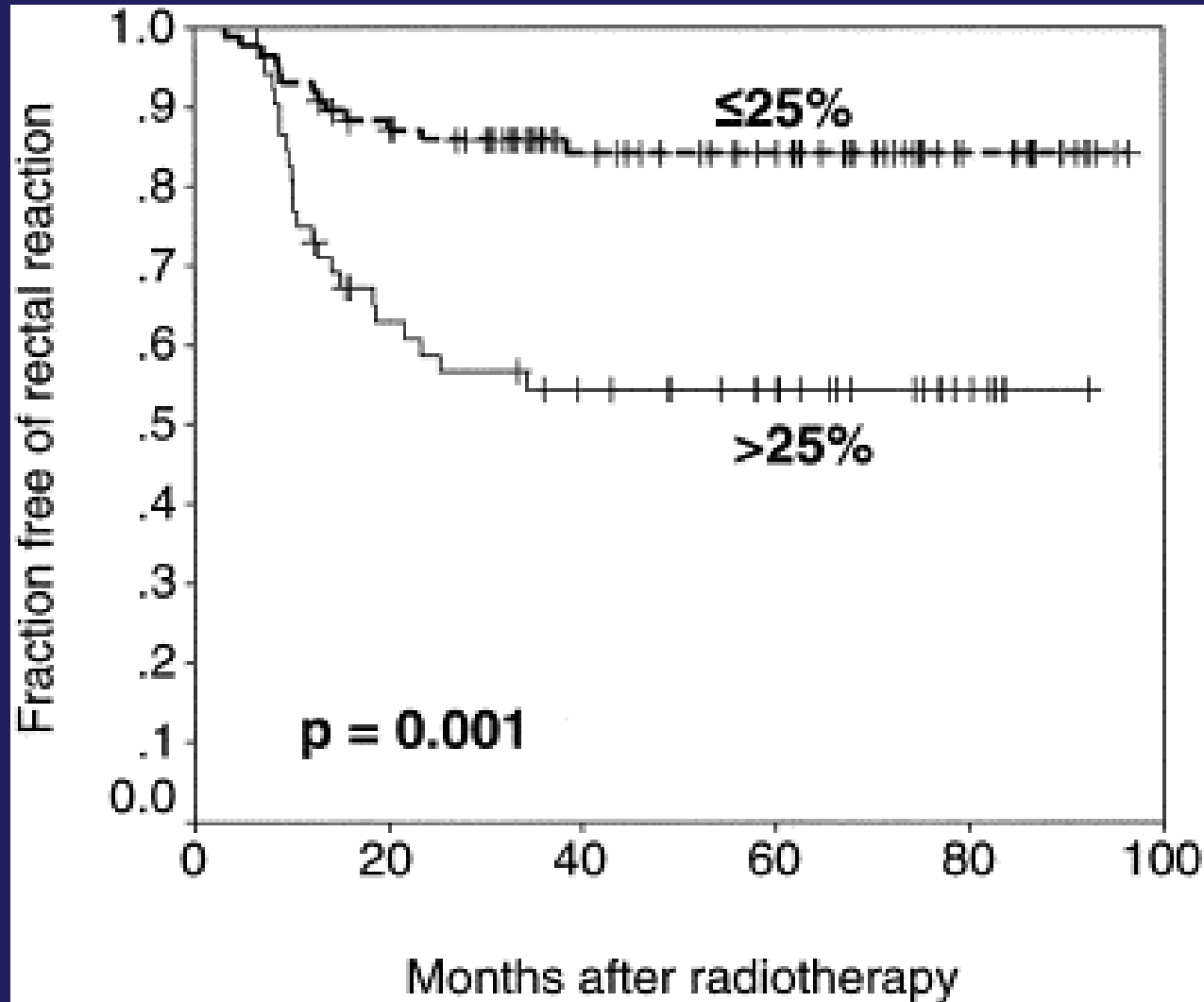


More Grade ≥ 2 rectal complications in 78 Gy arm [IJROBP 53, 2002]

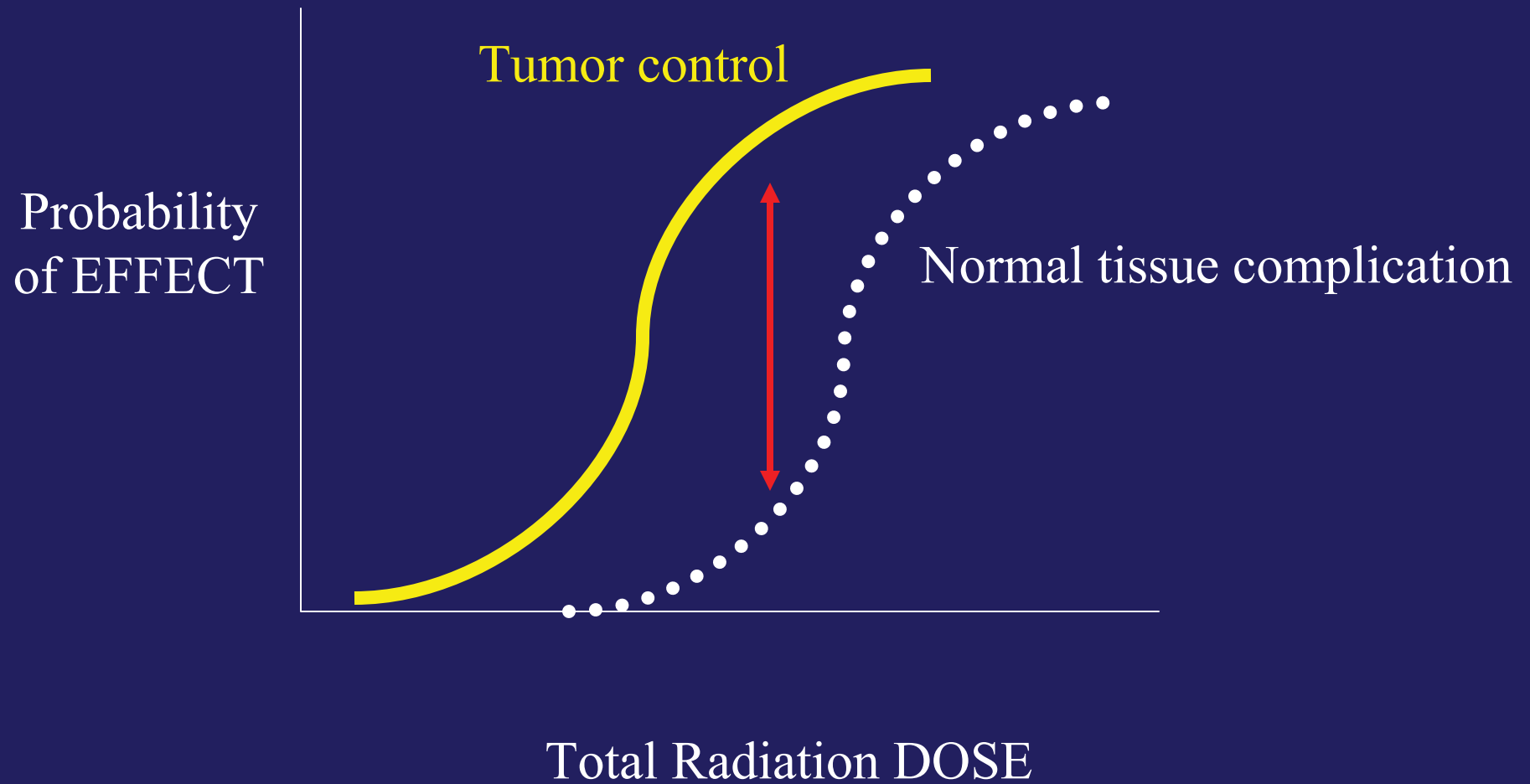


Dose-volume effect

More rectal toxicity when $>25\%$ receives over 70Gy

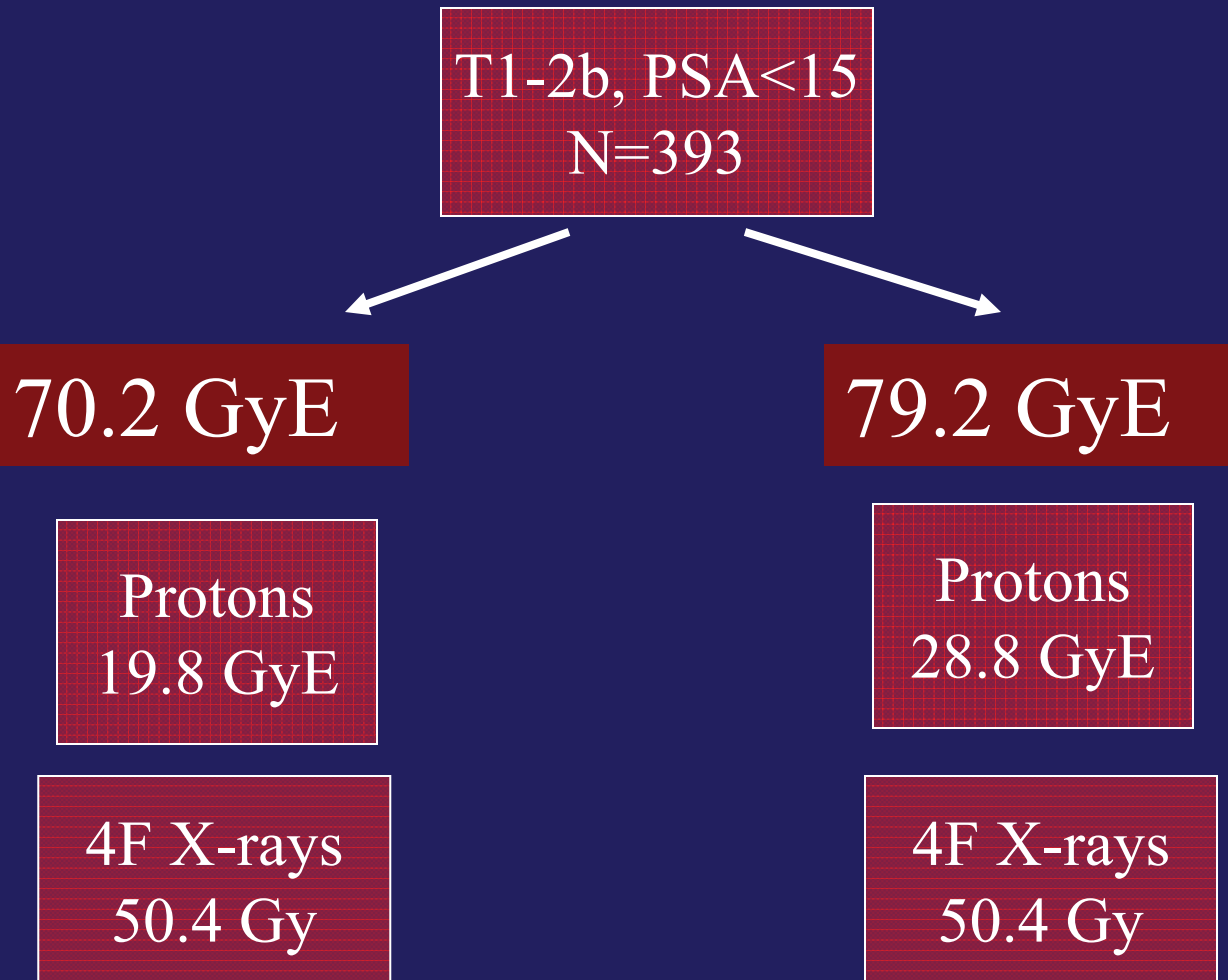


Therapeutic ratio



PROG 95-09

Proton-photon randomized trial



JAMA 294, 2005

MGH Perineal boost

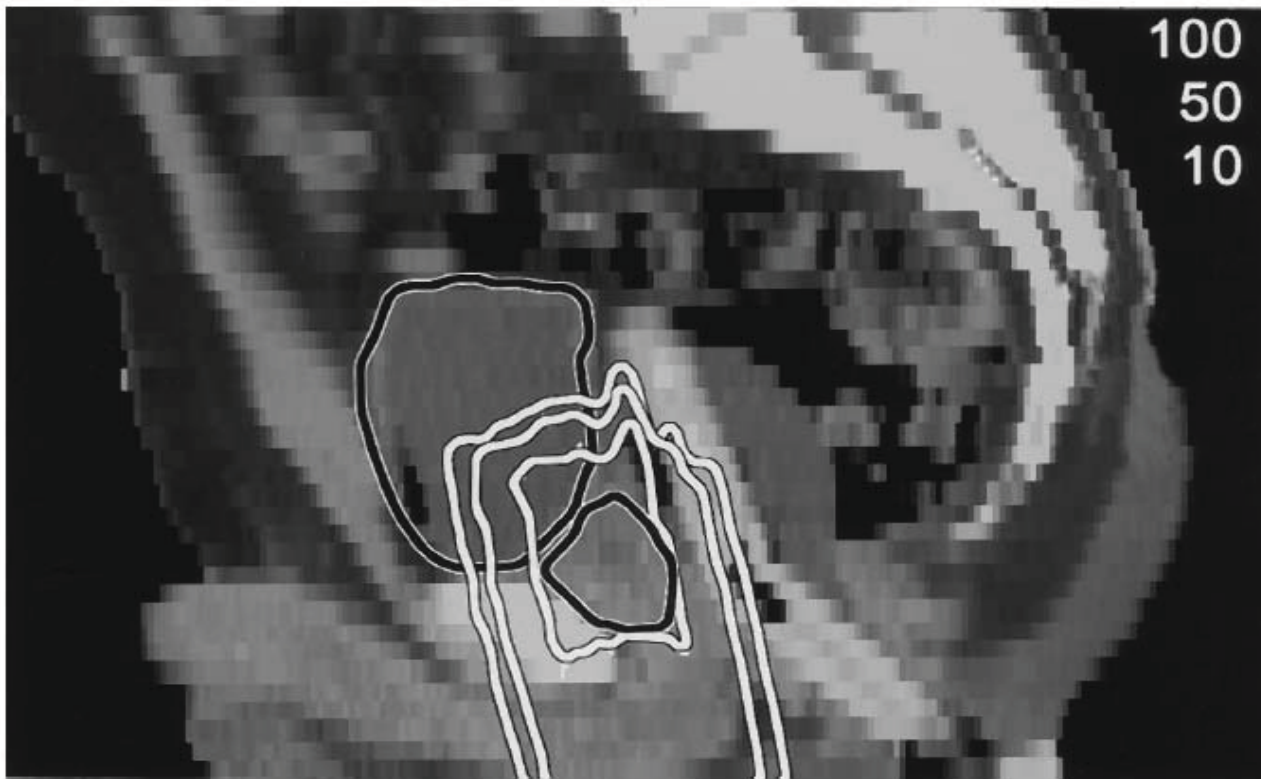
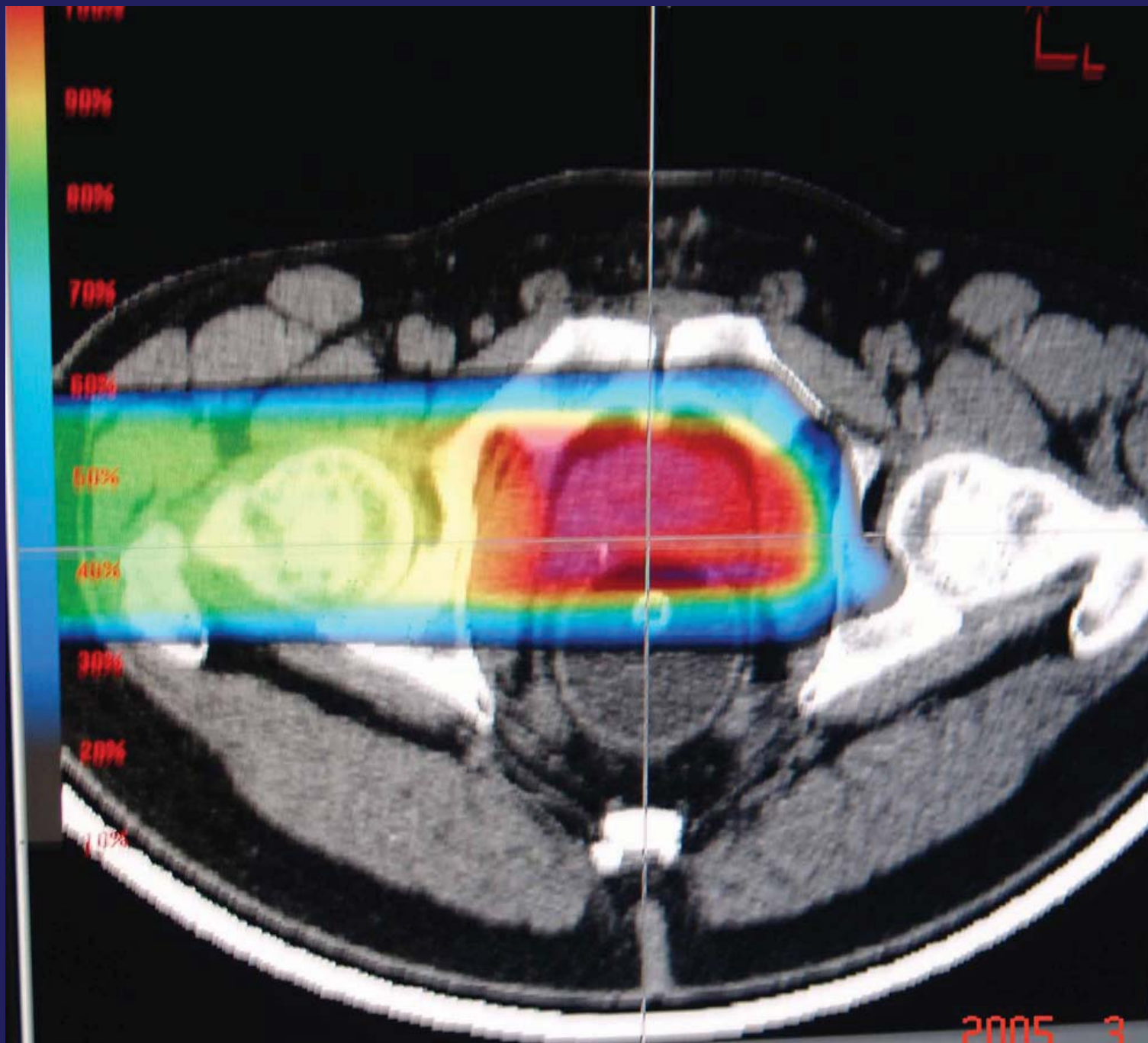


FIG. 1. Sagittal CT reconstruction shows perineal proton boost technique and how beam high dose region incorporates prostate, prostatic urethra and bladder neck.

Journal of Urology 167:123, 2002

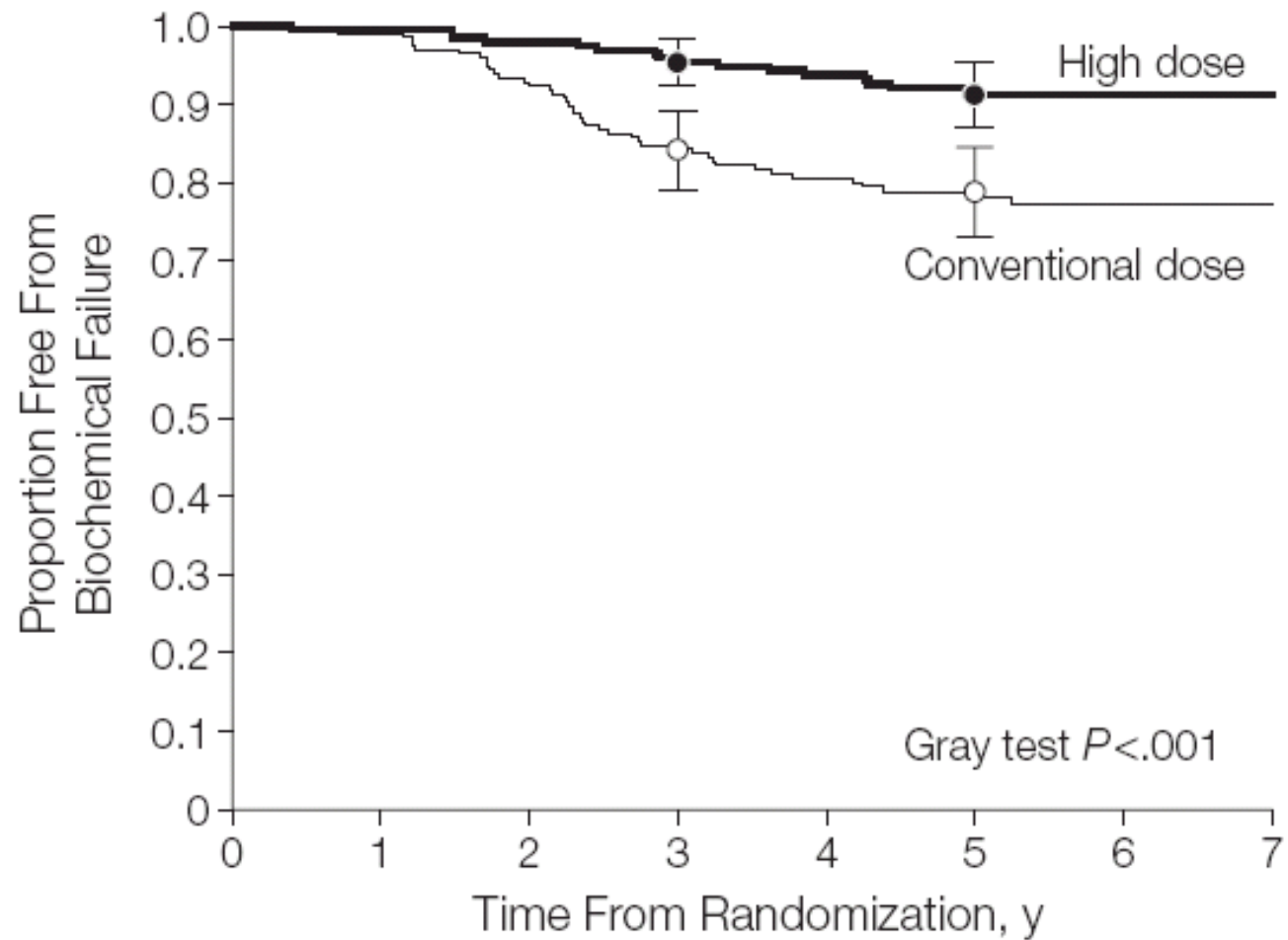


Proton-photon trial: PSA-Failure free survival



[JAMA 294:1233-39, 2005]

Proton-photon trial: PSA-Failure free survival CORRECTED calculation (JAMA 299, 2008)



92% PSA-FFS!

Late side effects: grade 2-3 rectal by trial

MDACC

70 Gy 13%

78 Gy 26%

Proton-photon

70.2 CGE 9%

79.2 CGE 18%

•Subsequent analysis showed worse quality of life in high vs. low dose x-rays. (Urology 2003).

•Subsequent analysis showed similar QOL in high vs. low dose protons. (ASCO 2007).

Comments

- The best PSA control from any prospective external beam trial
(92% compared to <70-65% for MDACC & Dutch trials)
- Proton technique was not optimal and used simple beam arrangement (one beam a day)

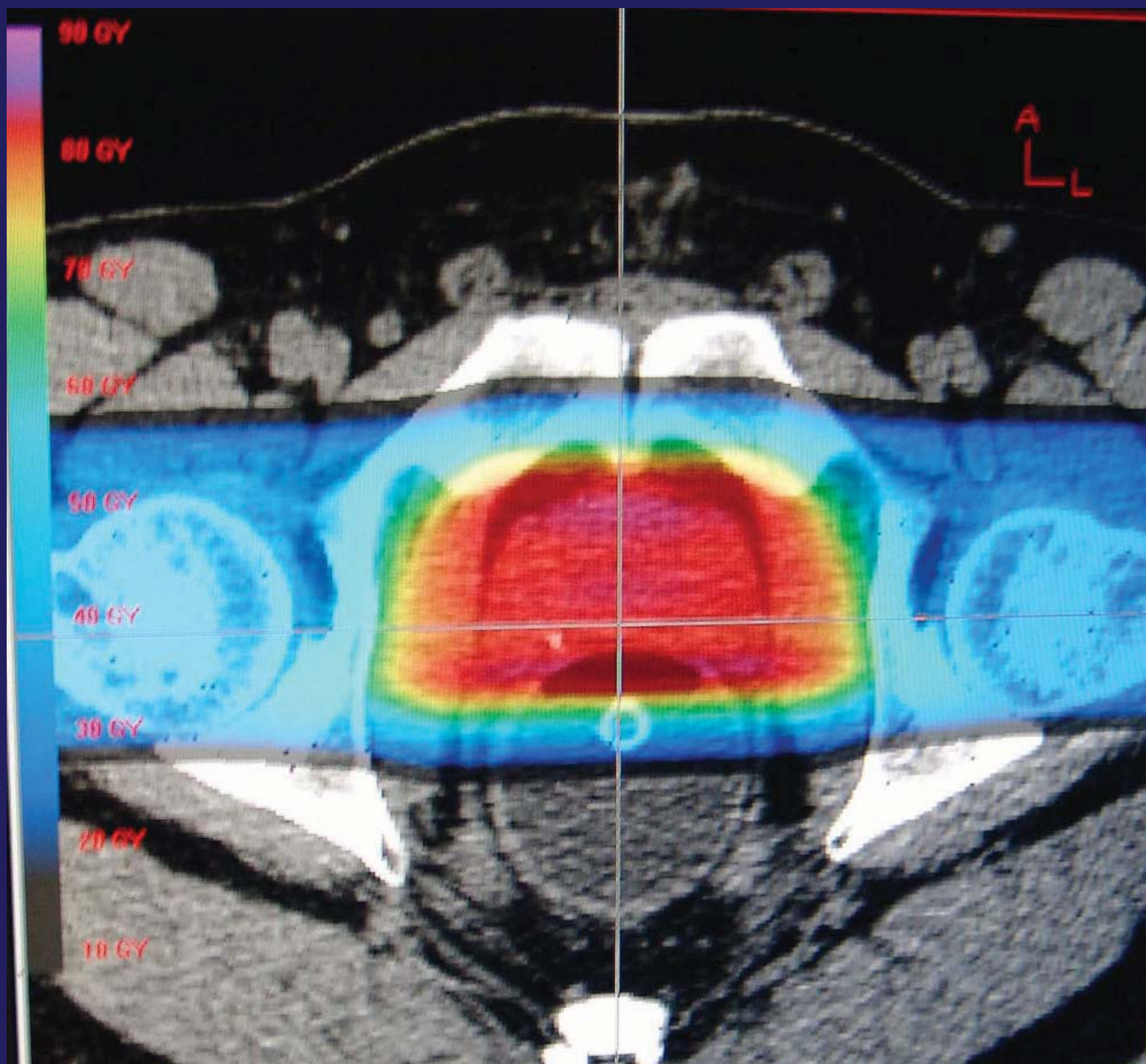
**PROTON THERAPY FOR PROSTATE
CANCER: THE INITIAL LOMA LINDA
UNIVERSITY EXPERIENCE**

JD Slater, CJ Rossi, LT Yonemoto, et al.

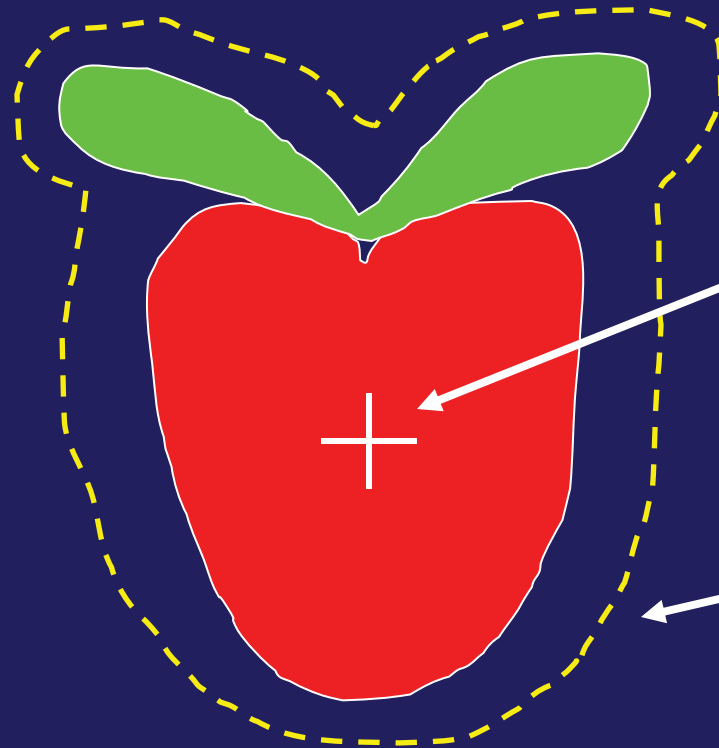
Int J Radiat Oncol Biol Phys 59:348-52, 2004

Patients and Methods

- 1255 men with prostate cancer treated between 1991-1997 w/
 - Combination protons + X-rays (731)
 - Protons only (524)
- Early years protons (30CGE/15fx) to prostate and SV followed by x-rays (45Gy) to 1st-2nd echelon lymph nodes
- Subsequent years depended upon LN risk



Prescription point

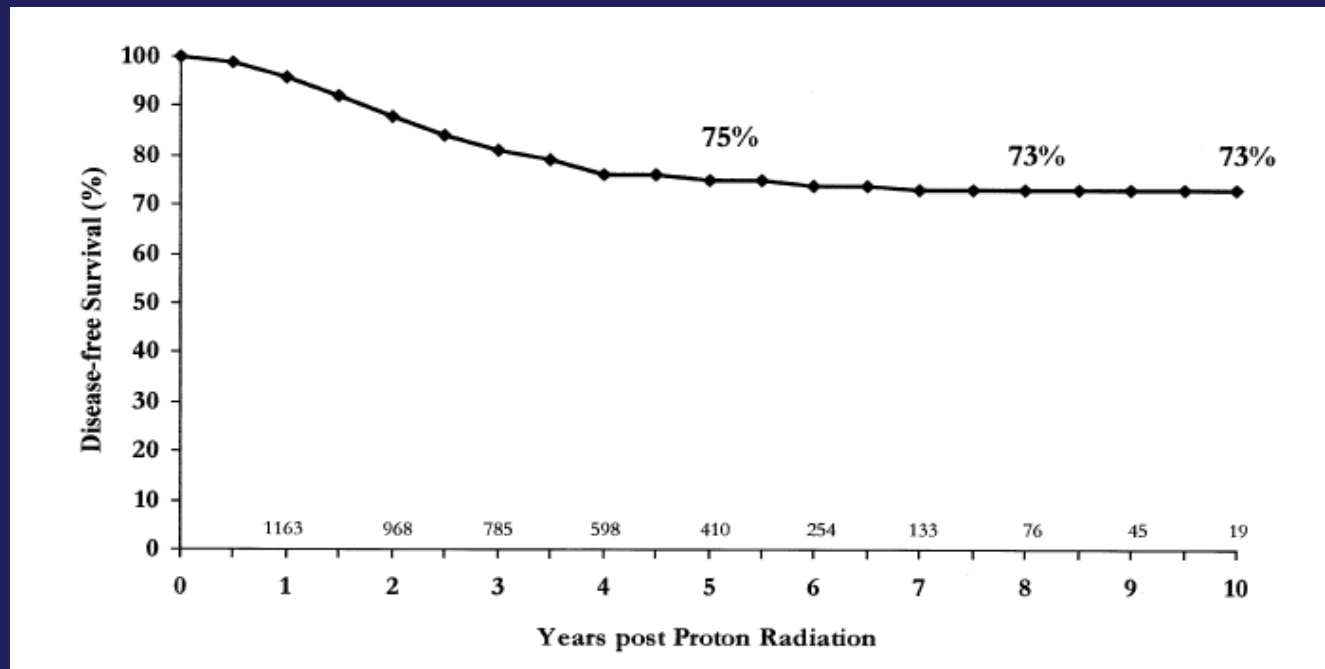


74CGE
prescribed to
isocenter

Dose to volume
~ 90-95% of
prescription

Results

- Median FU 62 months [1-132]
- Overall 8-y PSA-FFS (ASTRO) 73%
- DFS differed by PSA and Gleason



Morbidity

- RTOG toxicity
 - Acute GI/GU Grade 3-4 < 2%
 - Late GI Grade 3-4 < 2%
 - Late GU Grade 3-4 < 2%
 - 5y and 10y actuarial rate of being free of Grade 3-4 GI/GU ~99%
 - Prior report 3-y RTOG Grade 2 GI/GU incidence of ~5% (Urology 53, 1999)
 - No significant difference between combination or protons only

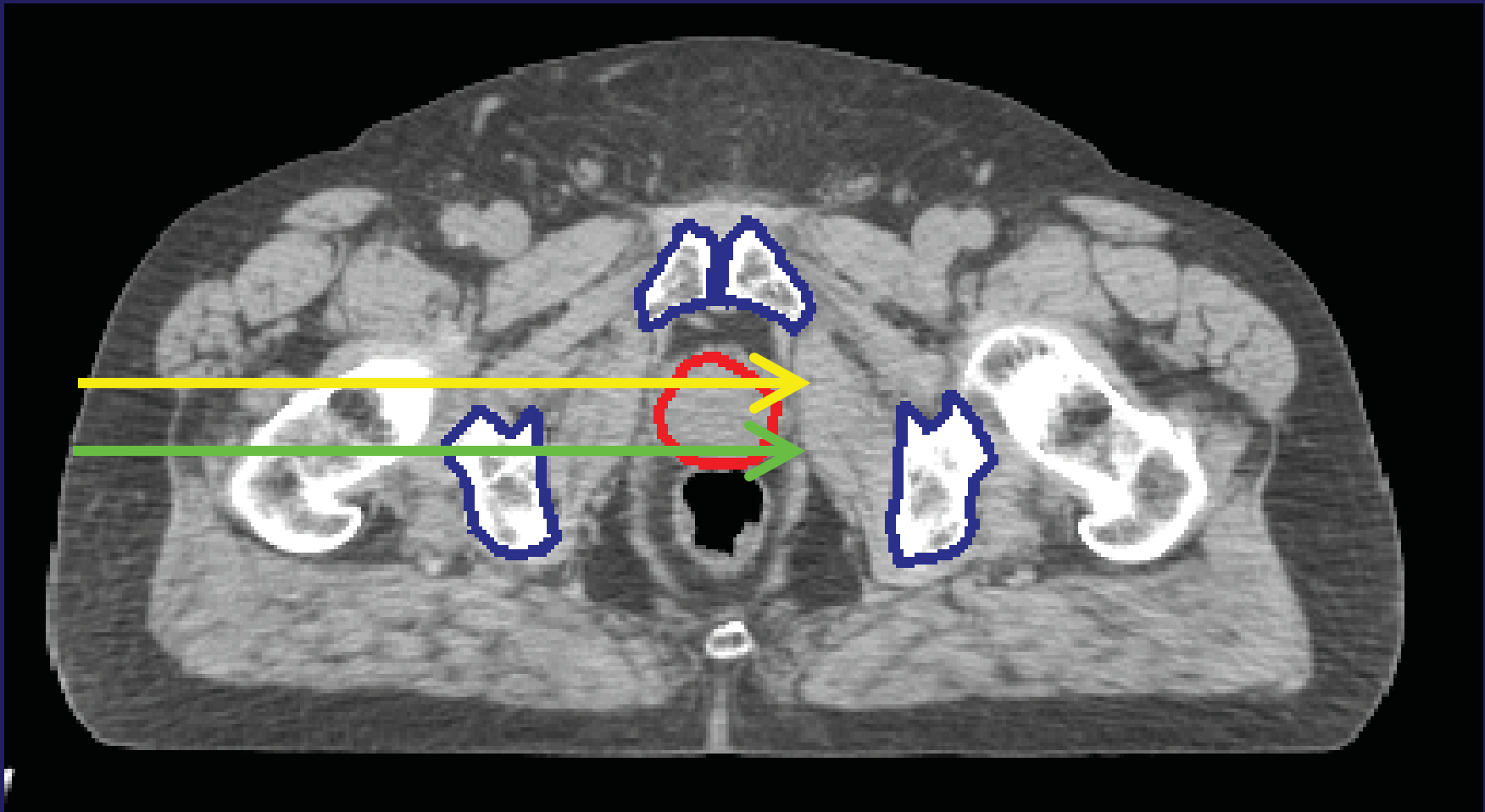
- Combination of x-rays and protons as well as protons alone
- Some patients received nodal radiation
- Protons were effective and safe
- Dose prescribed to isocenter rather than target volume
 - Lower dose compared to current standards
- Further dose-escalation has been done and ongoing trials looking at doses ~82 CGE
- Simplest possible beam arrangement used (one lateral field per day)

ACR 0312

A PHASE II STUDY USING PROTON BEAM RADIATION THERAPY FOR EARLY STAGE ADENOCARCINOMA OF THE PROSTATE

- T1c-T2c, Gleason 5-10, PSA<15
- Total dose 82 CGE
- Small field
 - CTV1 (Prostate w/ no margin)
 - 32 CGE (2 CGE)
- Wide field
 - CTV2 (Prostate & proximal SV)
 - 50 CGE (2 CGE)

Range depends on radiologic path length



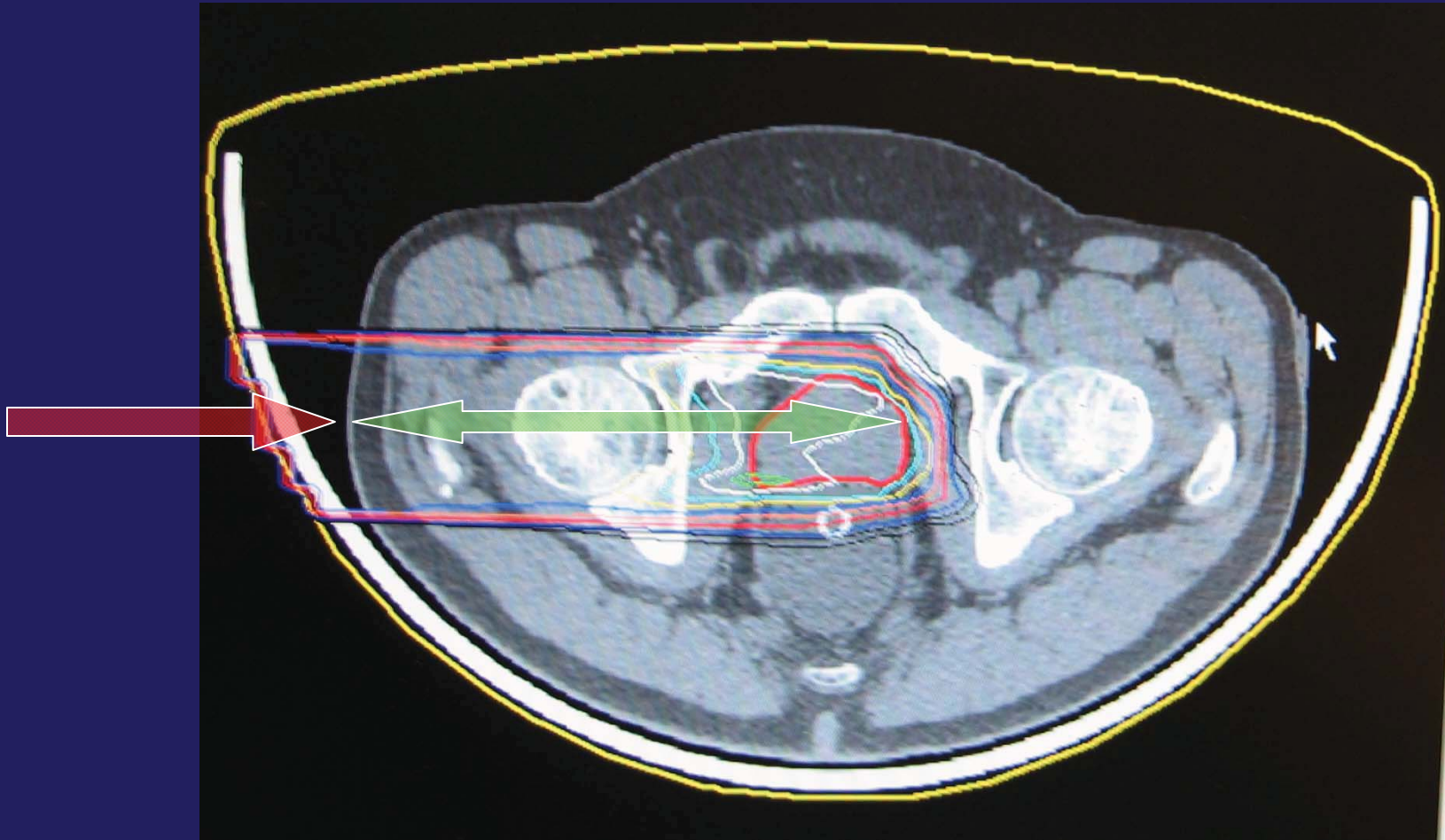
- Immobilization and reproducible setup is more critical for protons than IMRT
- Reproduce radiologic path length
- “Pro-active” target localization

Loma Linda “pod”

Special thanks to Dr. Slater and Dr. Rossi



Effect of the Pod



Storage is an issue



Cut out wedge
for er-balloon



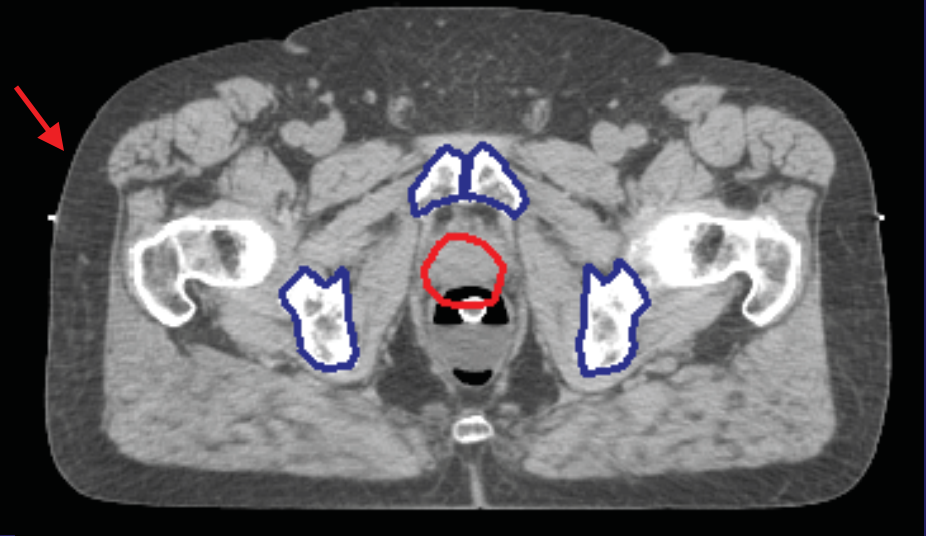
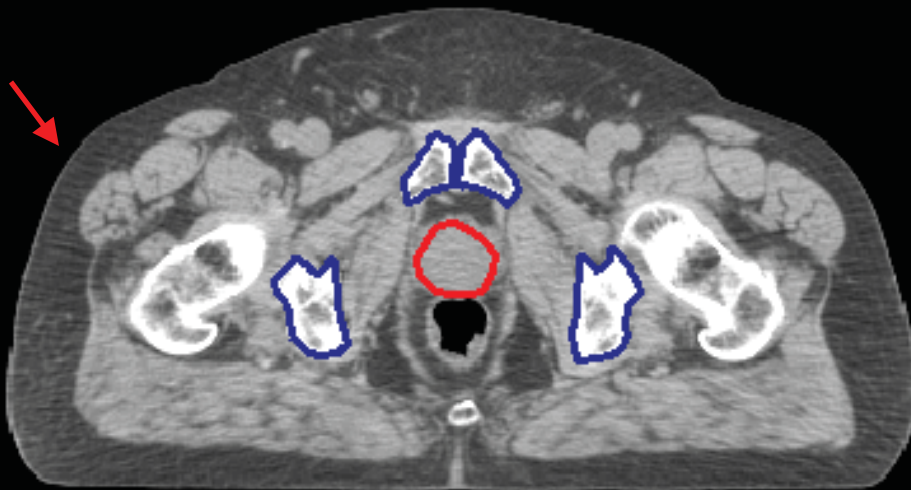
Knee and foot cradles
are index-able



Patient 1

Conventional

Wedge knee + rectal balloon



43.3cm

Measured through
The center of prostate

41.2cm

Knee-foot cradle

- Easy to use
- No storage issues
- Good shape to external pelvic contour and hip bones
- Reproducible setup
 - Ongoing CT-on-rails w/ IMRT

Endo-rectal balloon

- Use daily w/ 65cc water
- Immobilize prostate
- Inter- and intrafxn motion
- Displace rectum
- Implication of 2-3mm shift w/ or w/out ERB
- Stop-cock **minimizes air** in balloon
- Target definition at simulation
- MRI-CT fusions
- Well-tolerated



Not all balloons are created equal

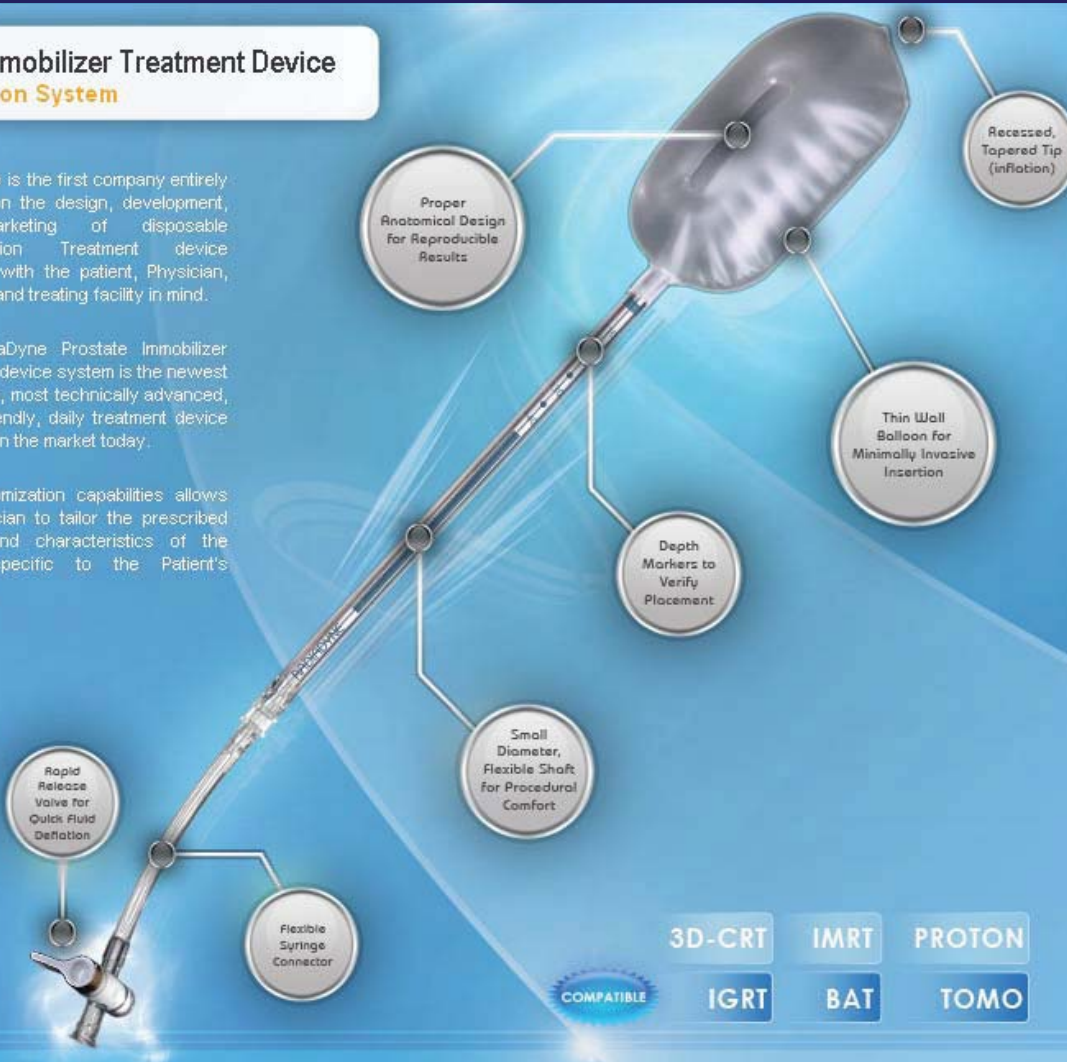


★ Prostate Immobilizer Treatment Device Rectal Balloon System

RadiaDyne is the first company entirely focused on the design, development, and marketing of disposable Immobilization Treatment device systems, with the patient, Physician, therapist, and treating facility in mind.

The RadiaDyne Prostate Immobilizer Treatment device system is the newest generation, most technically advanced, patient friendly, daily treatment device available on the market today.

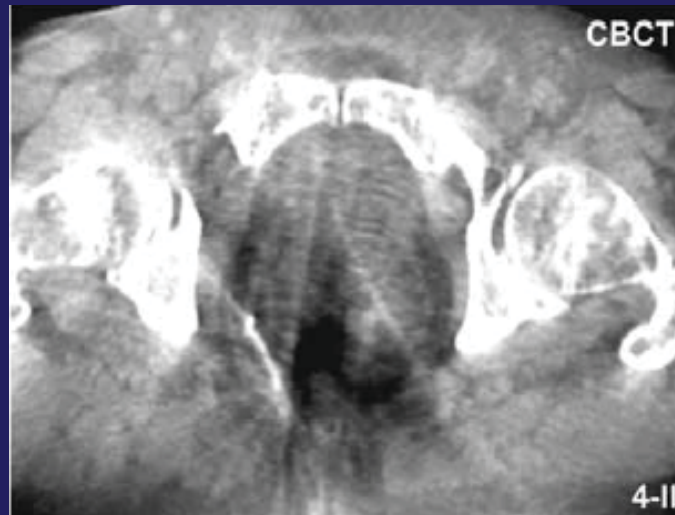
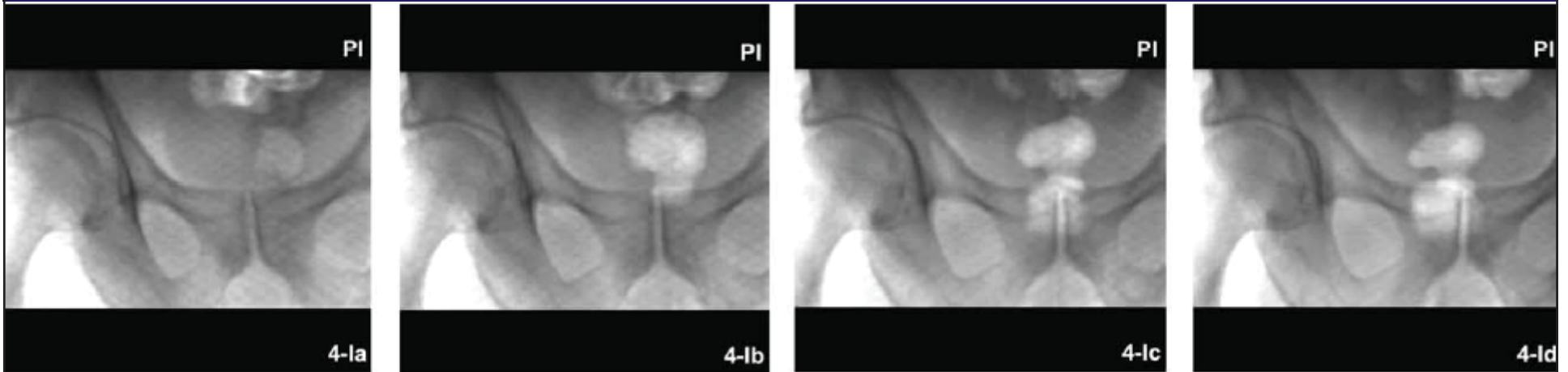
The customization capabilities allows the Physician to tailor the prescribed volume and characteristics of the device specific to the Patient's anatomy.



Is INTRA-fractional prostate motion a concern?

- Daily treatment 20-25 minutes to setup and deliver
- Prostate positional change during this interval largely due to transient rectal gas
- Positional change can be large (>5 mm), but usually transient

Transient rectal gas



Smitsmans et al. IJROBP 63, 2005

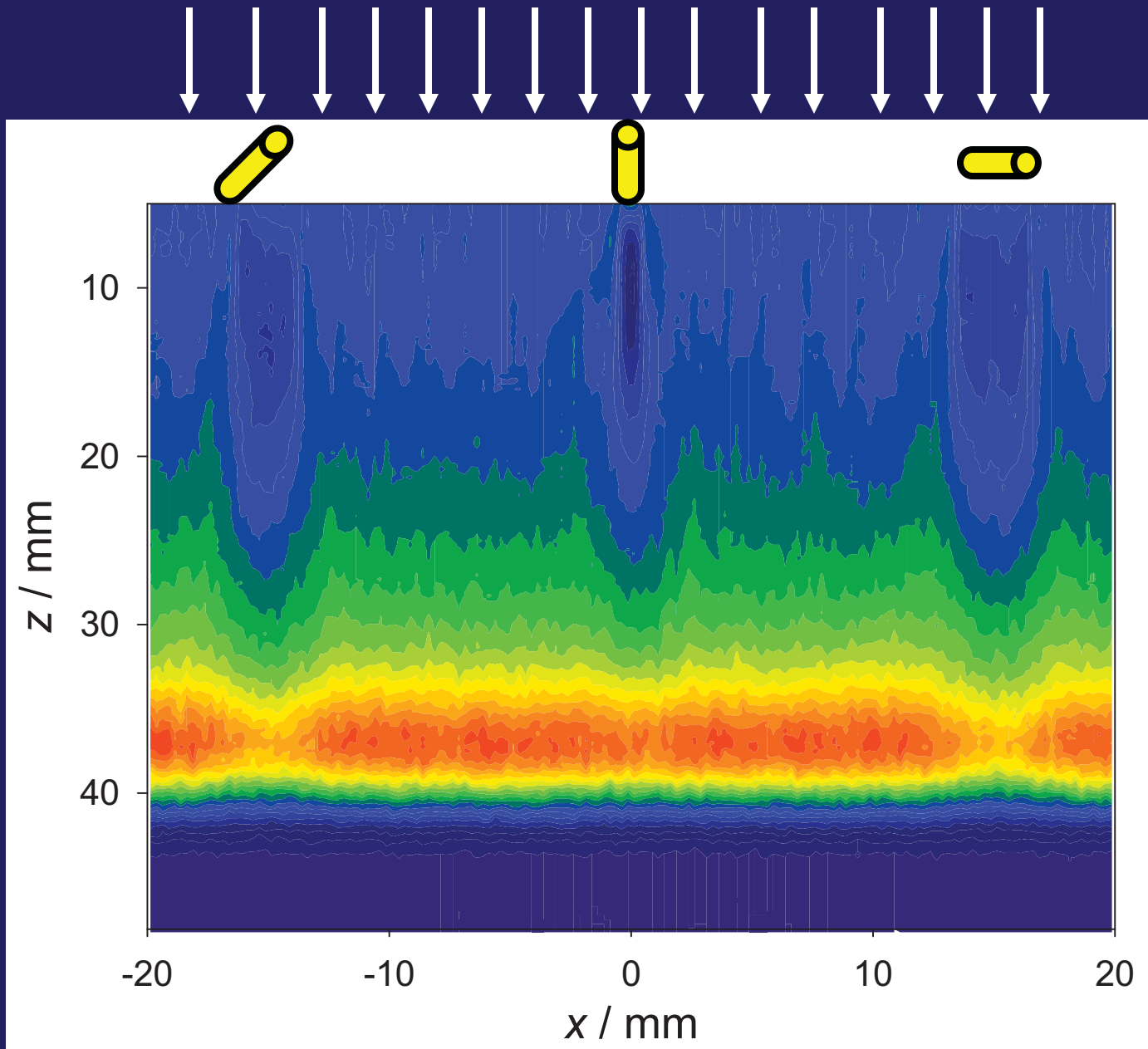
How to handle gas?



Fiducials

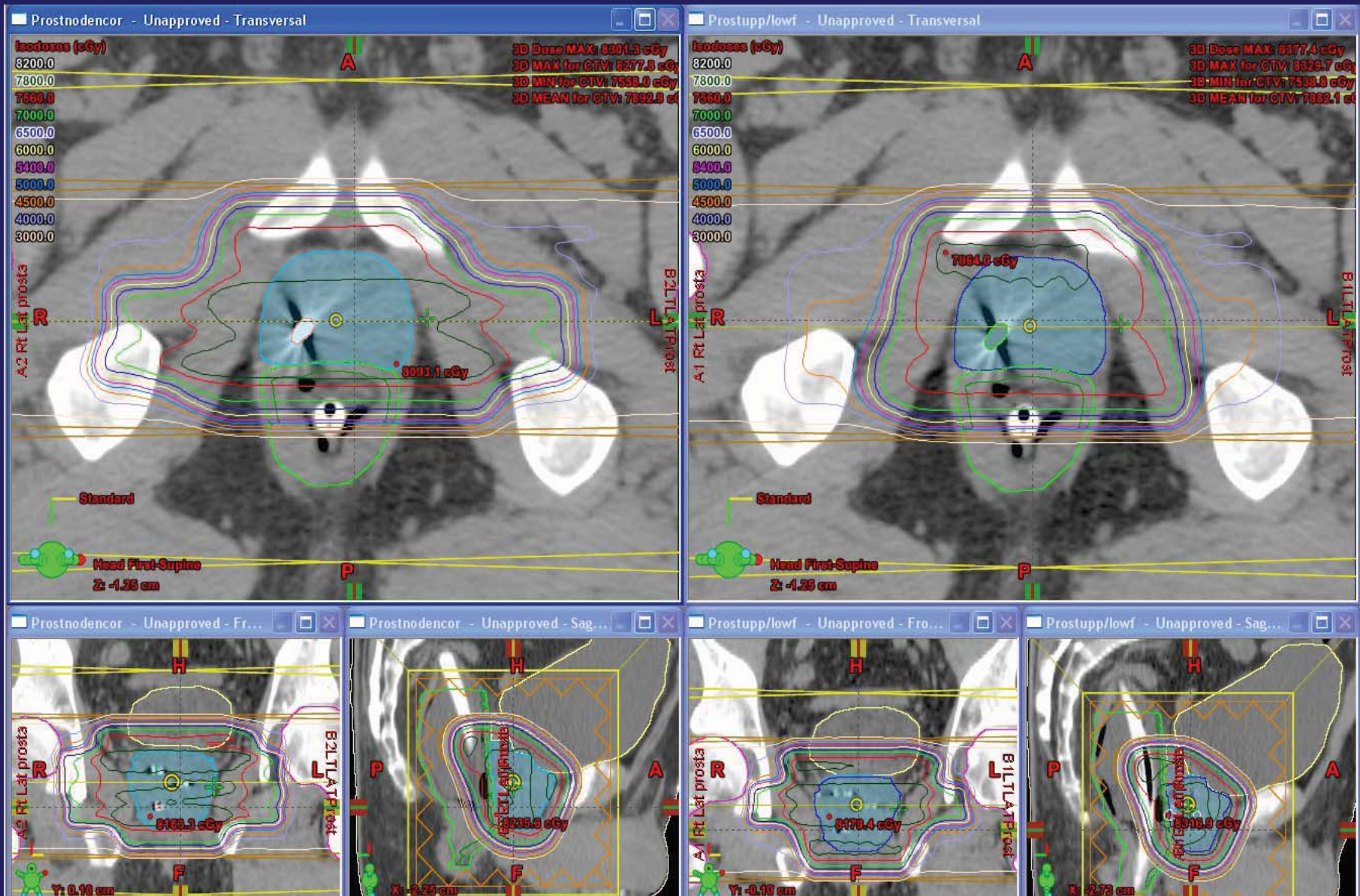
- Current fiducials optimized for MV imaging: **dense** (gold) and **large** (1.2 x 3mm)
- Fiducials may cause dose shadowing of dose (Newhauser et al.)
 - Size
 - Orientation
 - Density

Newhauser et al: Dose Perturbations from Au Cylinders



All 3 large fiducials to 3000 HU

No fiducials (over-ridden to tissue density)



To fiducial or not to fiducial

- PROS

- Target guidance

- CONS

- Endorectal balloon + bony alignment is adequate
- Large motion may change radiologic path length
- More work for dosimetry!
- Triple jeopardy
 - CT artifact results in additional uncertainty
 - Dose shadow
 - Volume averaging results in artificially large fiducial...effect on compensator design & dose heterogeneity

Fiducial markers



If you plan on using fiducials

- Use smallest and least dense material visible on your lateral KV OBI
 - Consider using fewer markers
- Consider pros and cons
- Do you really need it

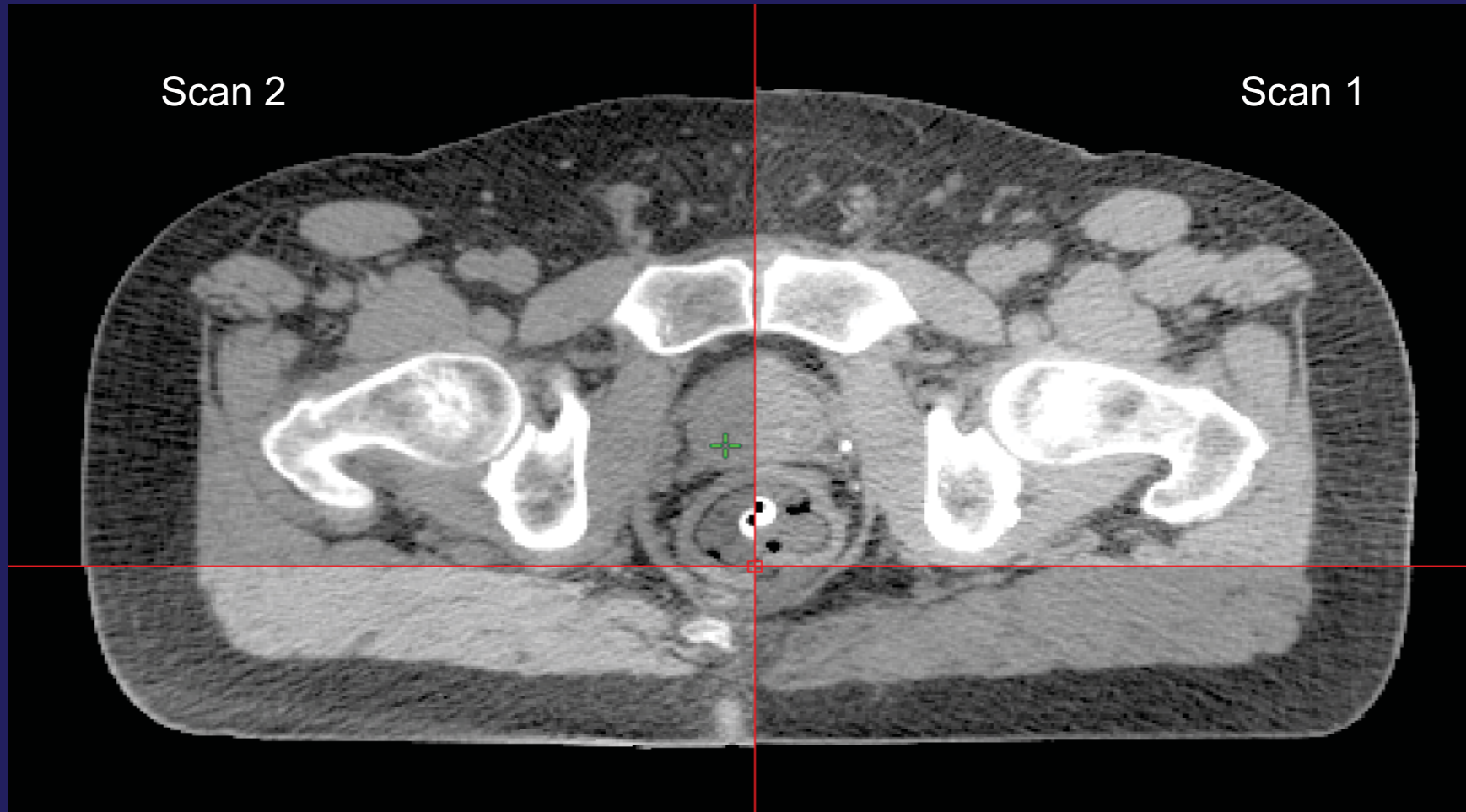
At simulation

- Supine in knee-foot cradle
- Empty rectum and semi-full bladder
- Endo-rectal balloon w/ 100cc water
 - Air bubbles assigned water density
- Initial setup marked on skin but not final isocenter

- **Repeated 20-60 minutes later**
- Physician reviews scan for reproducibility
 - Fusion based on bony anatomy

- Treatment plan performed on selected scan
 - **Optional “verification”** plan on other CT data set

Fusion at simulation between scan 1 and 2



No need for verification plan

Planning parameters

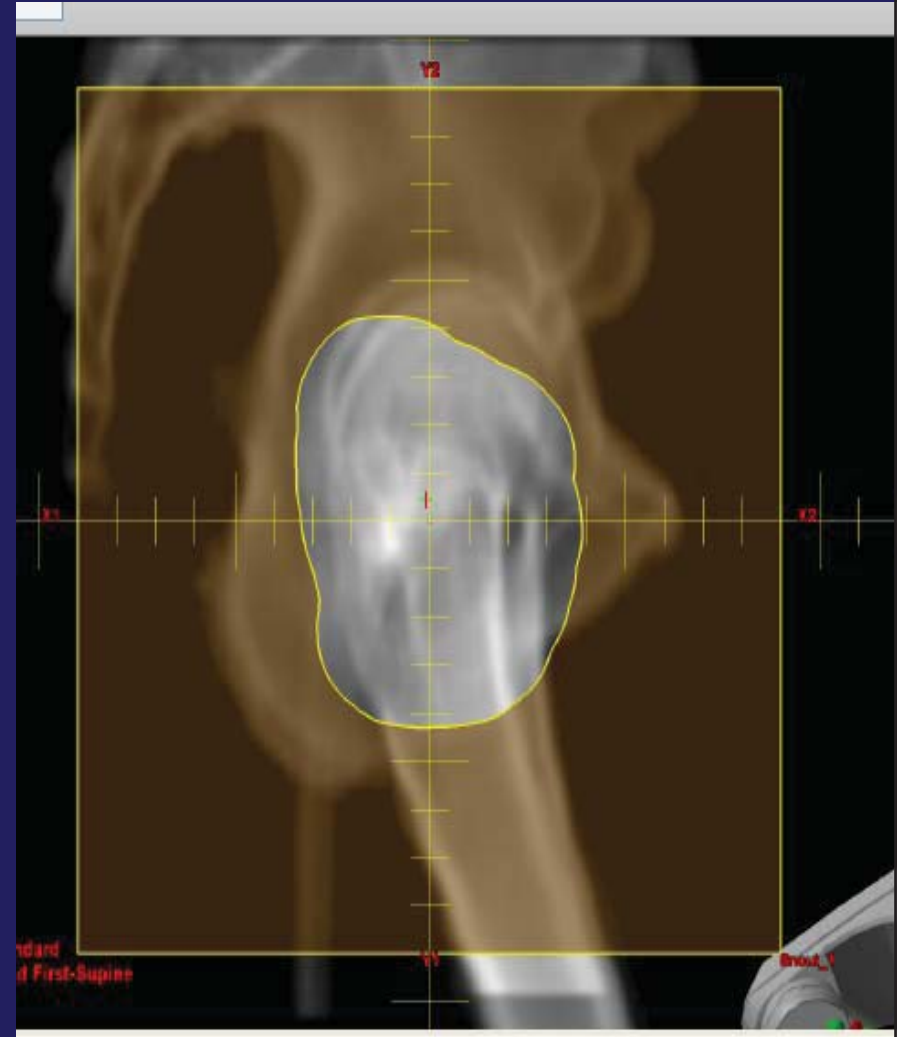
- Right & left lateral beams (daily)
 - Improved conformality
 - Potentially more forgiving and robust
 - Geometrically and biologically (RBE)
 - Trade off is patient throughput
- Initially 75.6 CGE (1.8CGE/fxn) for first 179 pts
- Now 76 CGE (2 CGE/fxn) to 100% CTV+margin
 - Usually prescribe to 98-96% isodose line
 - Mean CTV dose ~79 CGE
- CTV = Prostate + Proximal SV

- Setup uncertainty $\leq 5\text{mm}$
- Distal margin = $(0.035 \times \text{distal CTV radiological depth}) + (3\text{mm})^*$
- Proximal margin $\sim 1\text{cm}$
- Smear $\sim 0.9\text{ cm}$

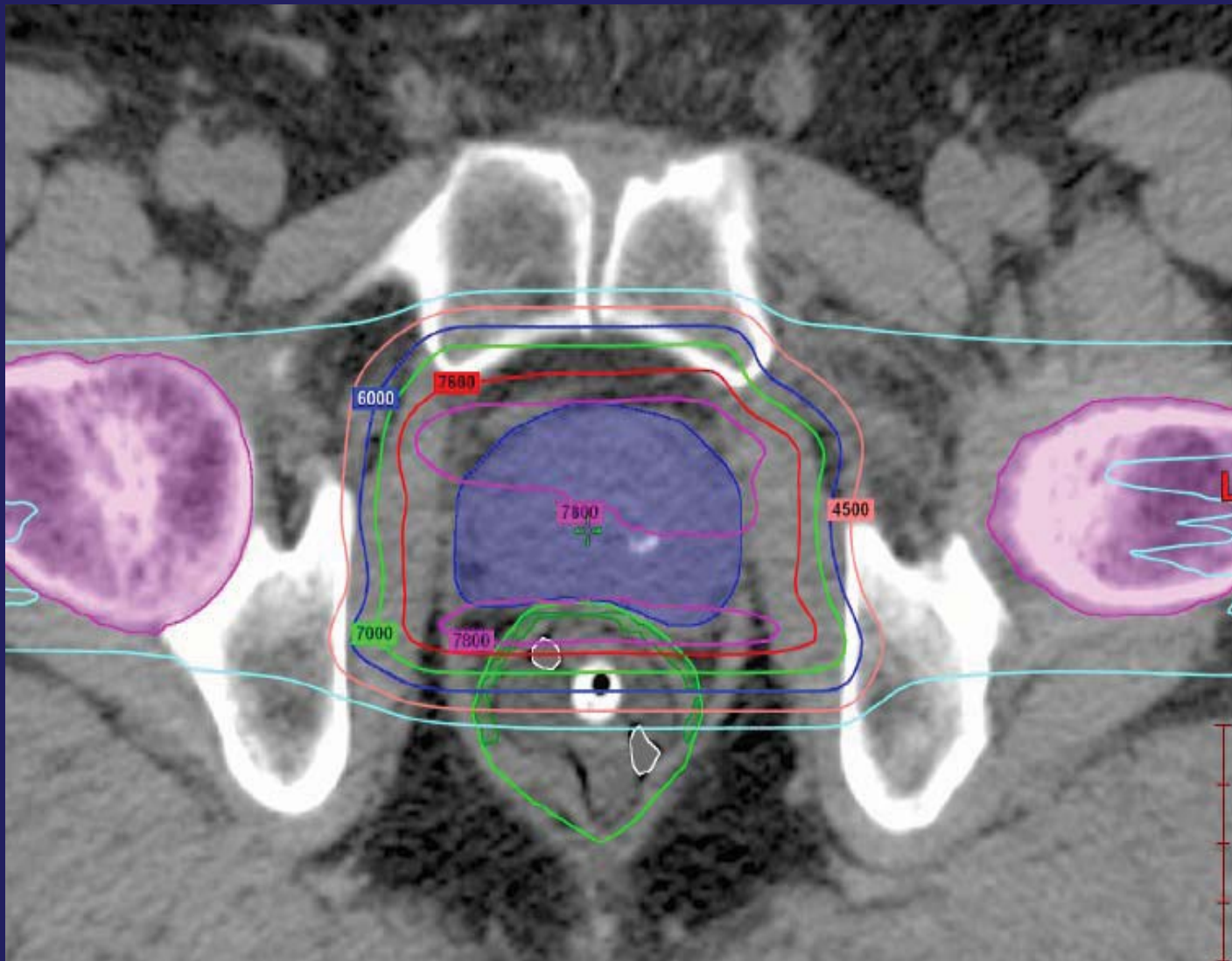
(*Beam range uncertainty)

Lateral Margin

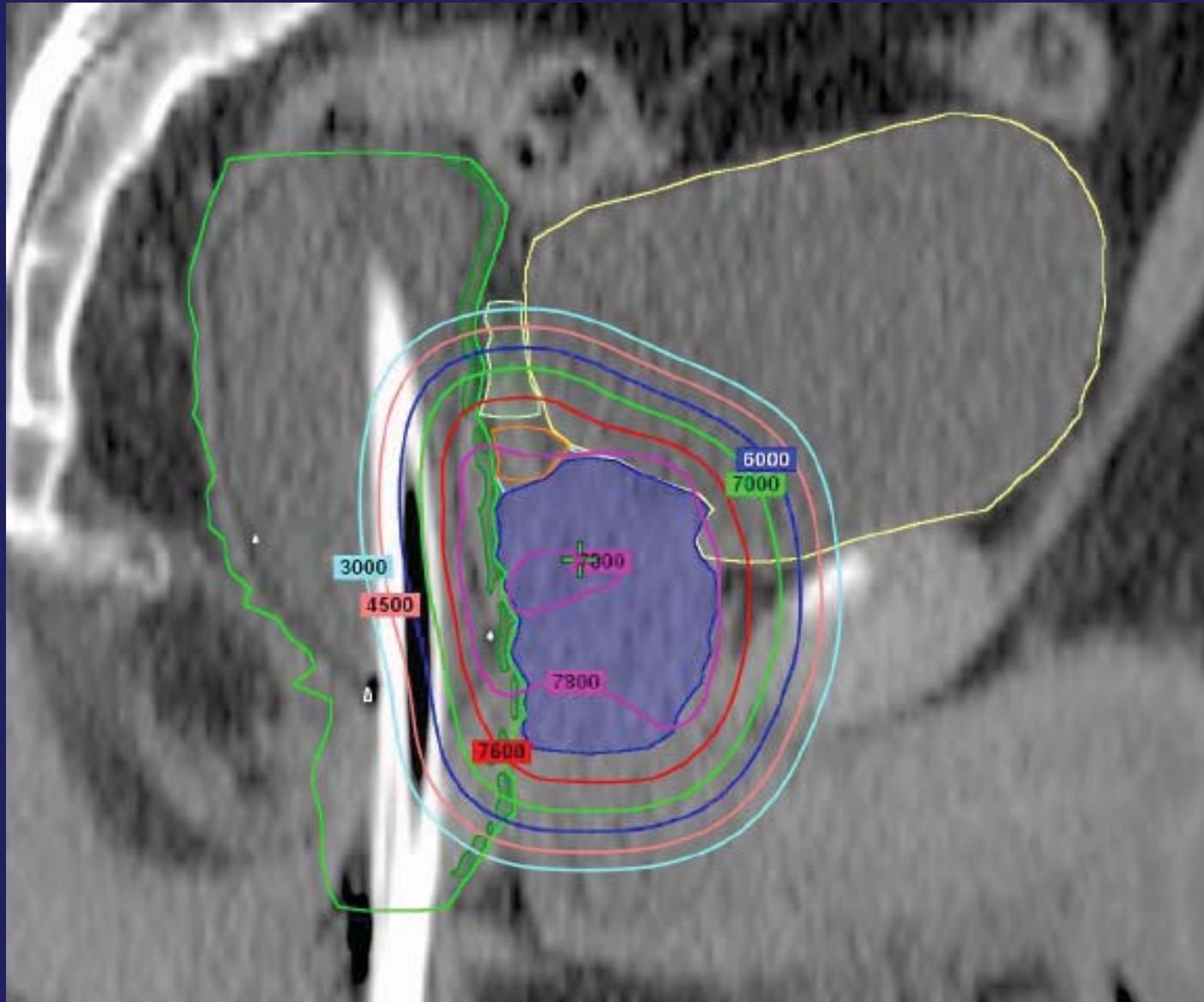
- $LM = \text{setup uncertainty} + \text{penumbra}$
- Setup uncertainty = 0.5cm
- 250 MeV beam penumbra (95-50%) = 1.2cm
- **$LM = 1.7 \text{ cm}$**



Two opposed lateral beams

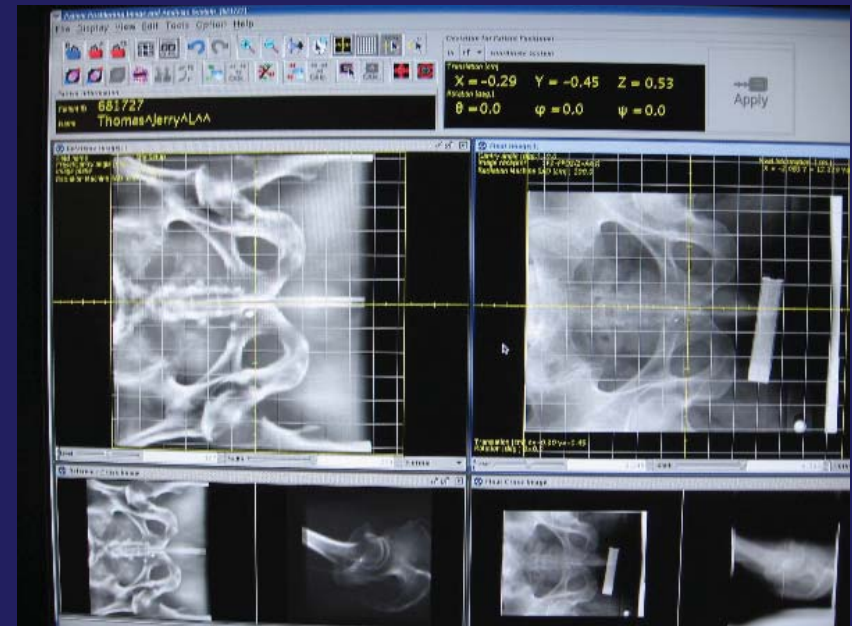
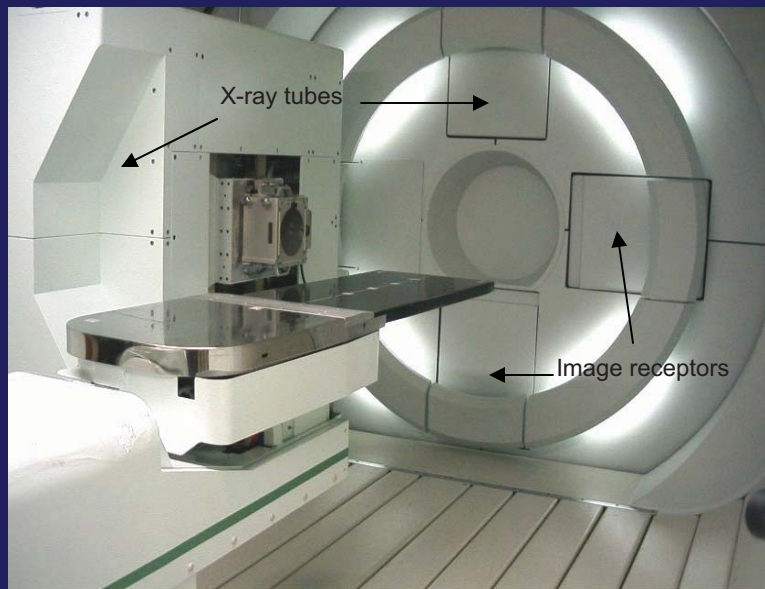


Sagittal view



Patient alignment at PTC-H

- Daily orthogonal kV x-ray images taken to align bony anatomy with reference DRR's using 2-D matching

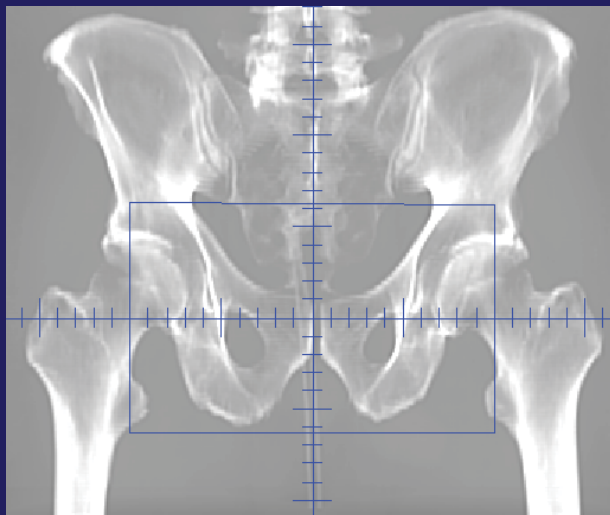


Positioning Image Analysis System, 'PIAS'

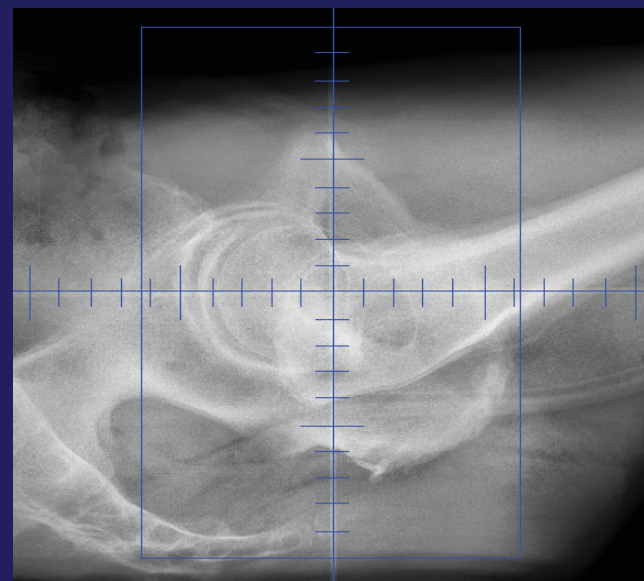
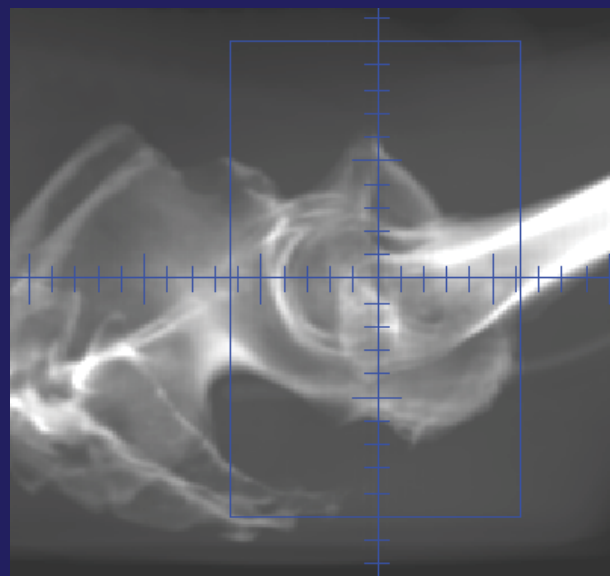
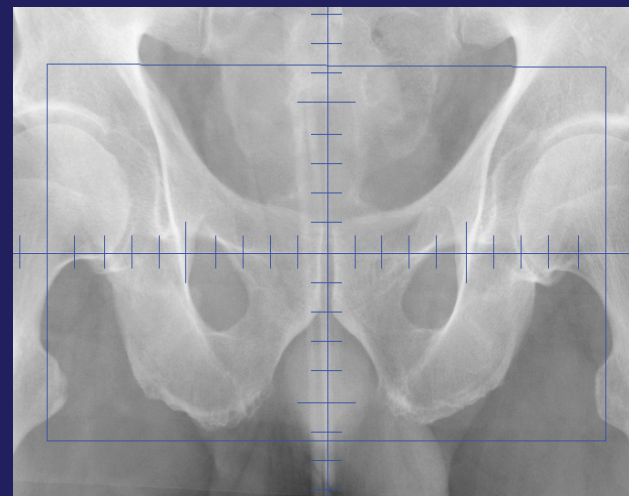


Hitachi

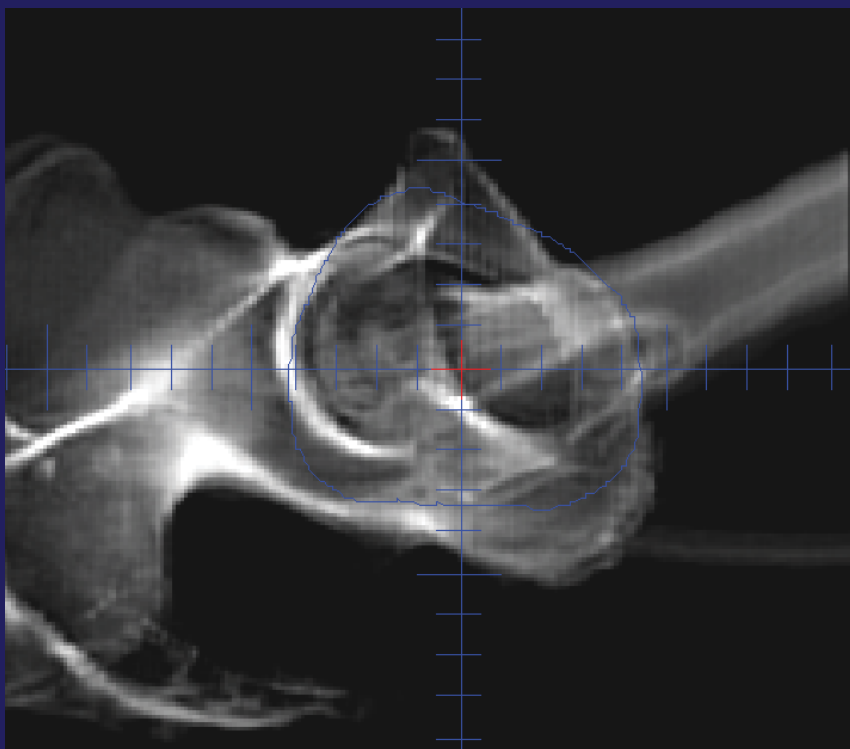
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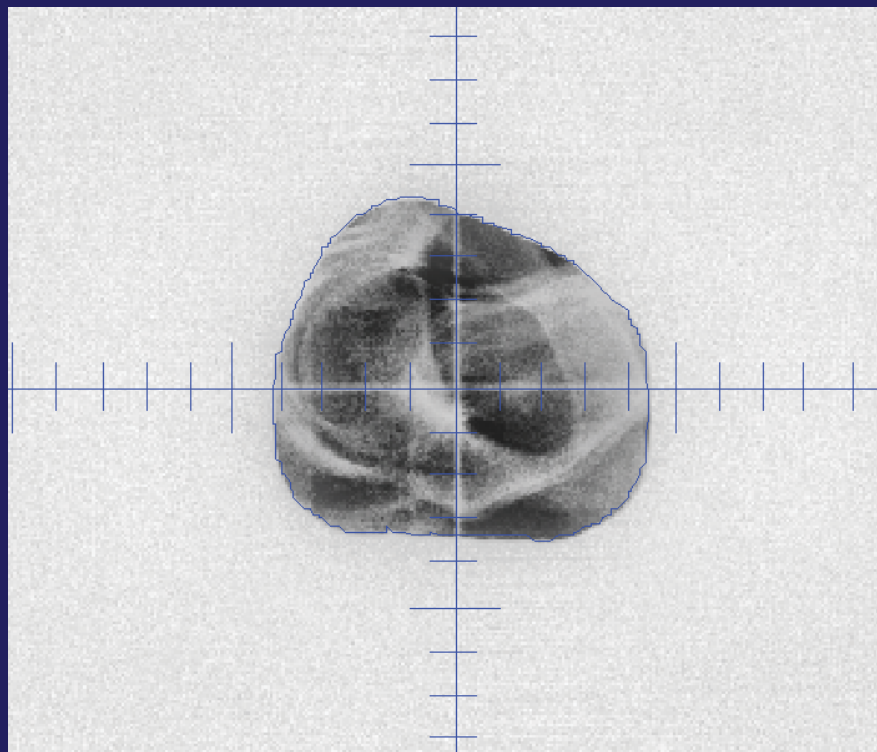
DAILY IMAGE



REFERENCE IMAGE

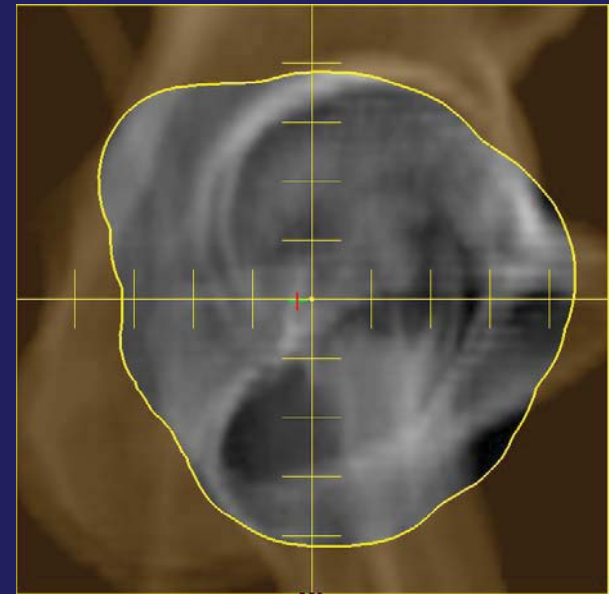
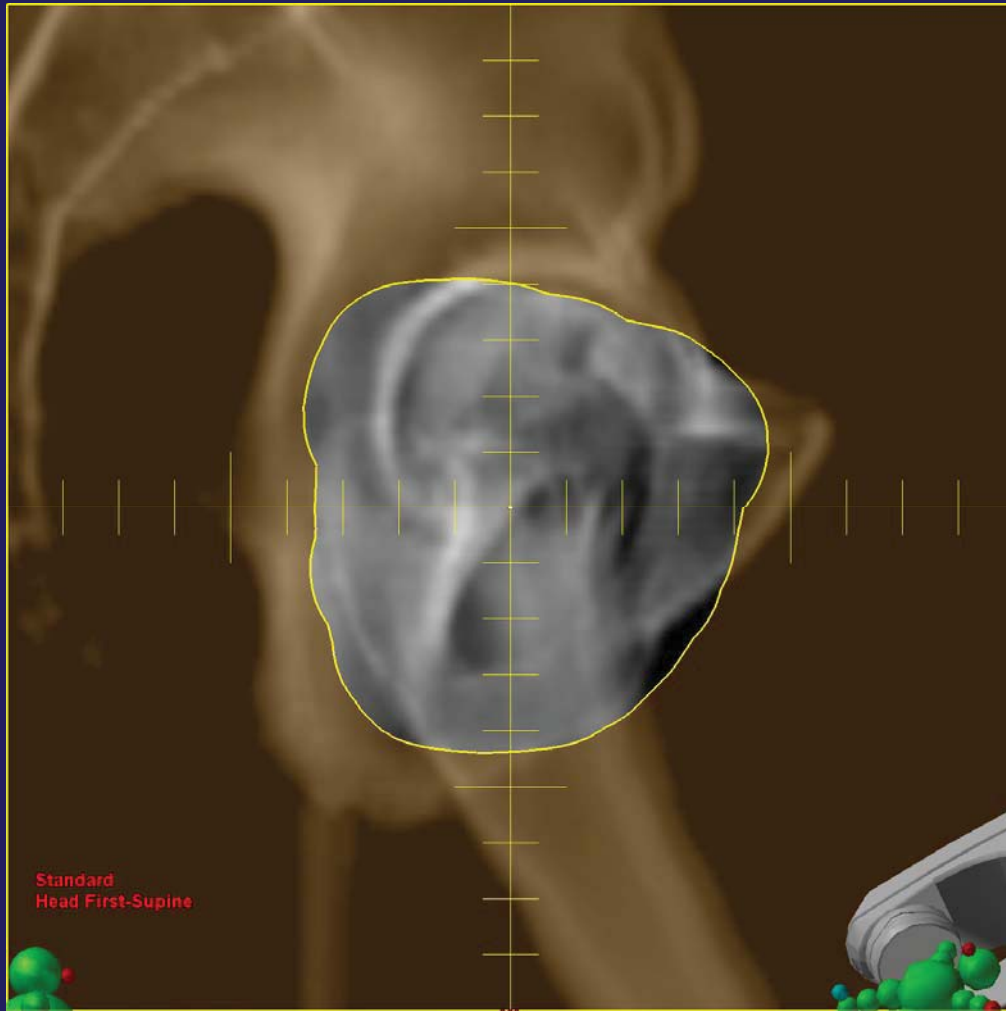


DAILY IMAGE





Medium vs. Small snout



Small snout

Pros:

- Less brass
 - RTTs
 - Fewer neutrons
 - \$\$
- Allows deeper range for lower energies
 - 225 vs. 250 MeV
 - Sharper penumbra

Cons:

- Limited field size
- May require snout change for larger targets or disease sites
- More commissioning

Long-term proton toxicity

- Single institution (LLUMC) reports 99% freedom from late grade 3-4 GI or GU at 10y
 - IJROBP 59:348-352, 2004
- Randomized study reported < 2% late Gr 3+ in high dose arm 79.2 Gy (median FU 5.5 y)
 - JAMA 294:1233-39, 2005

Is disease-free survival the most important factor for prostate cancer patients?

If patient fails therapy, it may not translate into a meaningful difference in survival

As disease control and survival improves (either cancer-related or other competing risks), quality of life more important

Quality of Life

(Beyond toxicity scales)

- Function vs. Irritation vs. Bother
- Baseline function
- Prospective vs. retrospective
- Patient vs. physician reported
- Validated instrument (e.g. E.P.I.C.)

MDACC protocol 2005-0956

“Prospective evaluation of quality of life after proton therapy for prostate cancer”

- Prospective
- Validated instrument (E.P.I.C.)
- Baseline → During Rx → Periodically post-Rx
- Correlate w/ dosimetric parameters

- Current enrollment 550 (since May 2006)
- Target accrual 600 men

Future directions

- Fractional dose-escalation
 - 78-80 CGE (2.0 CGE)
 - 72 CGE (2.4 CGE)
 - 66 CGE (3.0 CGE)
- Spot scanning...IMPT
- Combined modality therapy
- Alternative beam angles
- Combination protons + hormone therapy:
randomized trial

THANK YOU