Proton Therapy for Prostate Cancer

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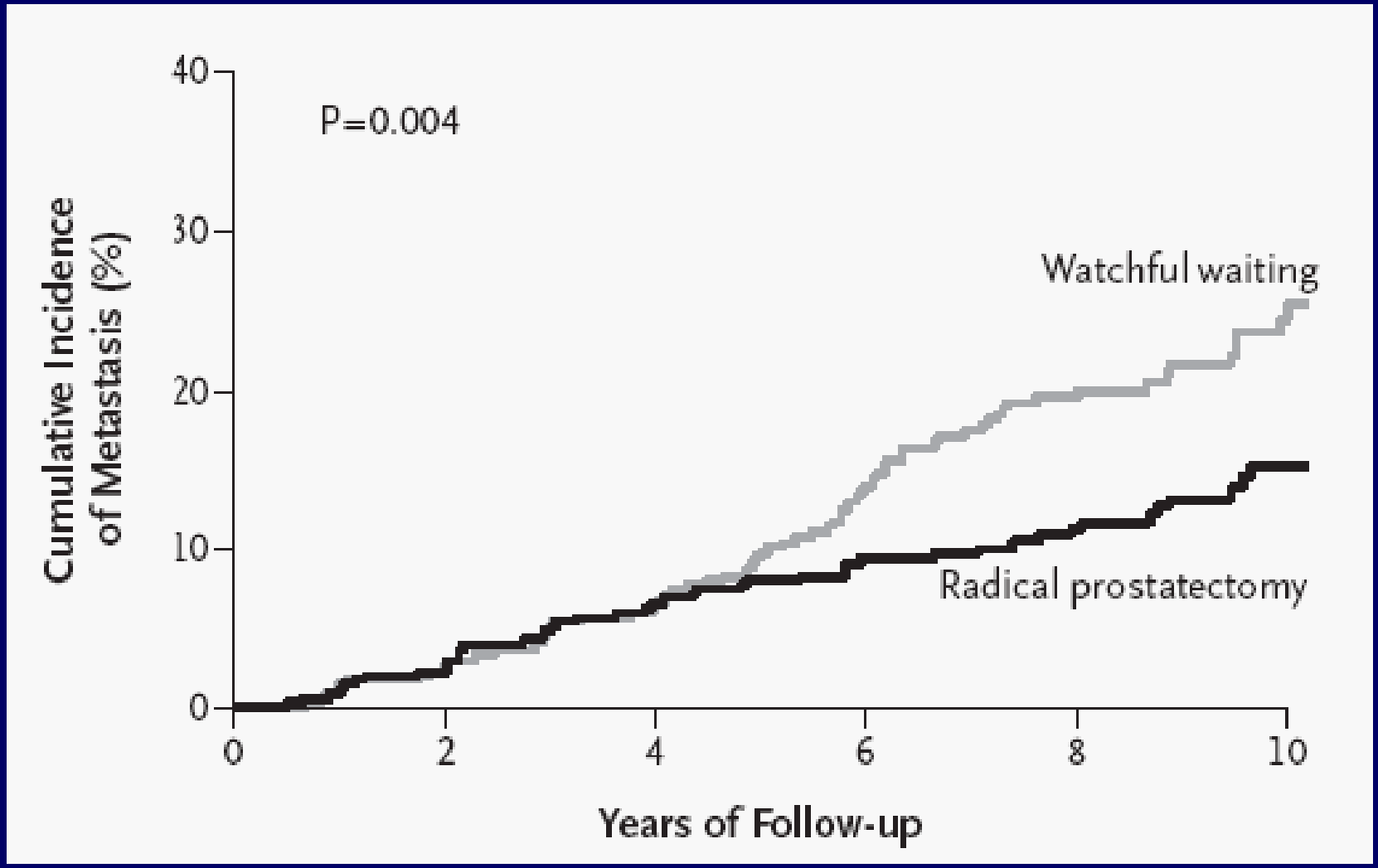
Is local therapy important for prostate cancer?

Swedish randomized trial: Distant mets



[NEJM 2005;352]

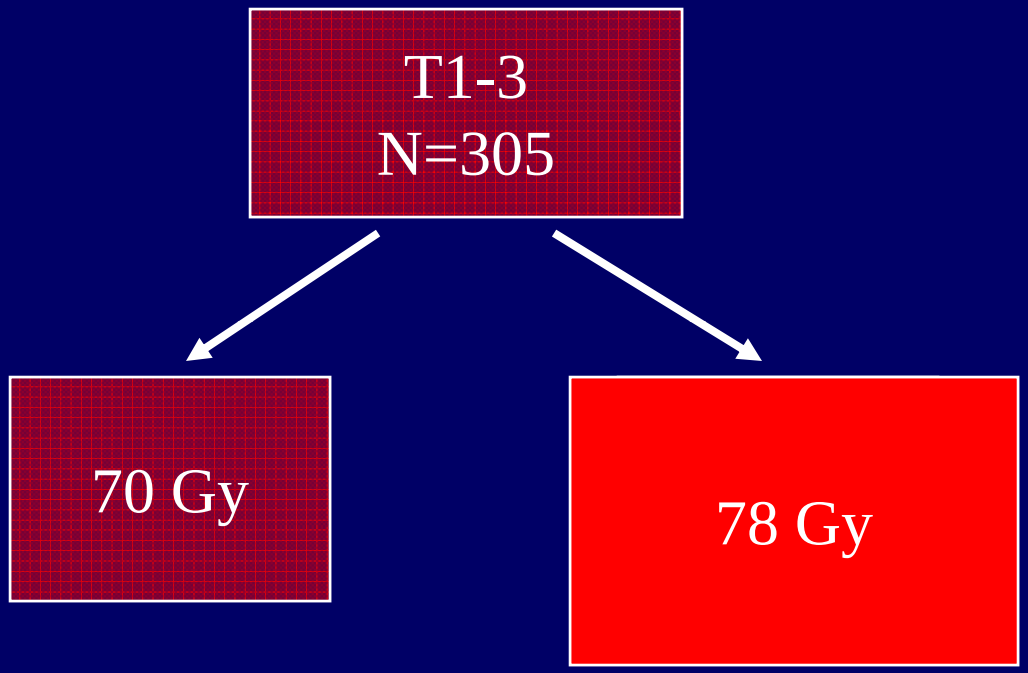
Randomized studies showing benefit to higher dose

- 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]

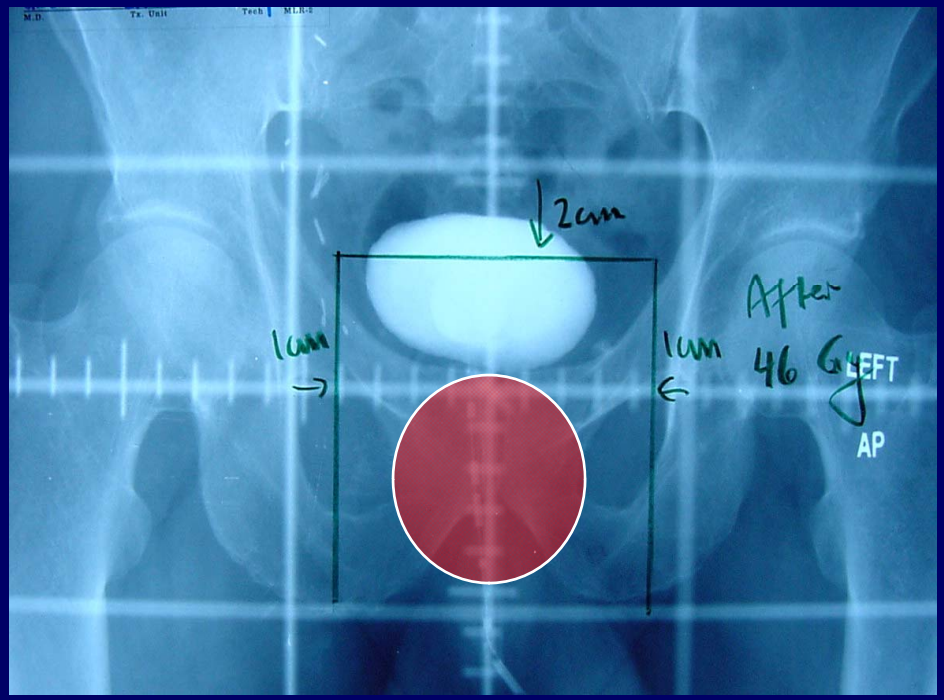
MDACC RANDOMIZED Dose-escalation Study

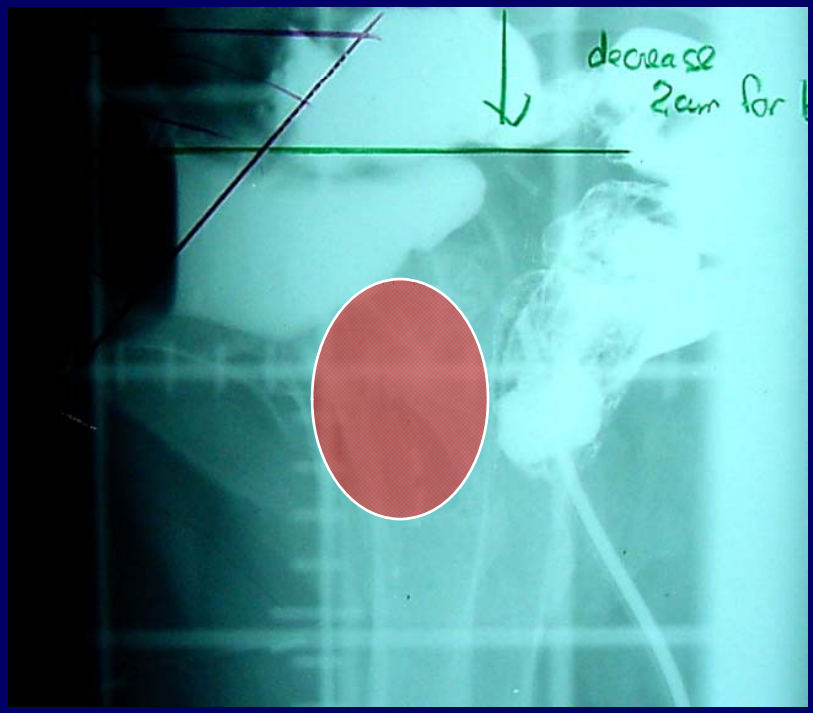


Significant difference in favor of 78 Gy
(Especially for pretreatment PSA >10)

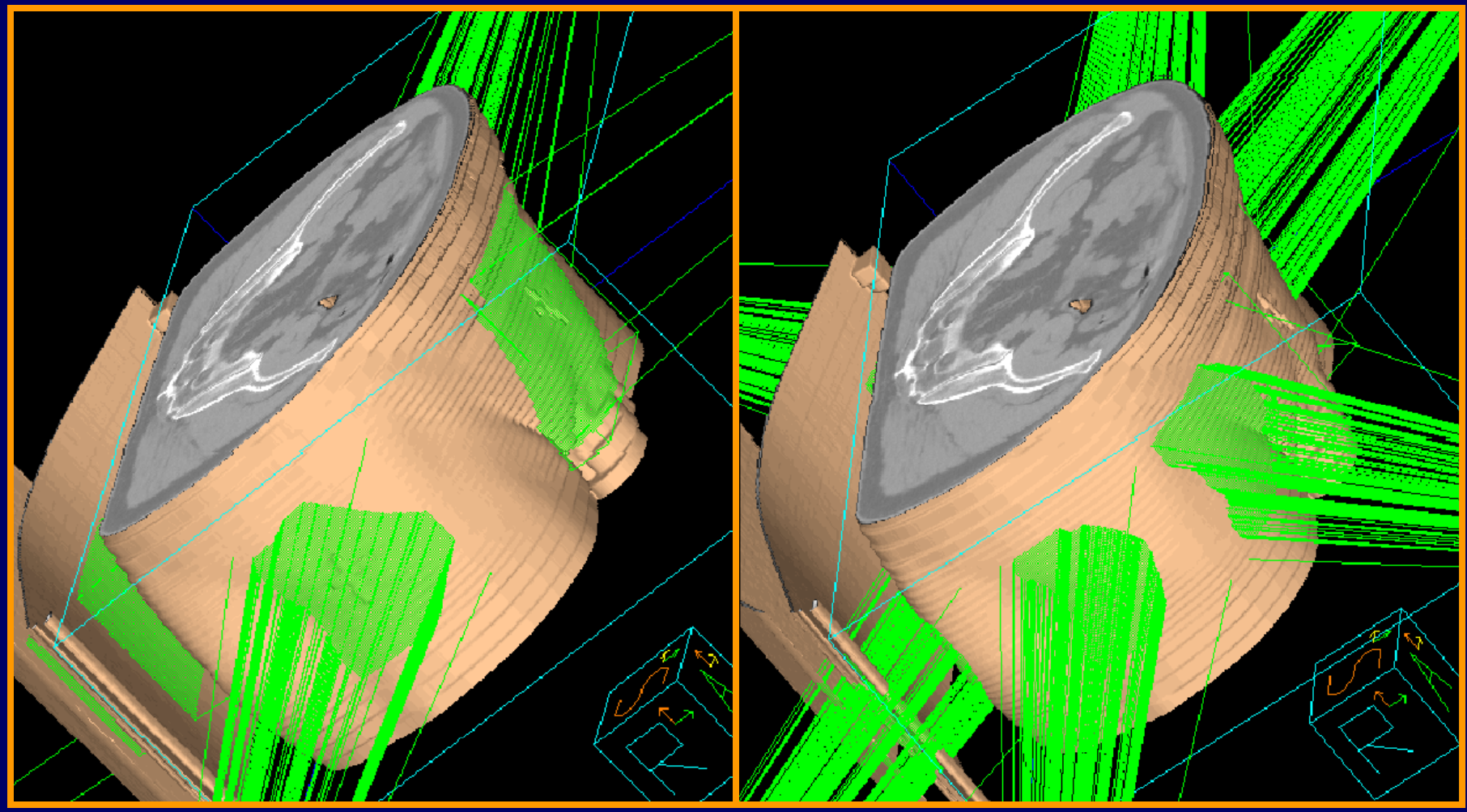
[JCO 18, 2000 & IJROBP 54, 2002]

Conventional RT – AP and LAT

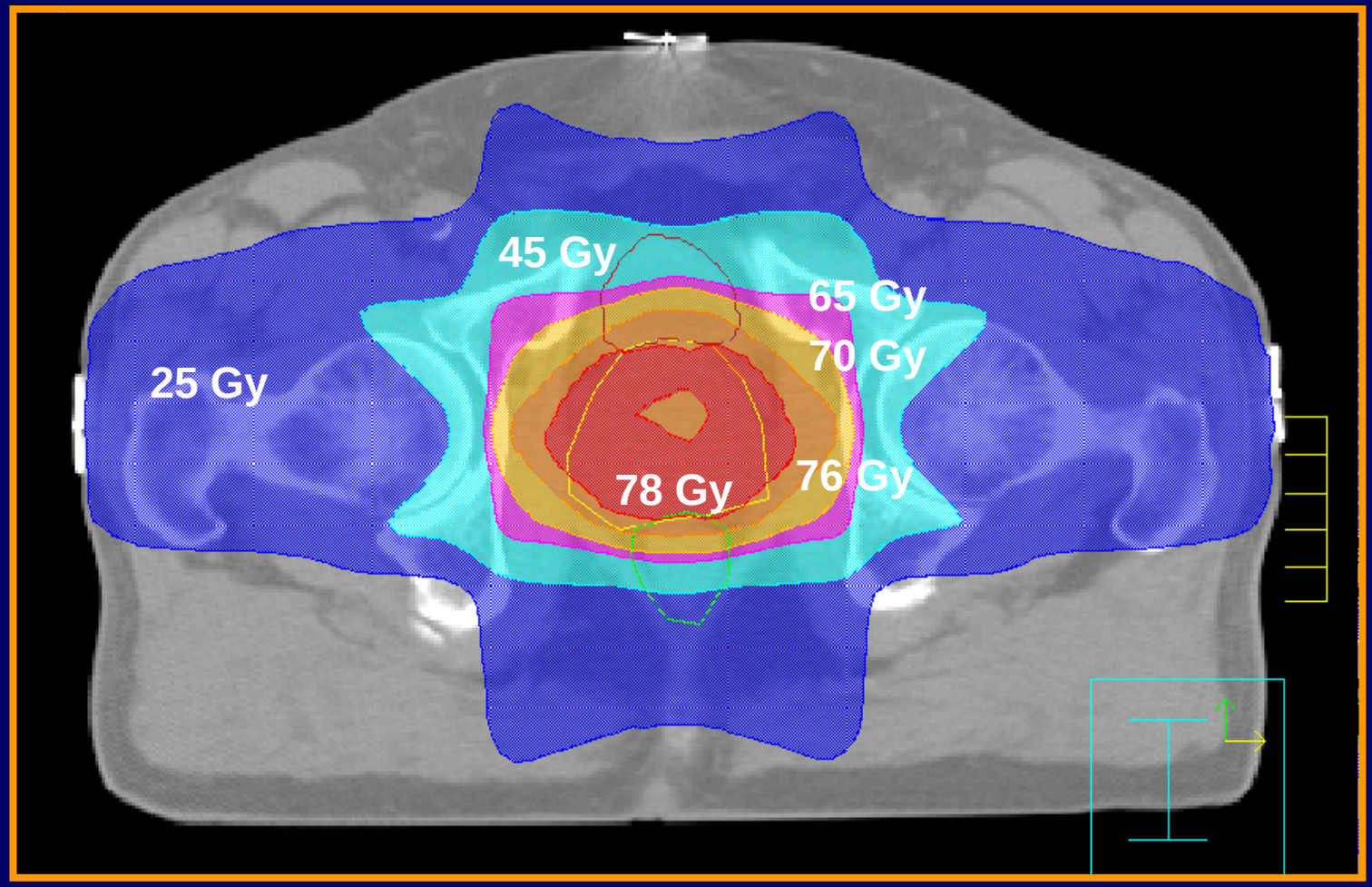




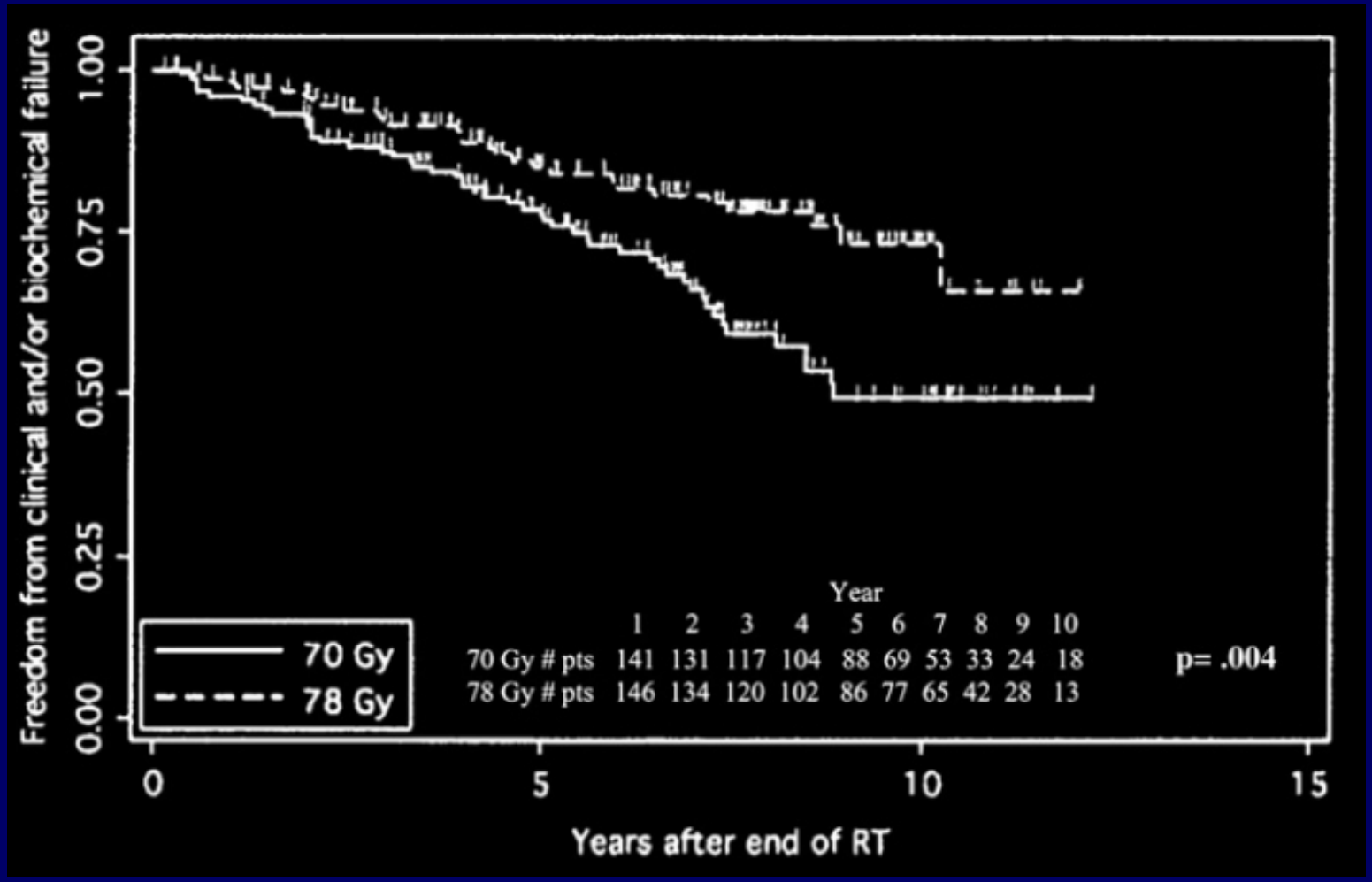
3D-Conformal RT



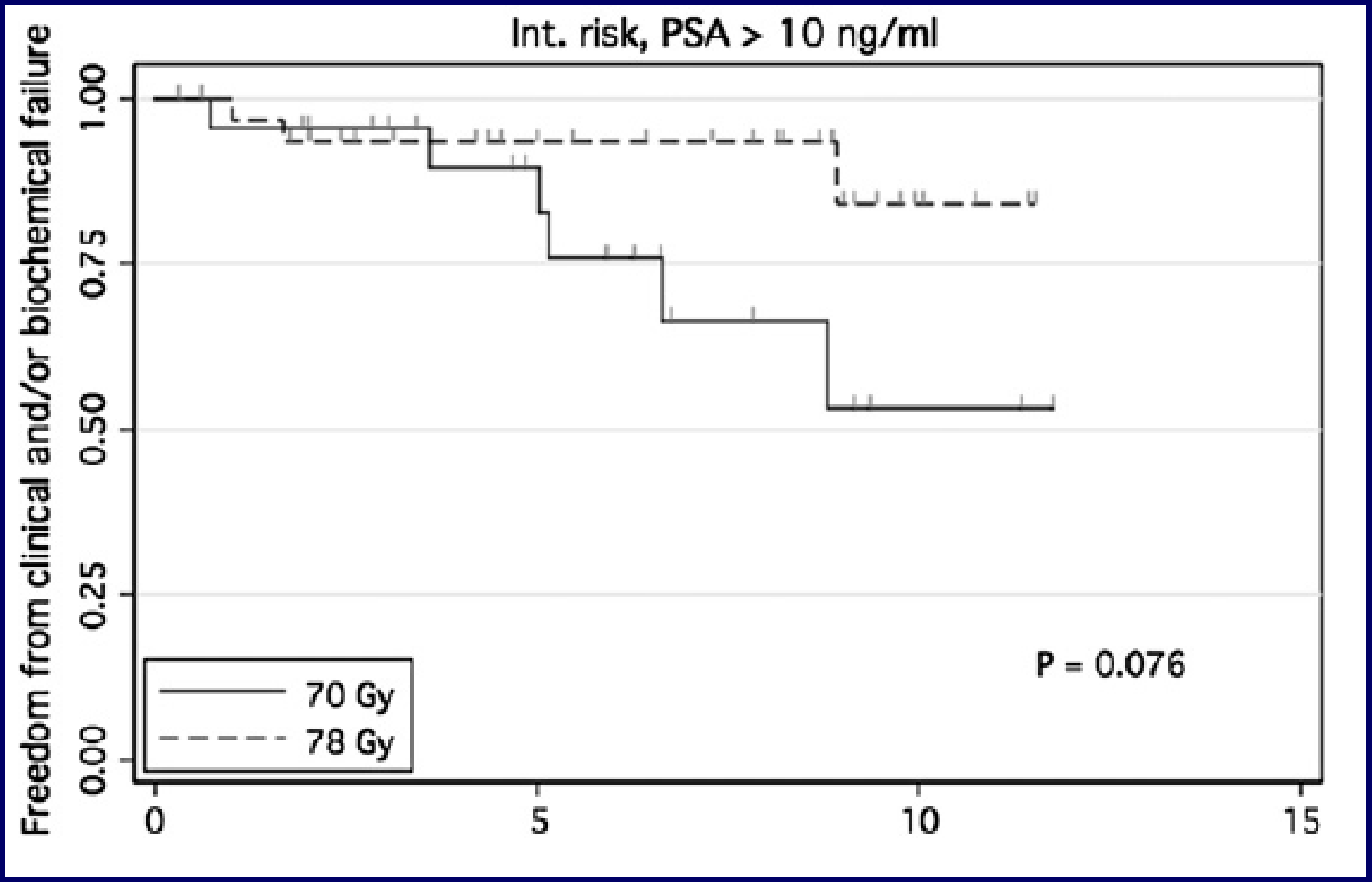
Conformal: 78 Gy to Isocenter



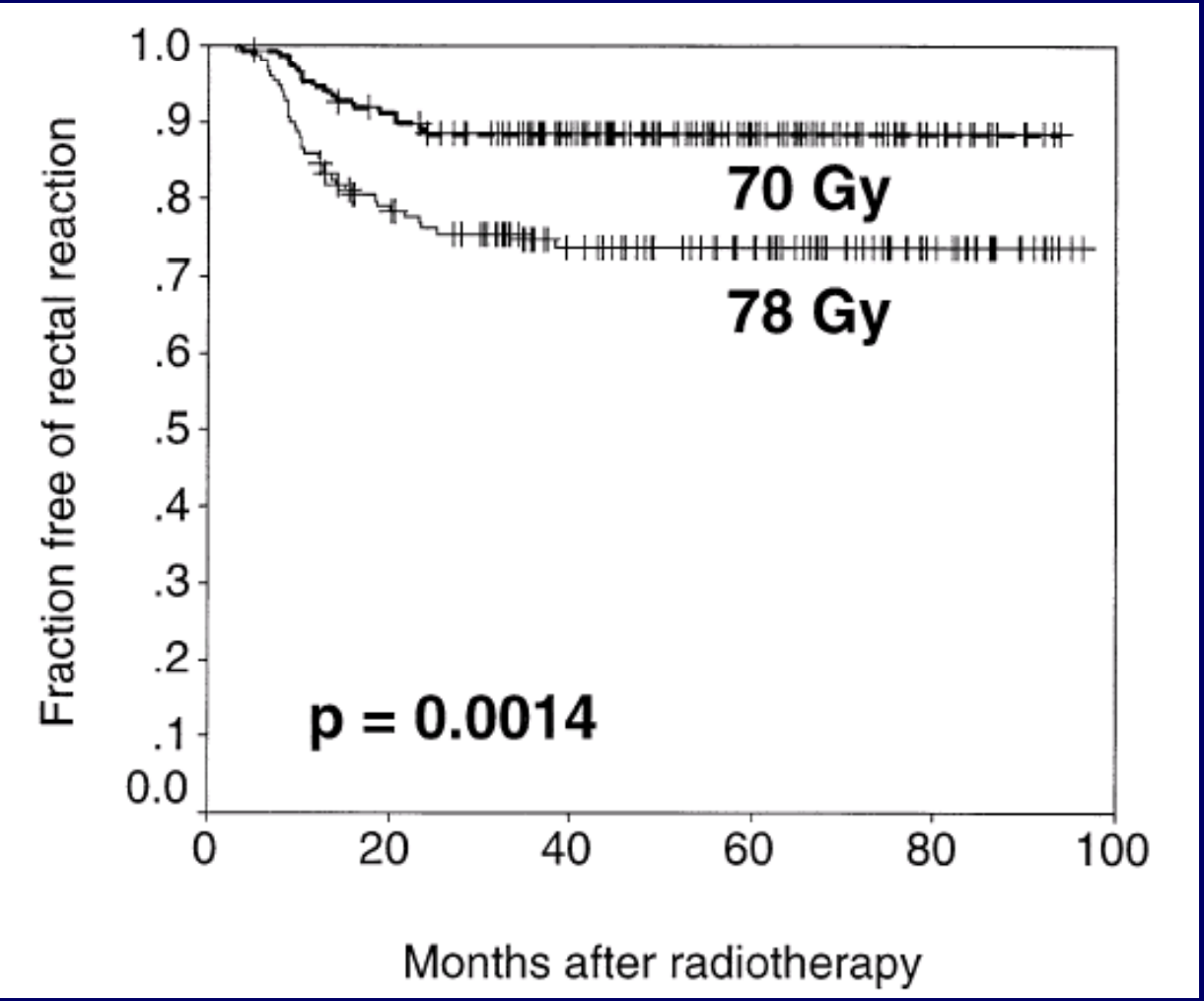
MDACC 78 vs 70 Gy: Freedom from failure



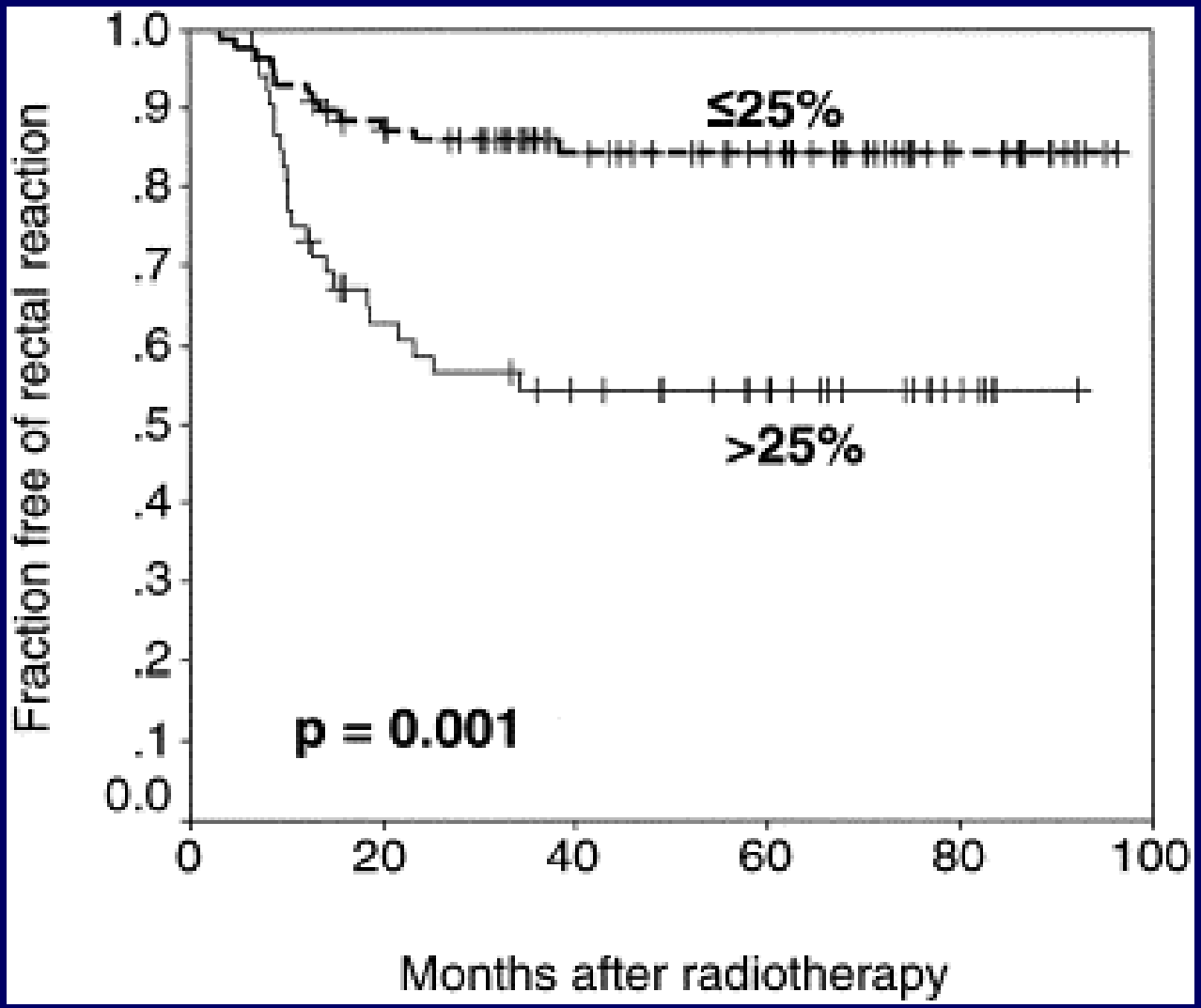
Int. risk 8-y failure rate: 94 vs. 65%



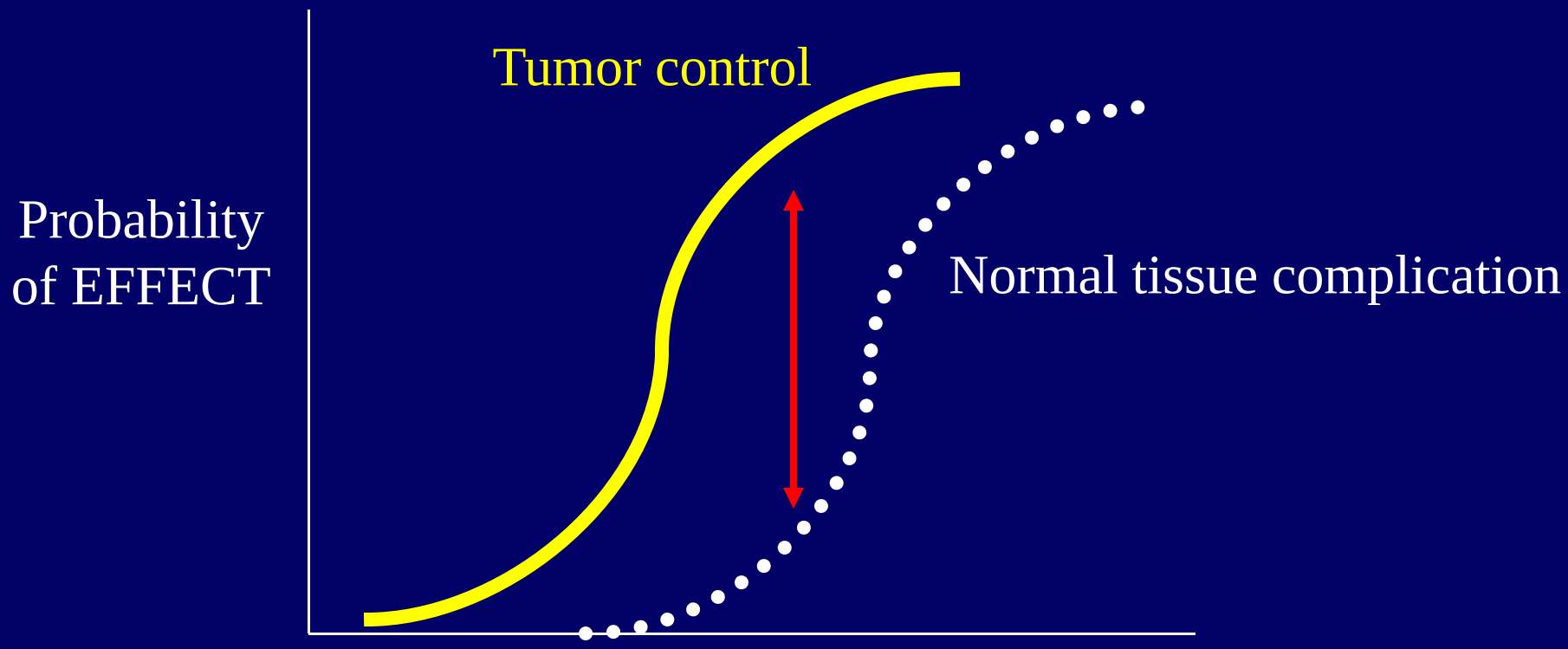
More Grade ≥2 rectal complications in 78 Gy arm [IJROBP 53, 2002]



Dose-volume effect
More rectal toxicity when >25% receives over 70Gy

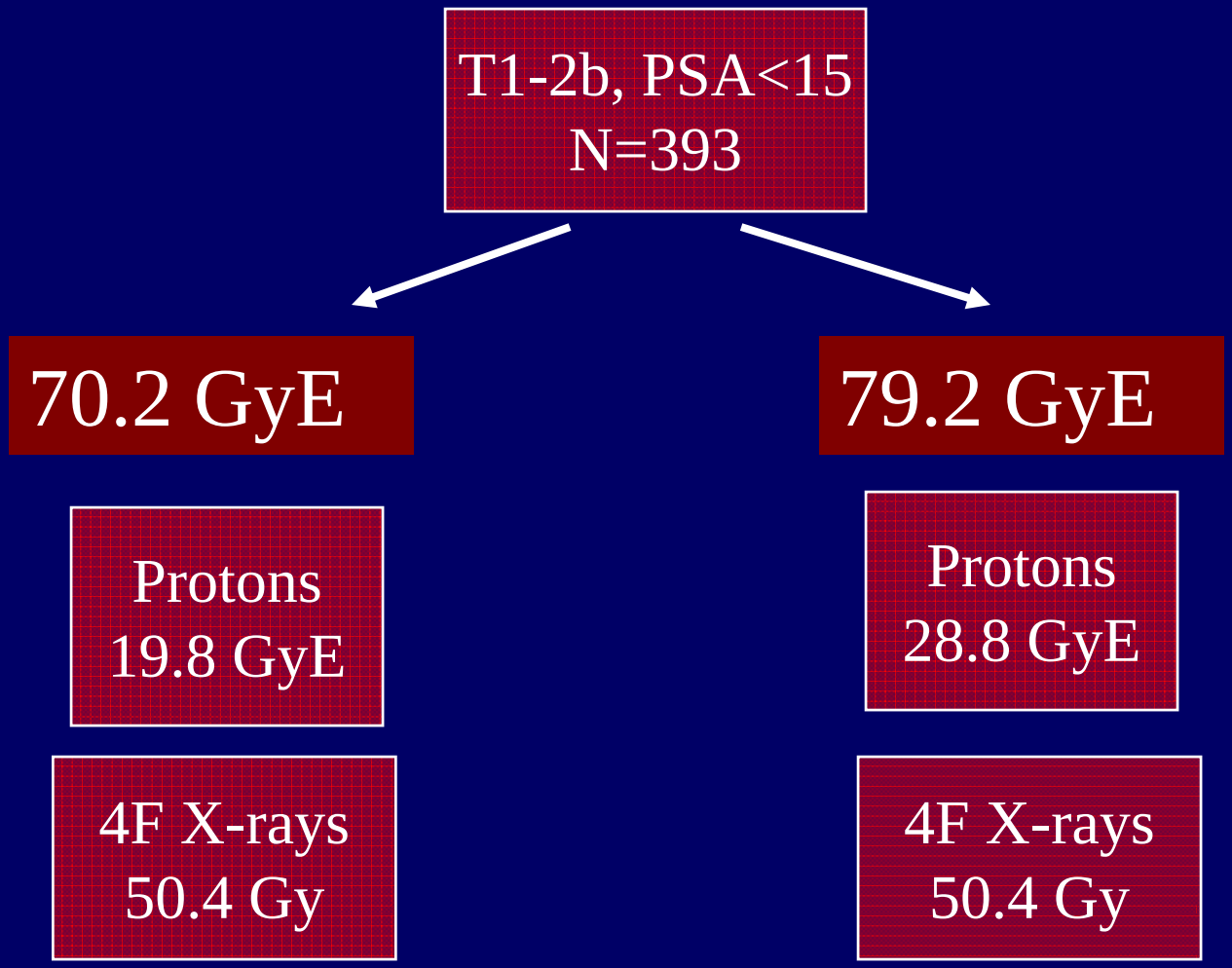


Therapeutic ratio



PROG 95-09

Proton-photon randomized trial



JAMA 294, 2005

MGH Perineal boost

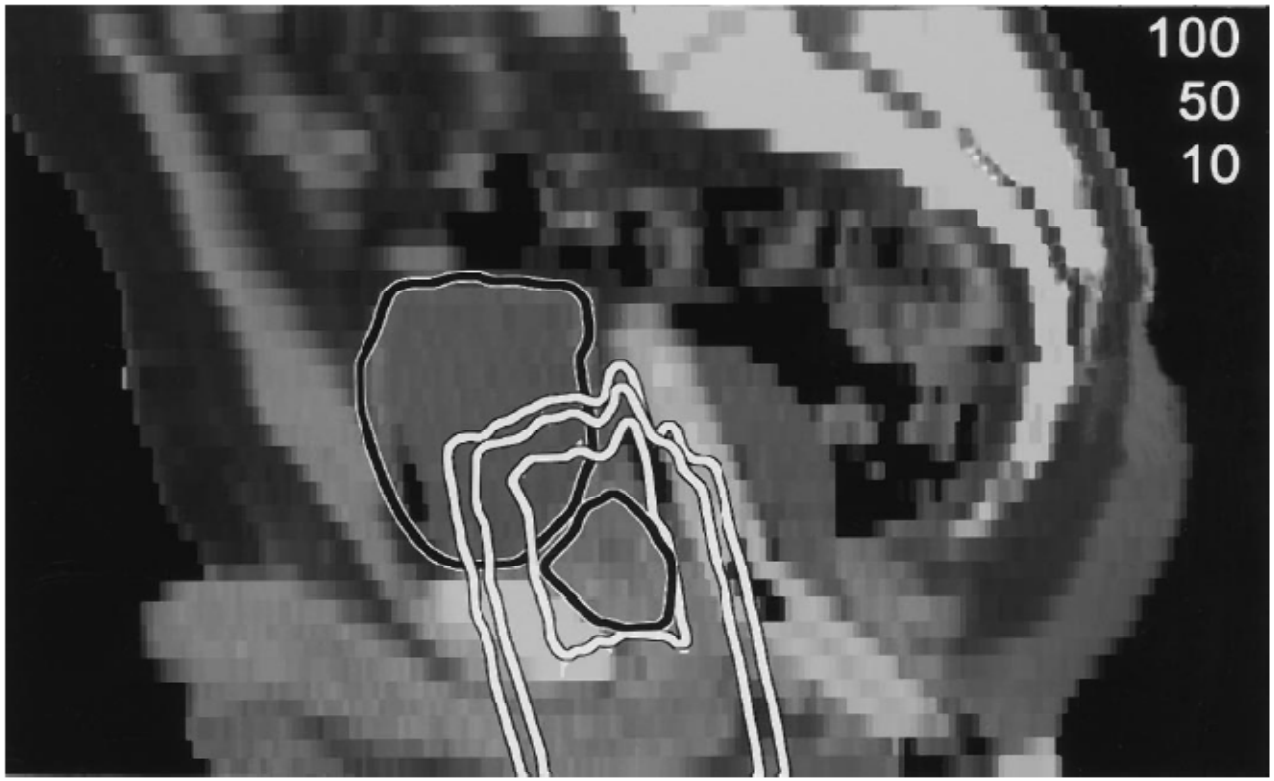
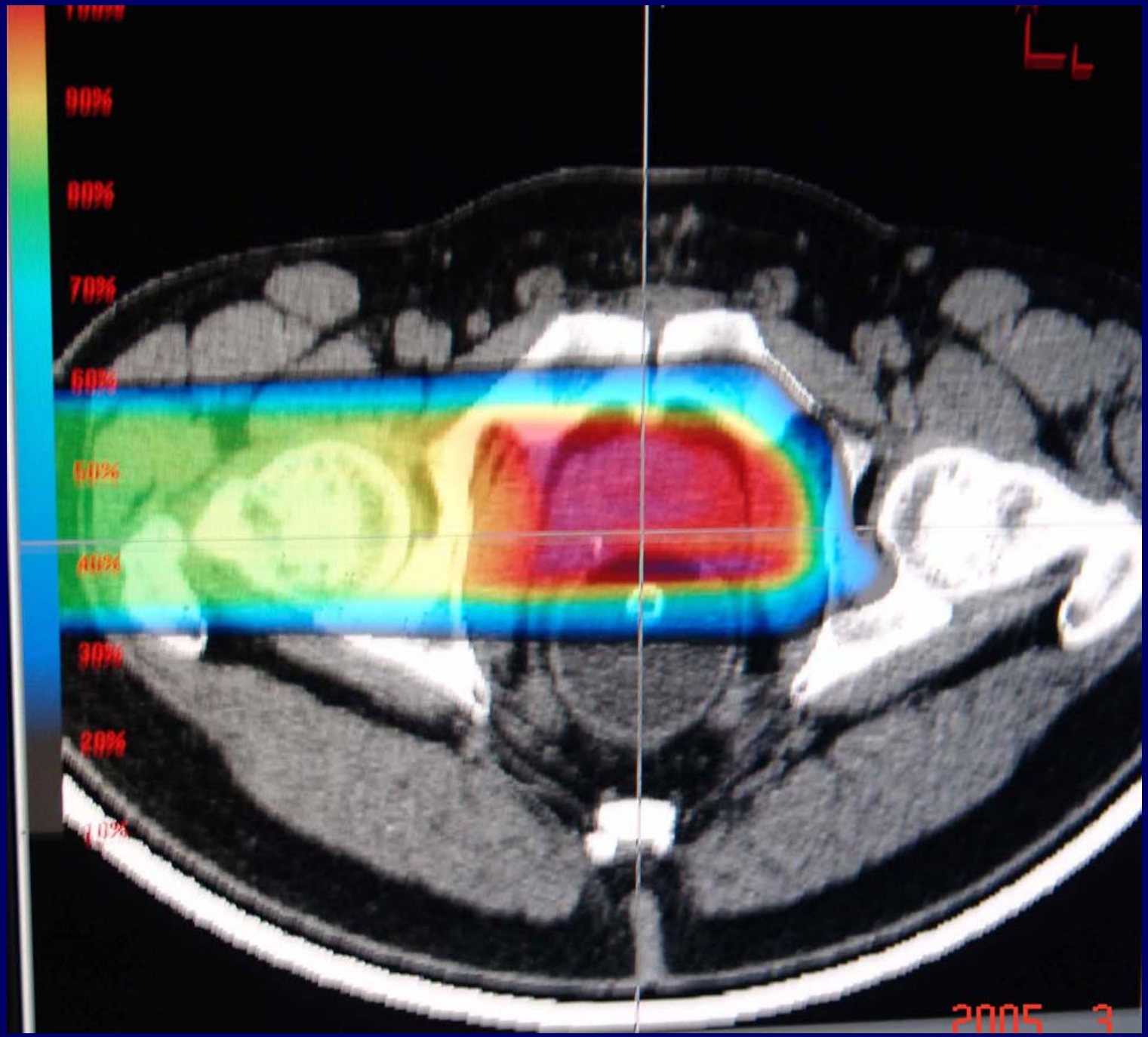
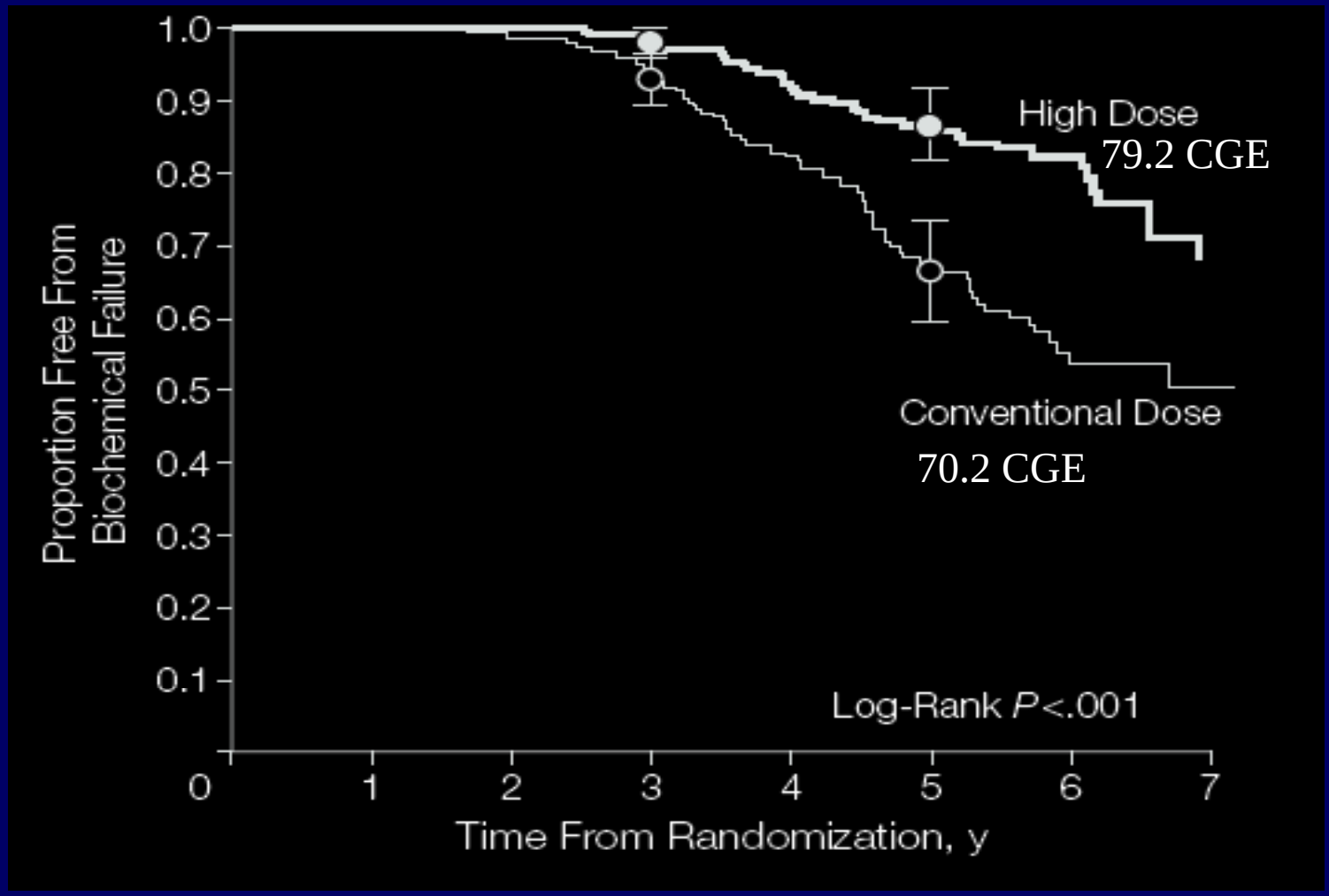


FIG. 1. Sagittal CT reconstruction shows perineal proton boost technique and how beam high dose region incorporates prostate, prostatic urethra and bladder neck.

Journal of Urology 167:123, 2002

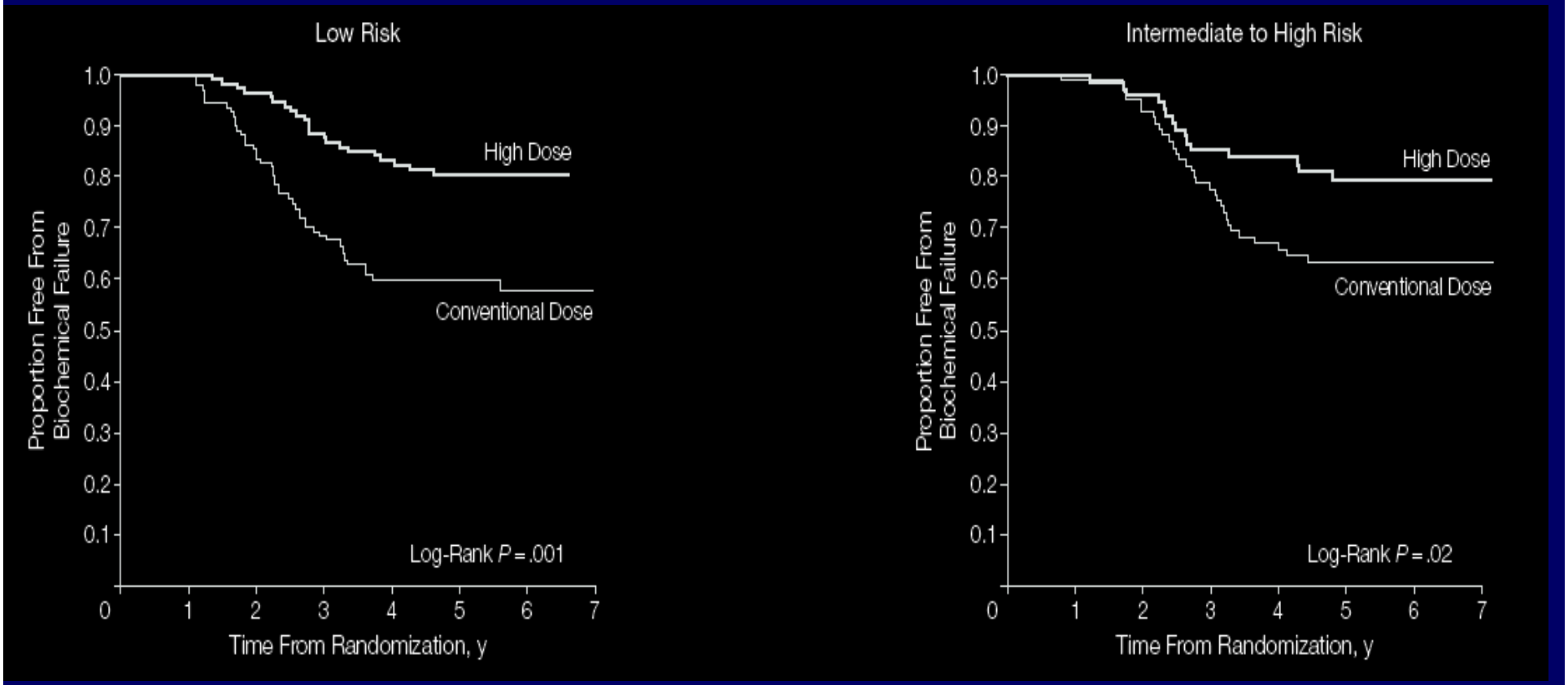

90%
80%
70%
60%
50%
40%
30%
20%
10%
2005

Proton-photon trial: PSA-Failure free survival



[JAMA 294:1233-39, 2005]

PSA control benefit for low-intermediate risk patients



Late side effects: grade 2-3 rectal

MDACC		Proton-photon	
70 Gy	13%	70.2 CGE	9%
78 Gy	26%	79.2 CGE	18%

Late GU side effects ~15-20% for all arms

Comments

- Majority of dose given with x-rays 50.4Gy with <29 CGE delivered via protons
- Proton technique may not have been optimal

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

Later years' technique depended upon Partin tables lymph node risk

>15% LN risk

Protons to P+SV
(~30CGE)

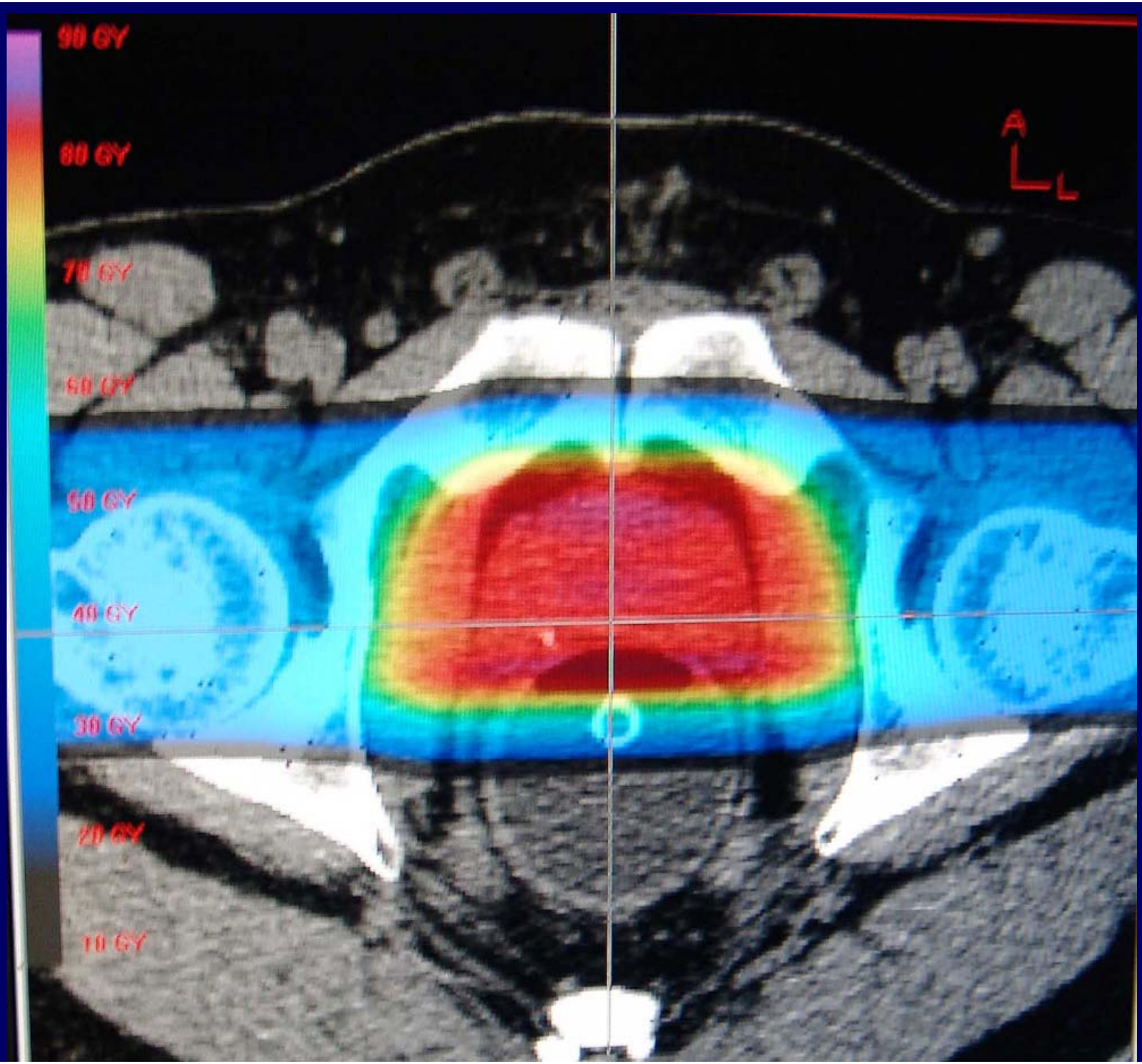
X-rays to Pelvic LN
(~45CGE)

<15% LN risk

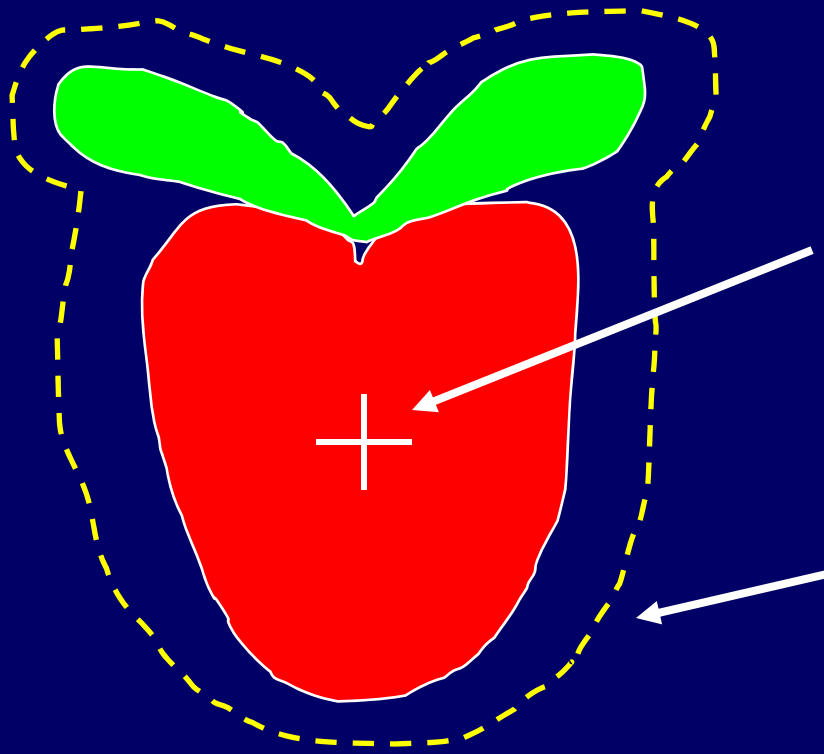
Protons to P+SV
Opposed lats-one field per day

(~74-75 CGE)

Dose prescribed to isocenter!

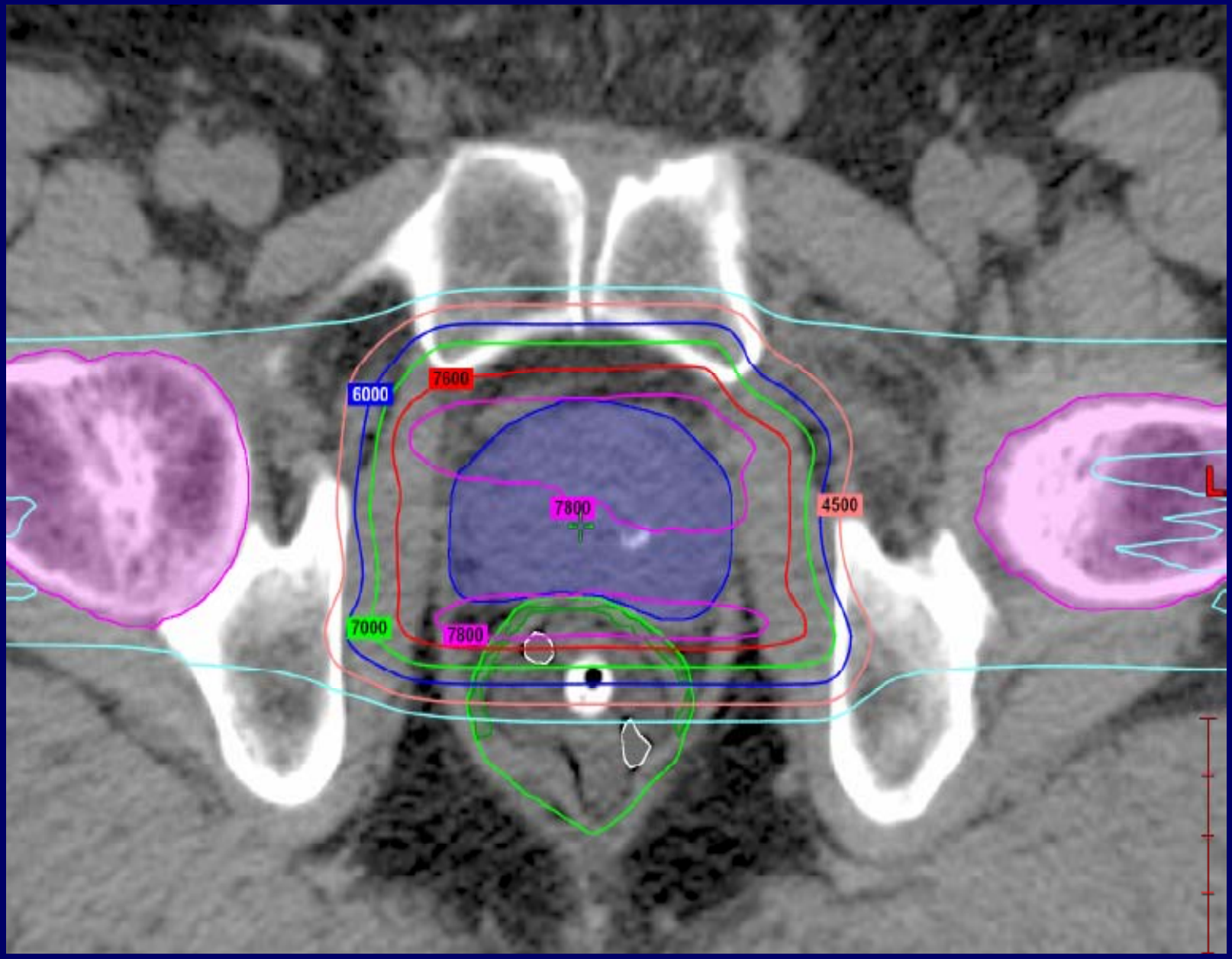

90 GY
80 GY
70 GY
60 GY
50 GY
40 GY
30 GY
20 GY
10 GY
A
L

Prescription point



74CGE
prescribed to
isocenter

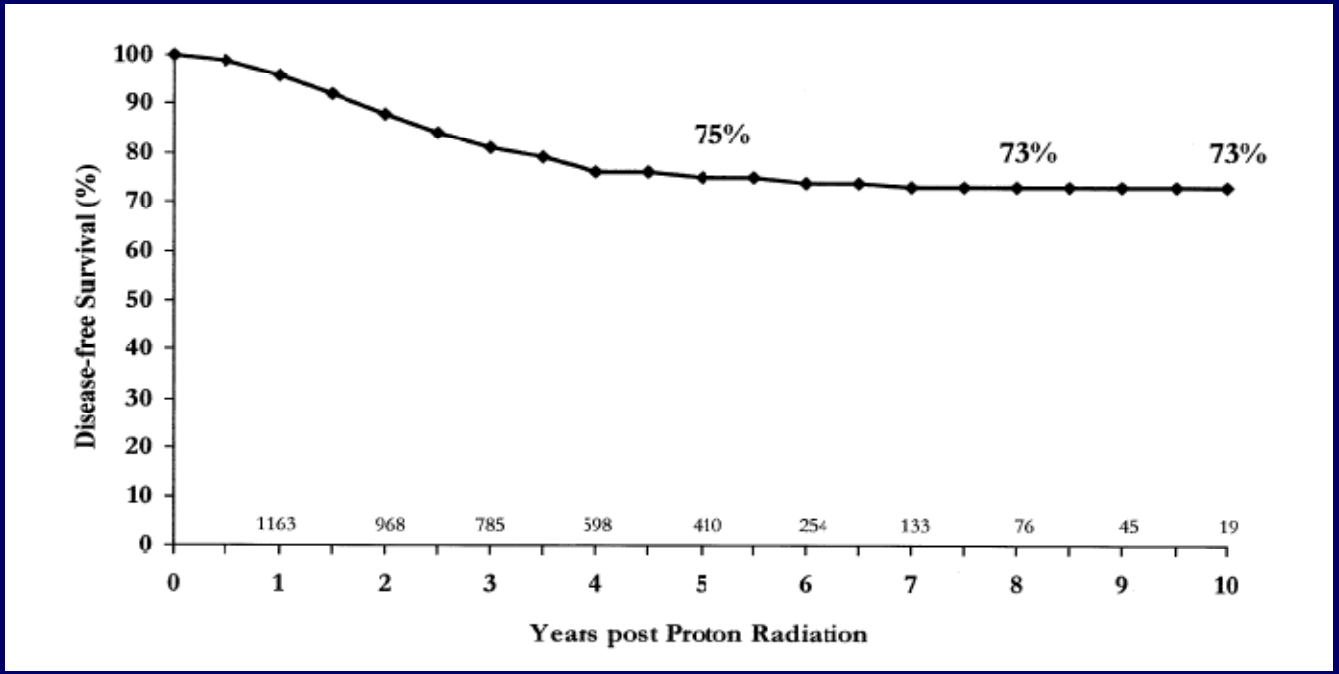
Dose to volume
~ 90-95% of
prescription



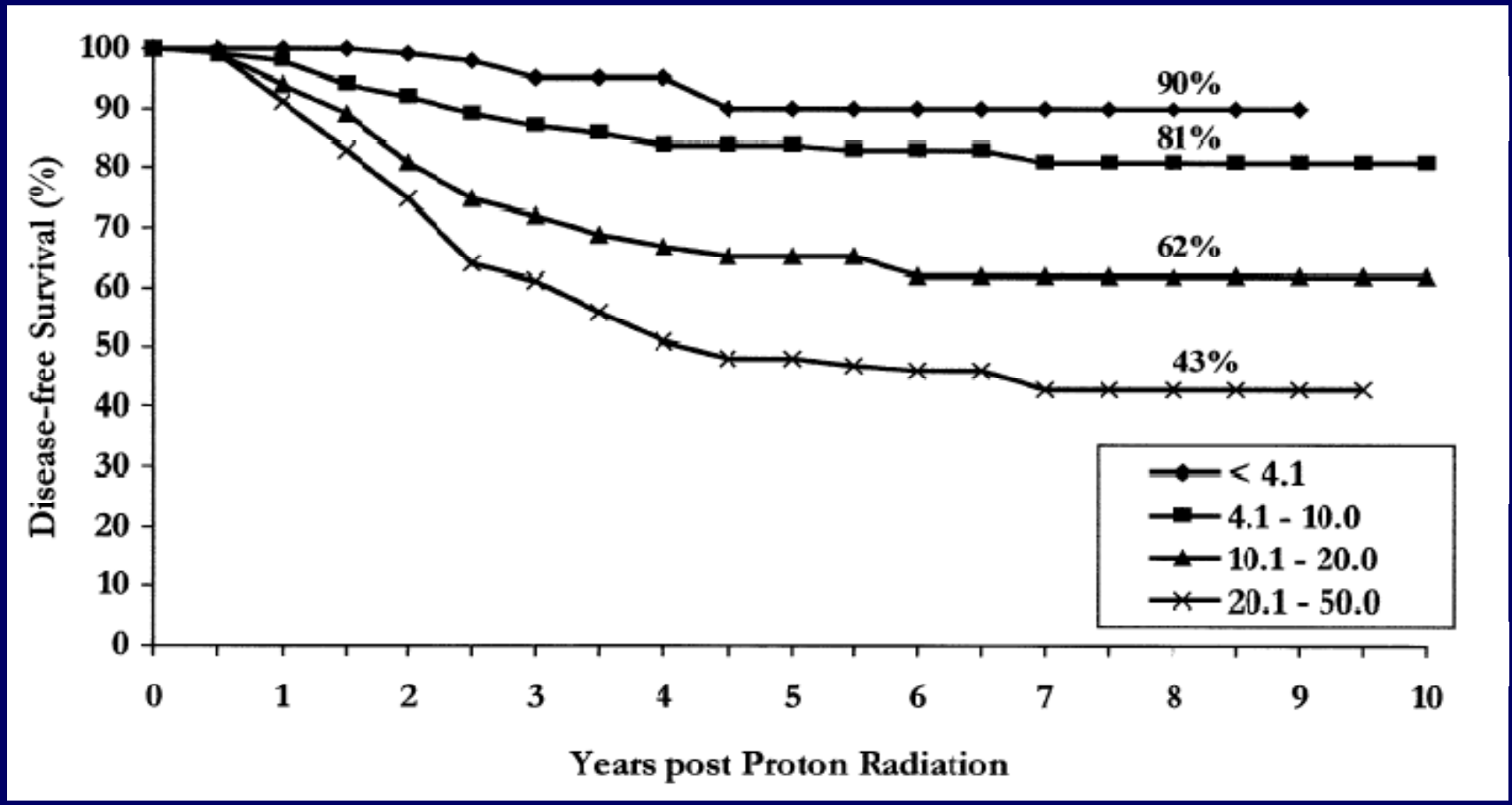
Where is your dose prescribed?

Results

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



DFS by initial PSA



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

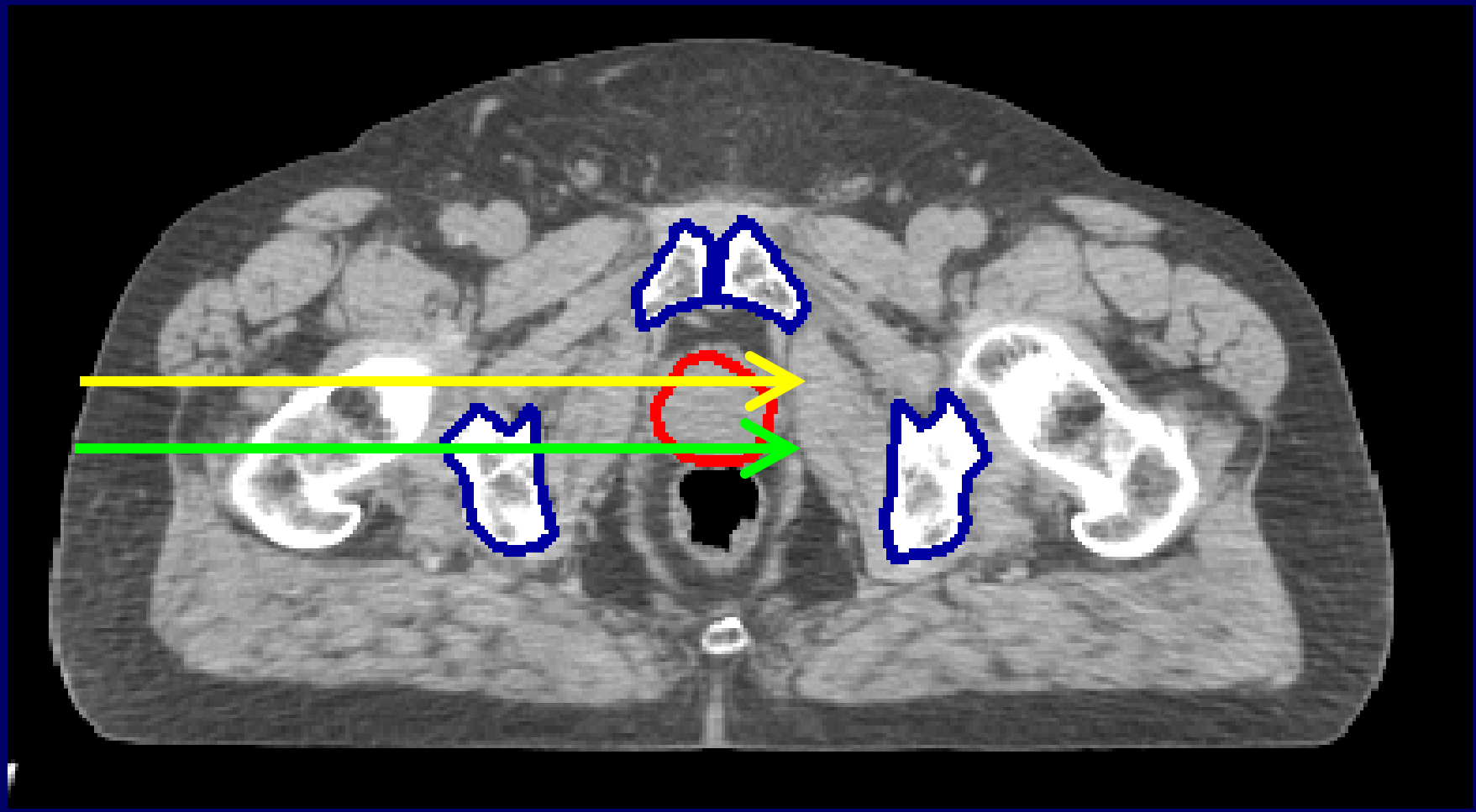
- Combination of x-rays and protons as well as protons alone
- Some patients received nodal radiation
- Protons were effective and safe
- Dose prescribed to isocenter rather than target volume
  - Lower dose compared to current standards
- Further dose-escalation has been done and ongoing trials looking 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



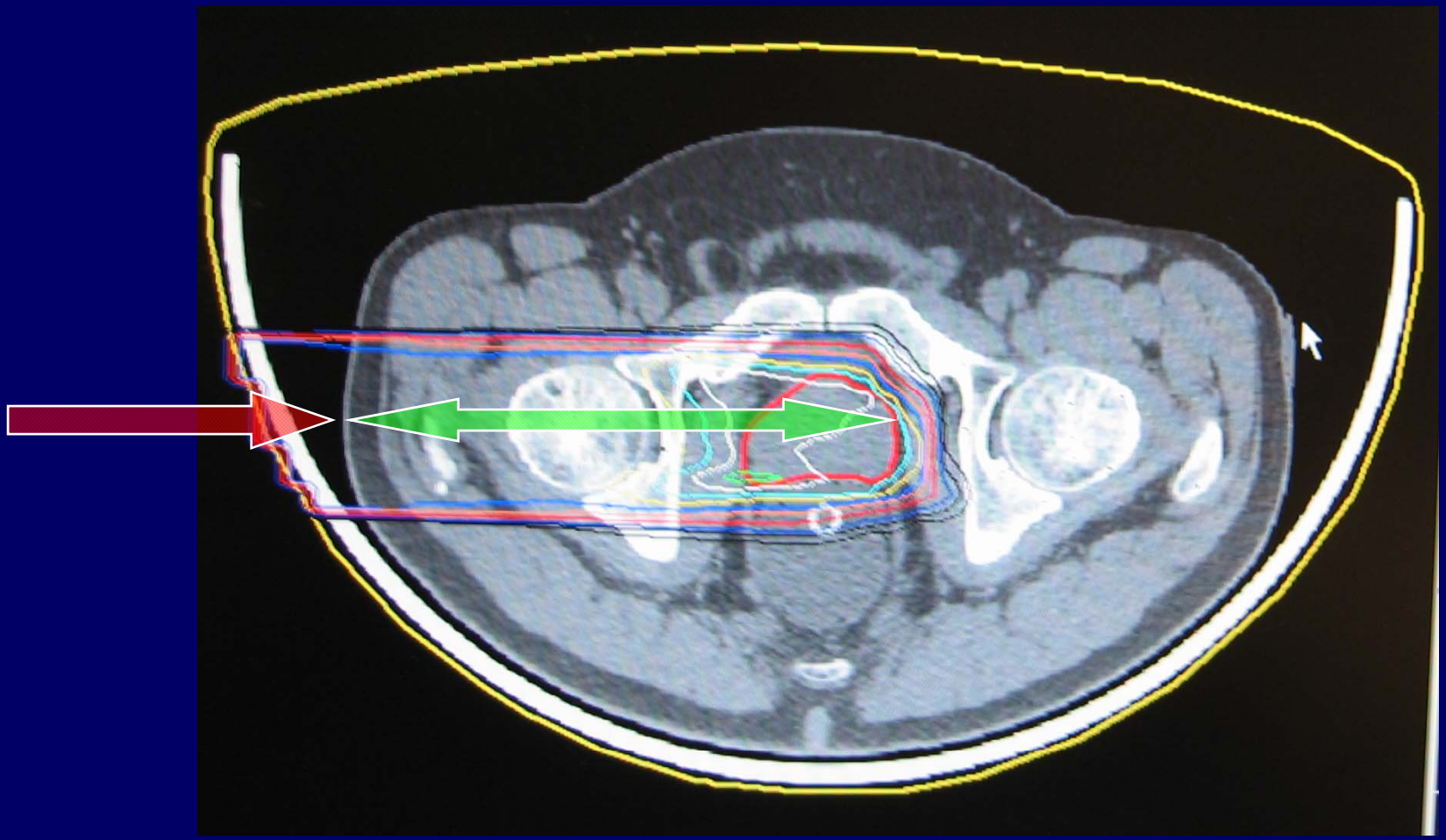
- Immobilization and reproducible setup is more critical for protons than IMRT

- Reproduce radiologic path length
- “Pro-active” target localization

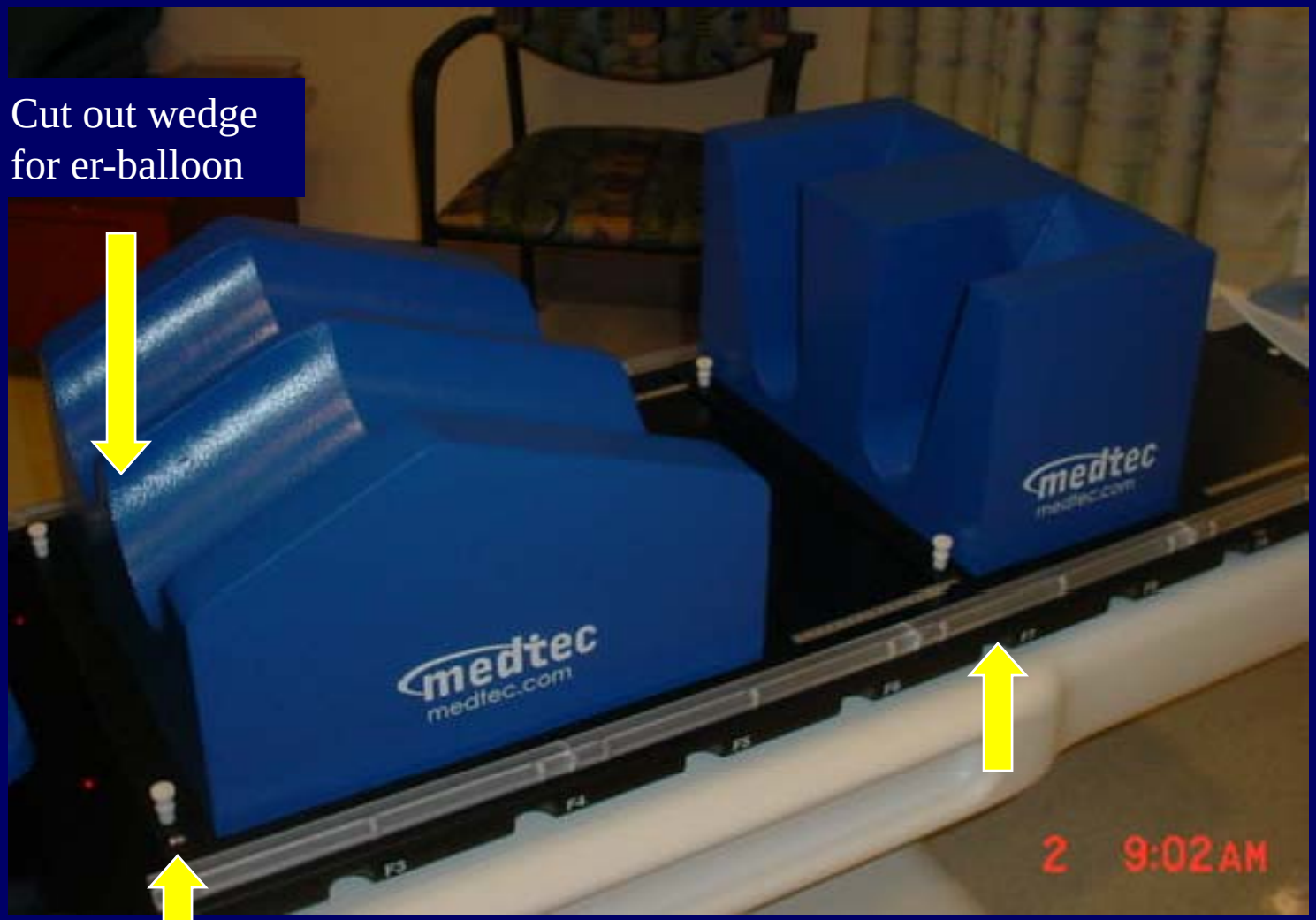
Loma Linda “pod”

Special thanks to Dr. Slater and Dr. Rossi

Effect of the Pod



Storage is an issue


Cut out wedge
for er-balloon
medtec
medtec.com
medtec
2 9:02 AM
Knee and foot cradles
are index-able


medtec
medtec.com
A B C
medtec
medtec.com
A B C
18 8:28

Patient 1

Conventional

Wedge knee + rectal balloon

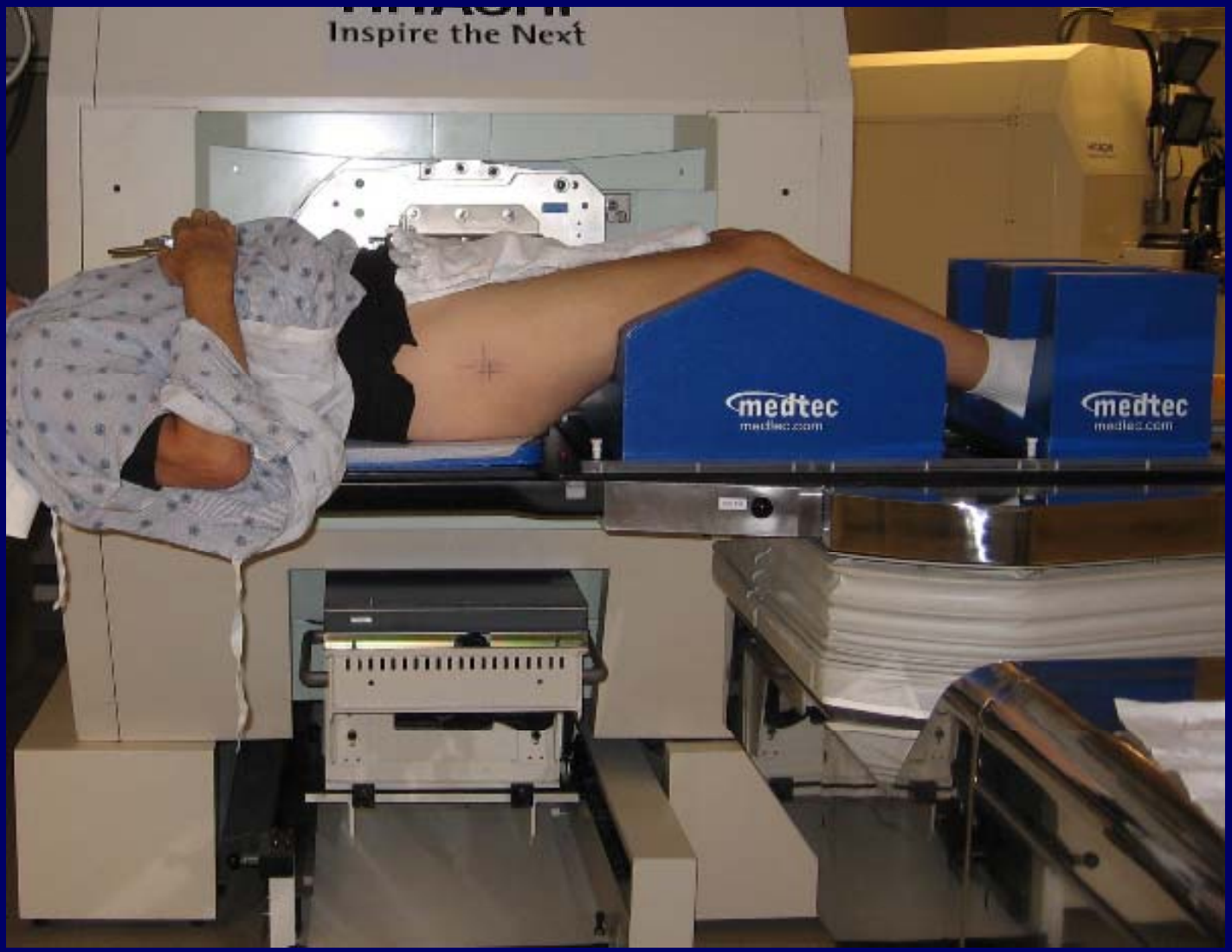
43.3cm

41.2cm

Measured through
The center of prostate

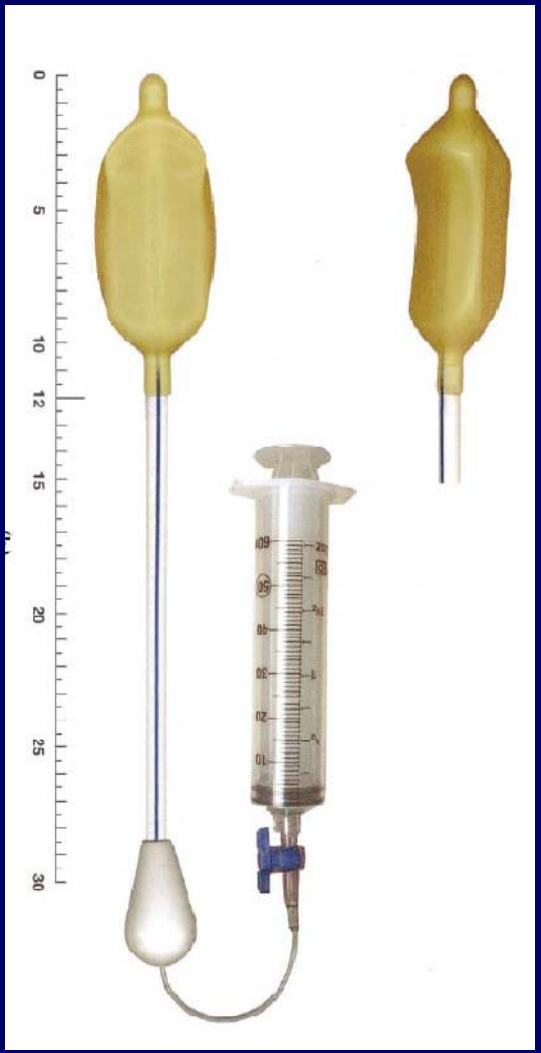
Knee-foot cradle

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


Inspire the Next
medtec
medtec.com
medtec
medtec.com

Endo-rectal balloon

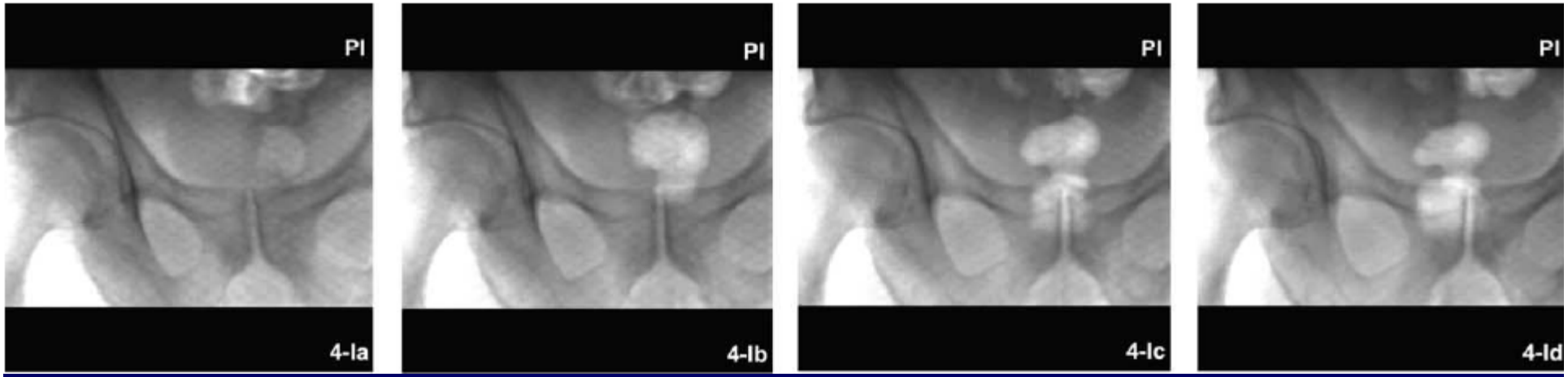
- Use daily w/ 65cc water
- Immobilize prostate
- Inter- and intrafxn motion
- Displace rectum
- Implication of 2-3mm shift w/ or w/out ERB
- Stop-cock **minimizes air** in balloon
- Target definition at simulation
- MRI-CT fusions
- Well-tolerated



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



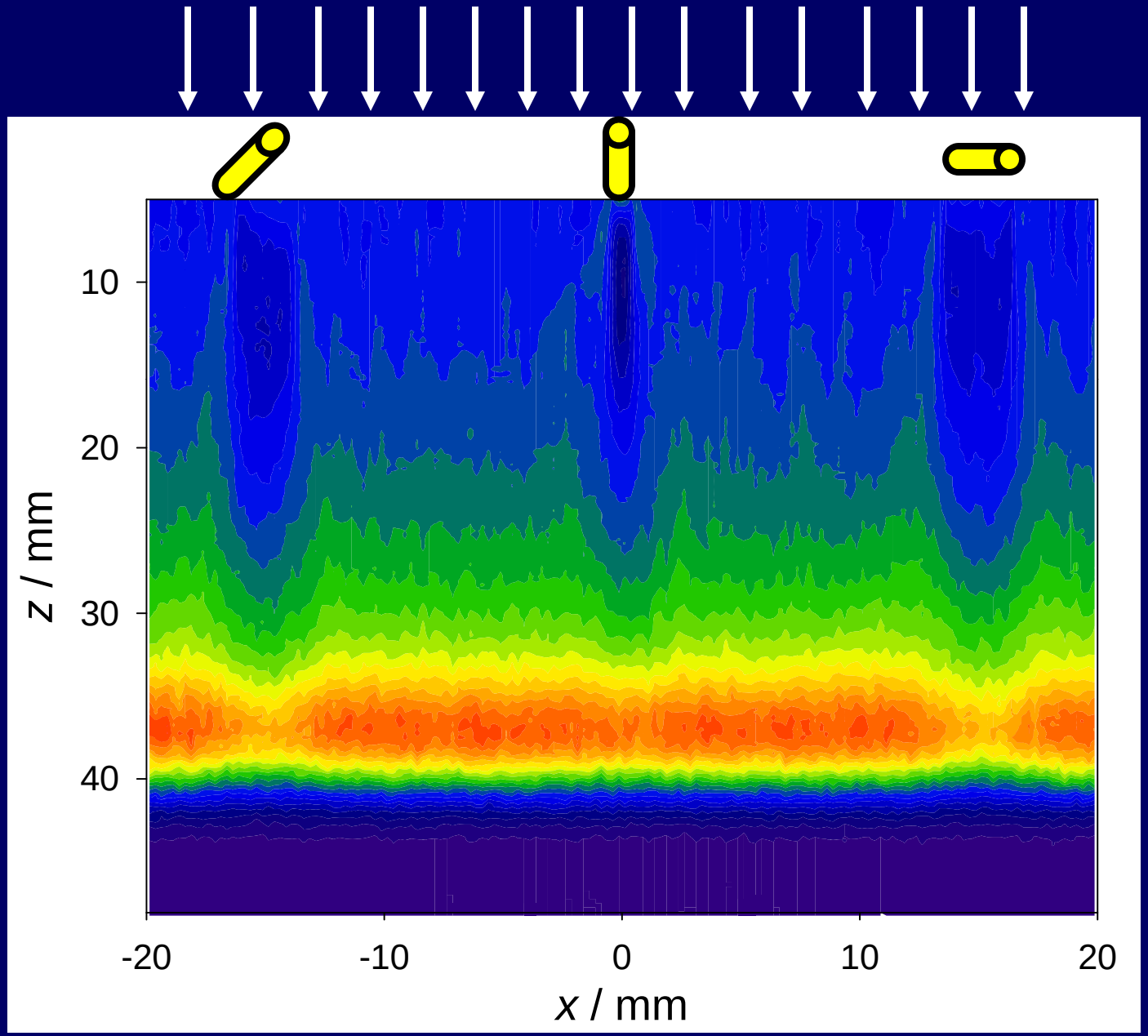
Smitsmans et al. IJROBP 63, 2005

How to handle gas?

Fiducials

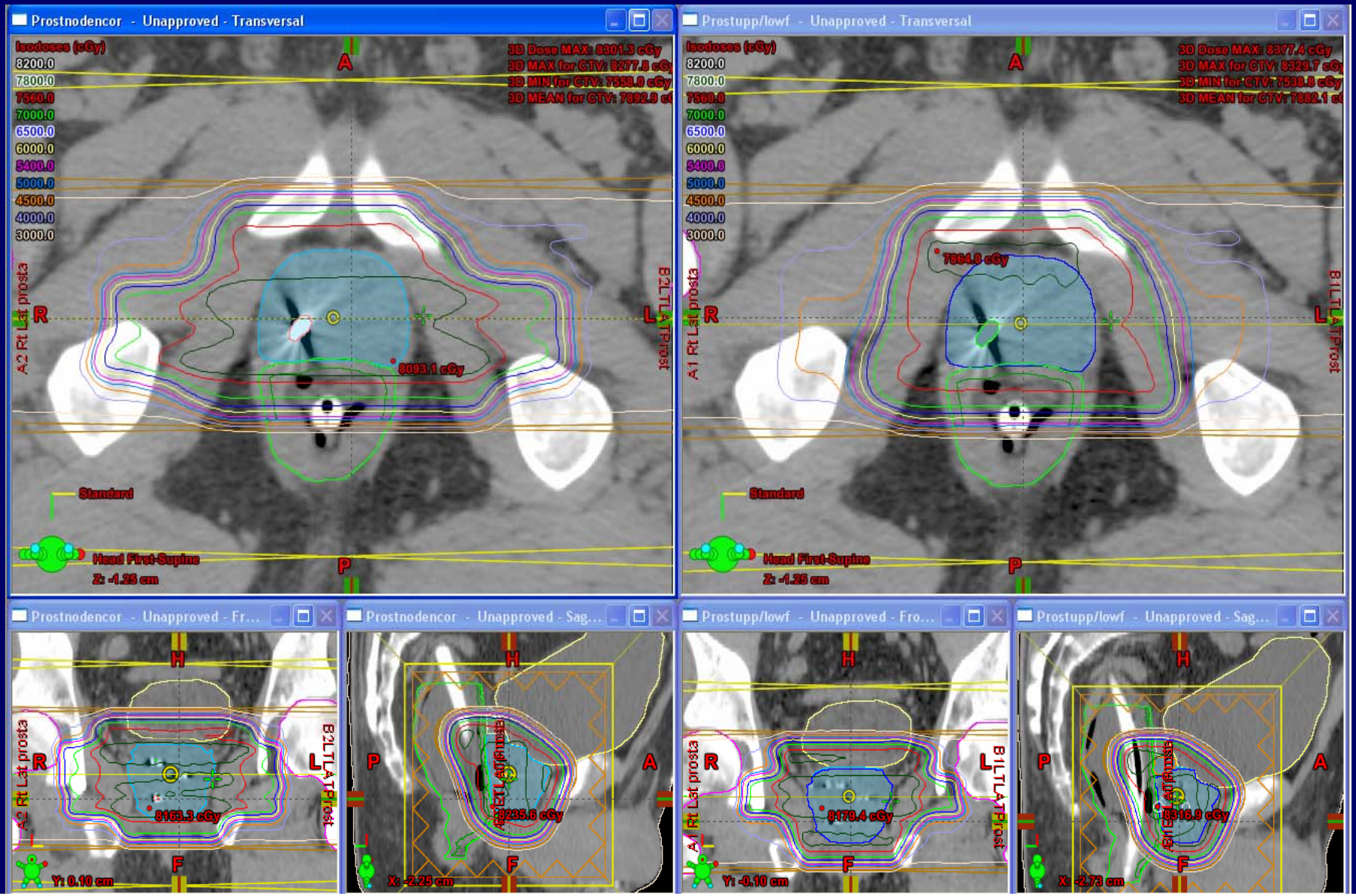
- Current fiducials optimized for MV imaging: **dense** (gold) and **large** (1.2 x 3mm)
- Fiducials may cause dose shadowing of dose (Newhauser et al.)
  - Size
  - Orientation
  - Density

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

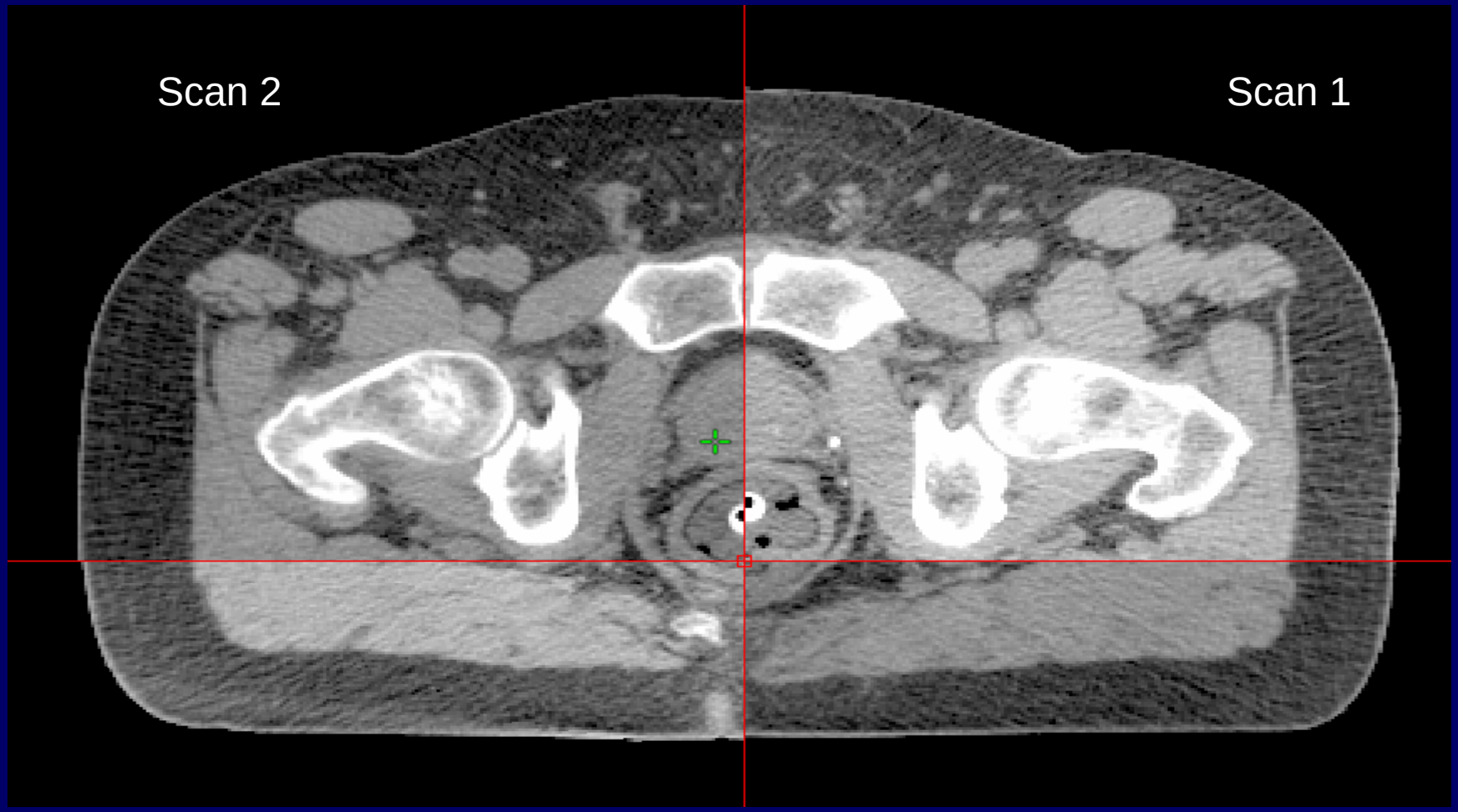
At simulation

- Supine in knee-foot cradle
- Empty rectum and semi-full bladder
- Endo-rectal balloon w/ 65cc 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 throughout

- 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

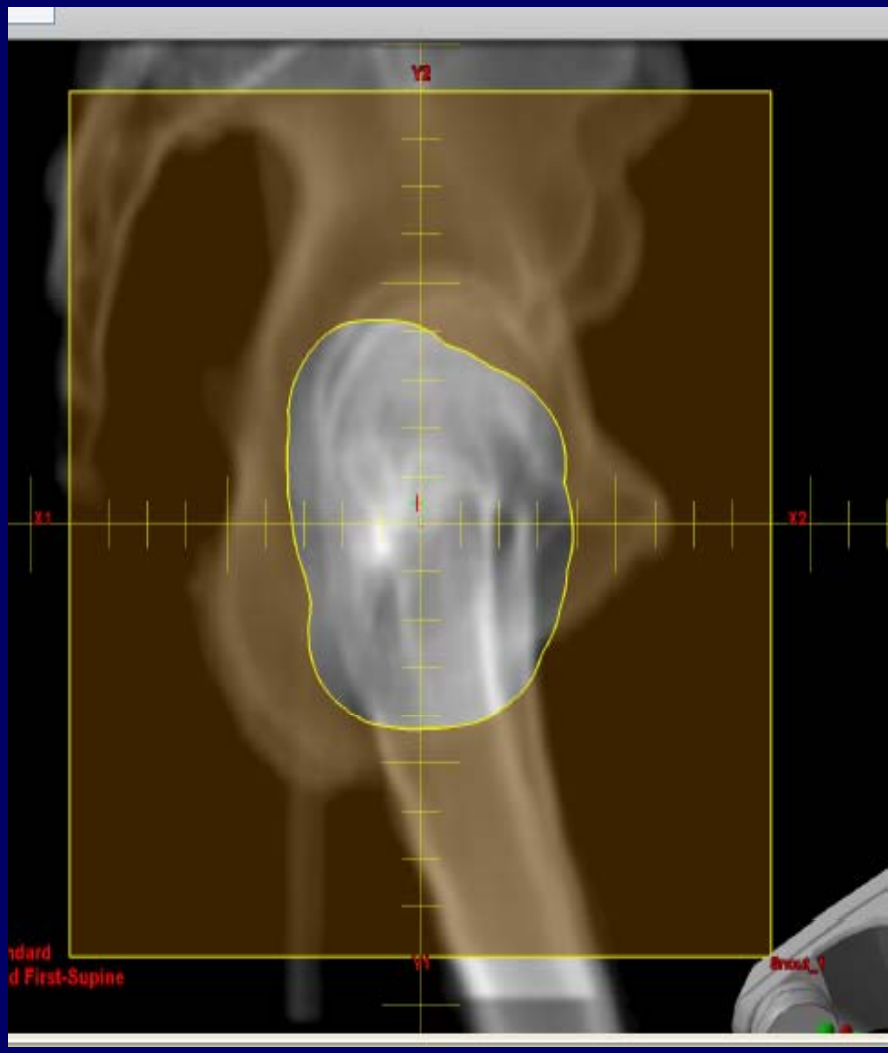
- CTV = Prostate + Proximal SV

- Setup uncertainty ≤5mm
- Distal margin = (0.035 x distal CTV radiological depth) + (3mm)*
- Proximal margin ~ 1cm
- Smear ~0.9 cm

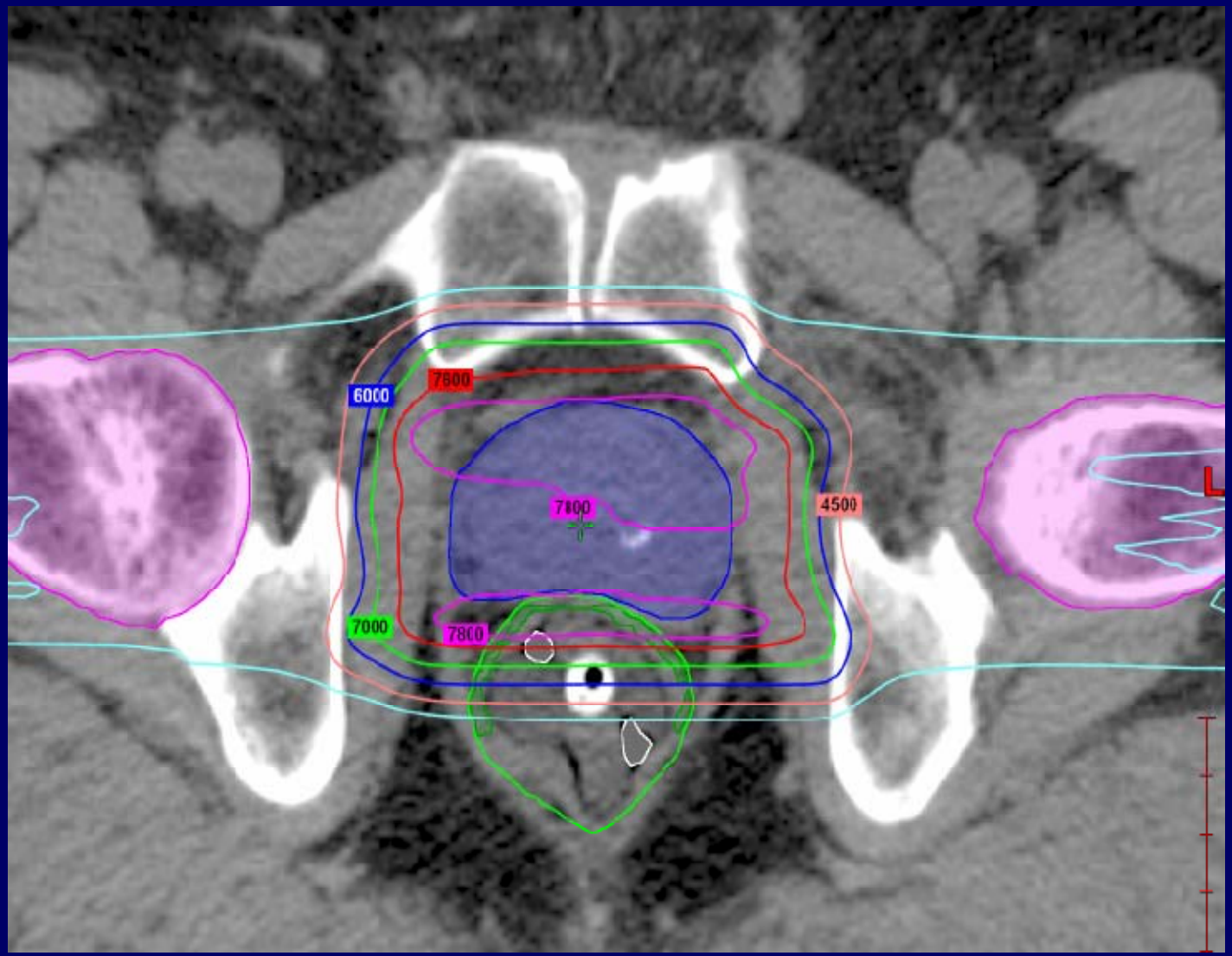
(*Beam range uncertainty)

Lateral Margin

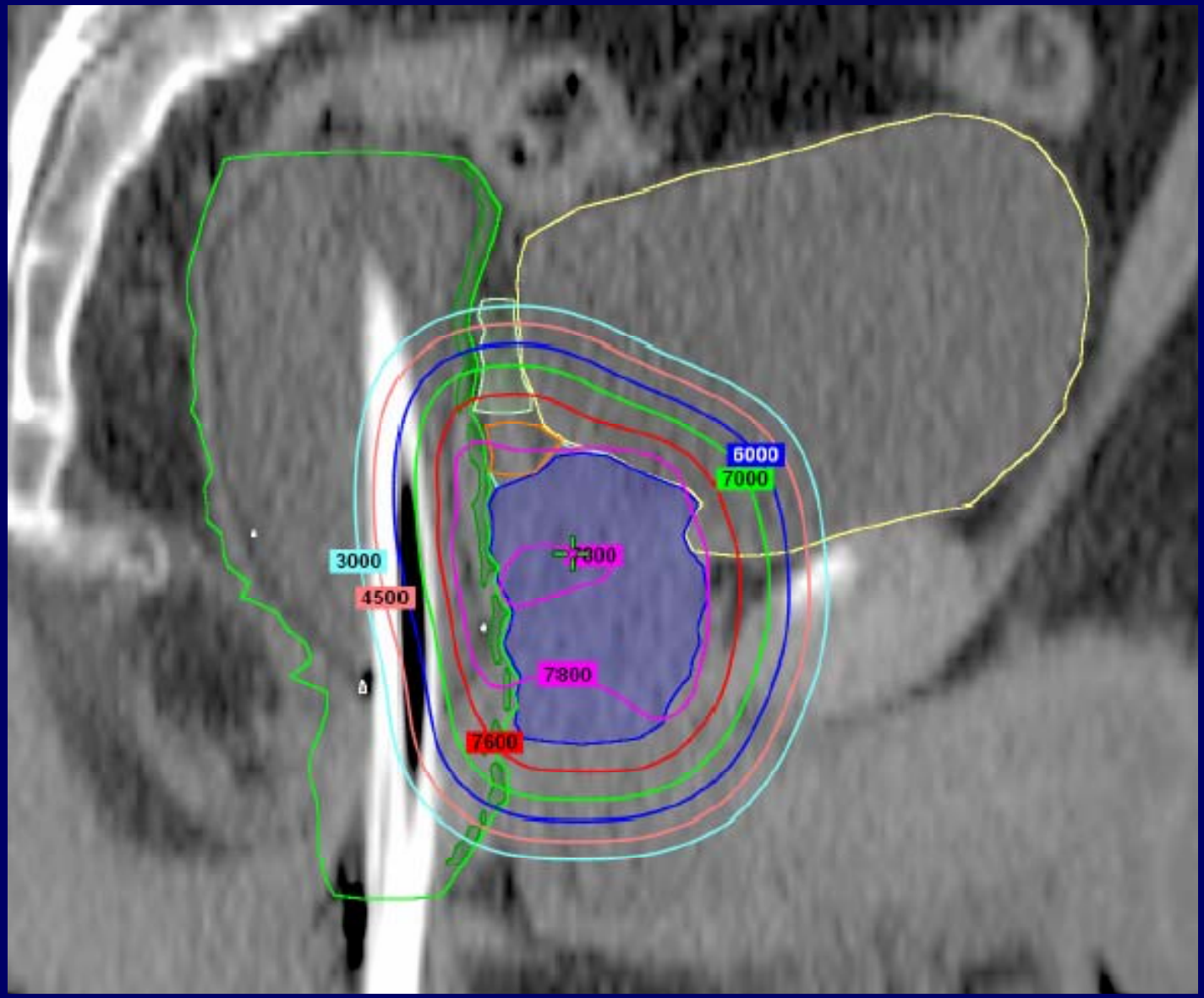
- LM = setup uncertainty + penumbra
- Setup uncertainty = 0.5cm
- 250 MeV beam penumbra (95-50%) = 1.2cm
- LM = 1.7 cm



Two opposed lateral beams

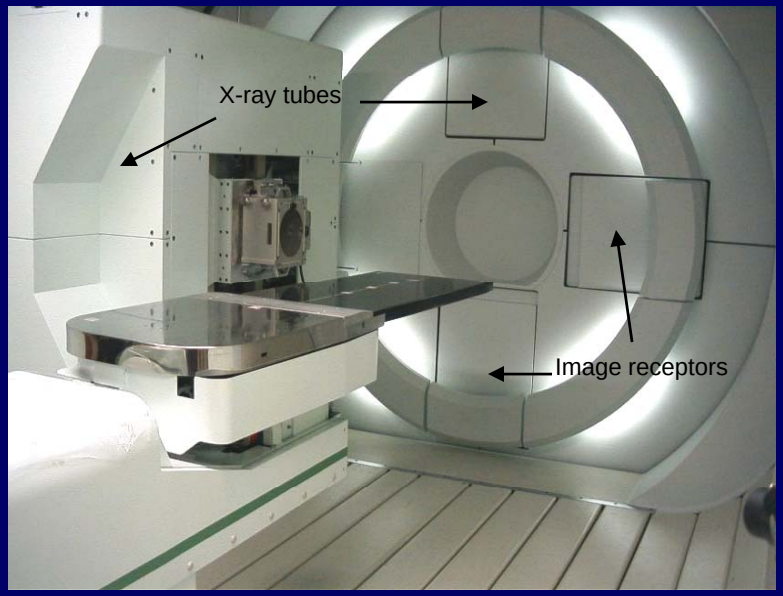


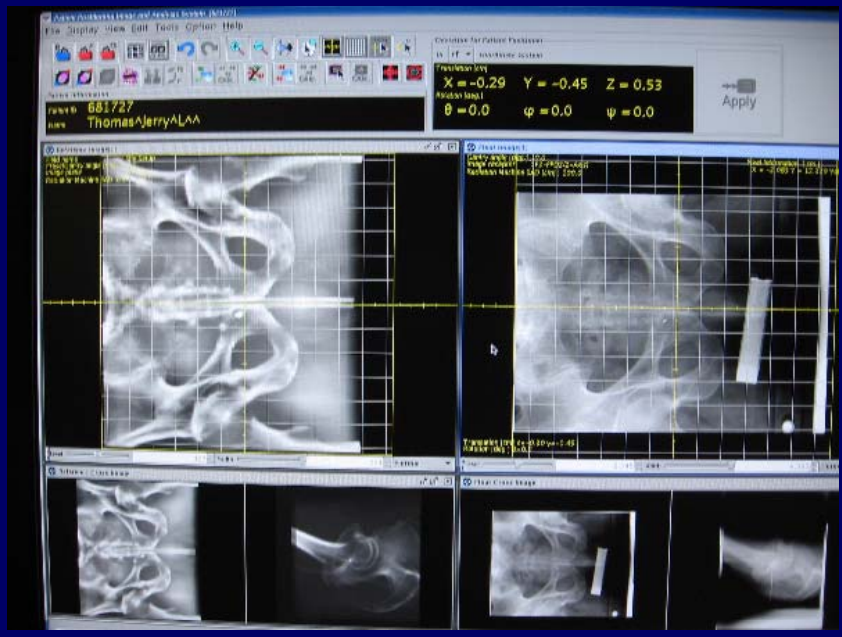
Sagittal view



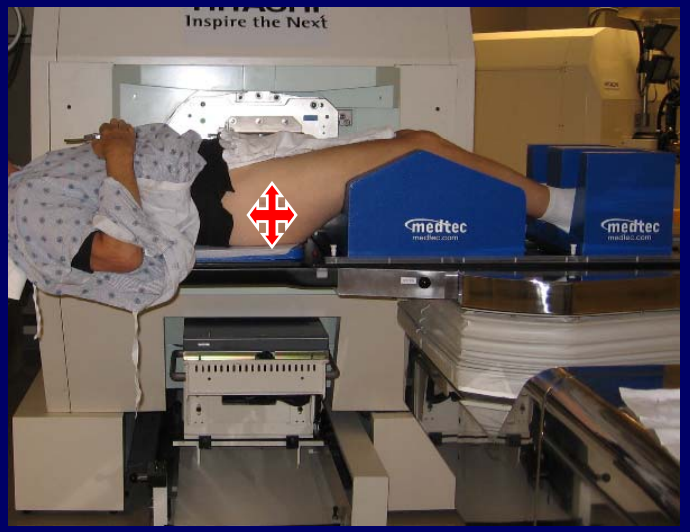
Patient alignment at PTC-H

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





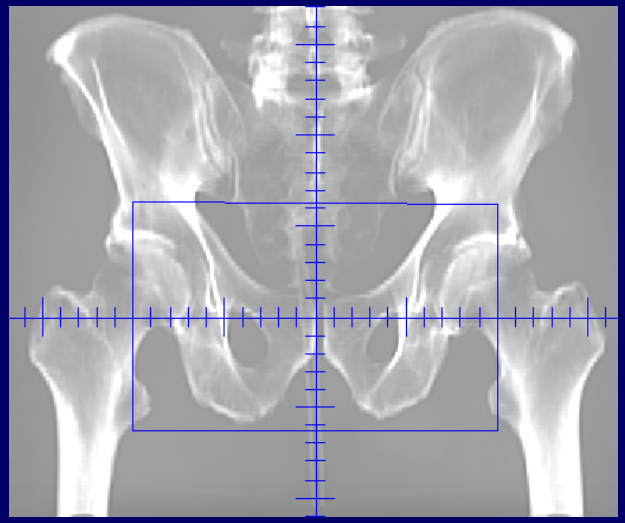
Positioning Image Analysis System, 'PIAS'

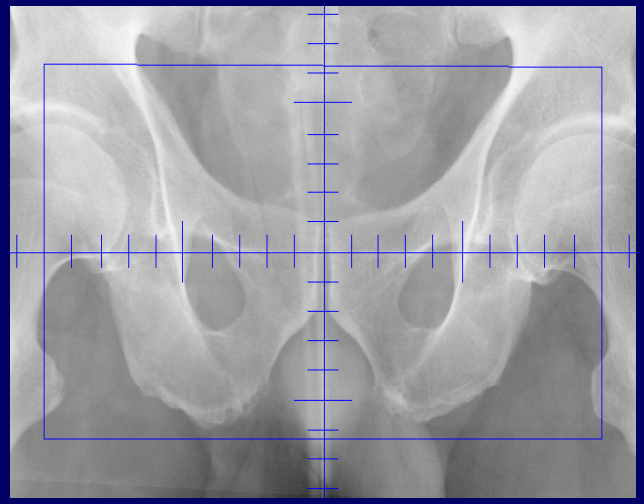


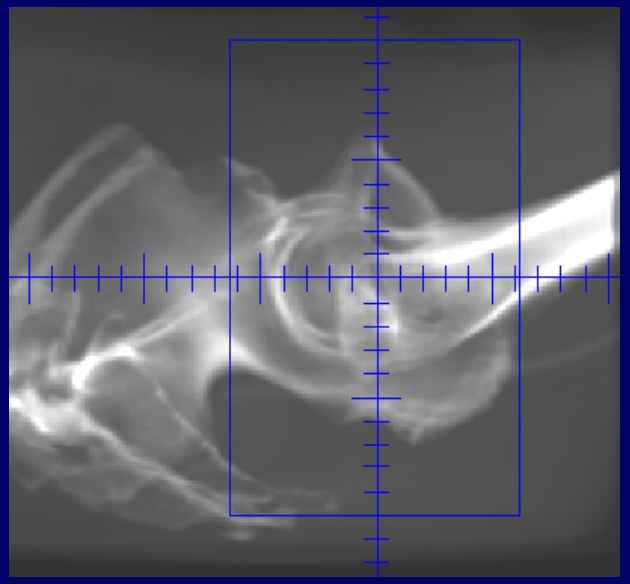
Hitachi

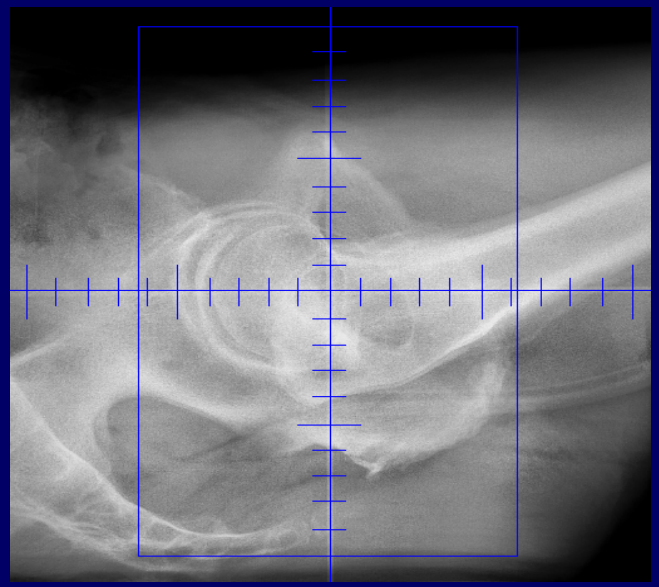
REFERENCE IMAGE

DAILY IMAGE



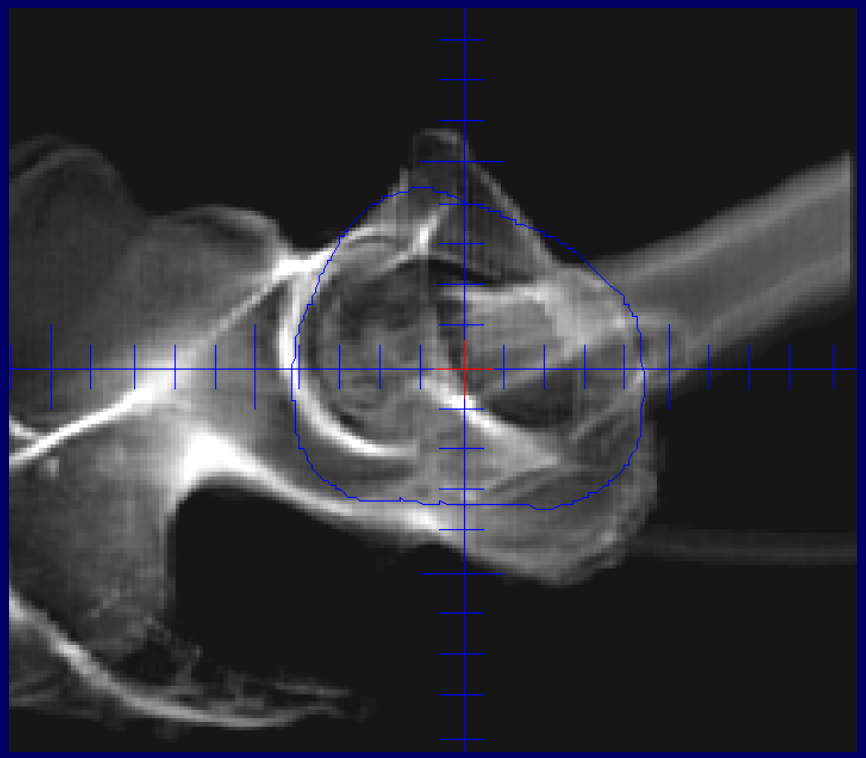


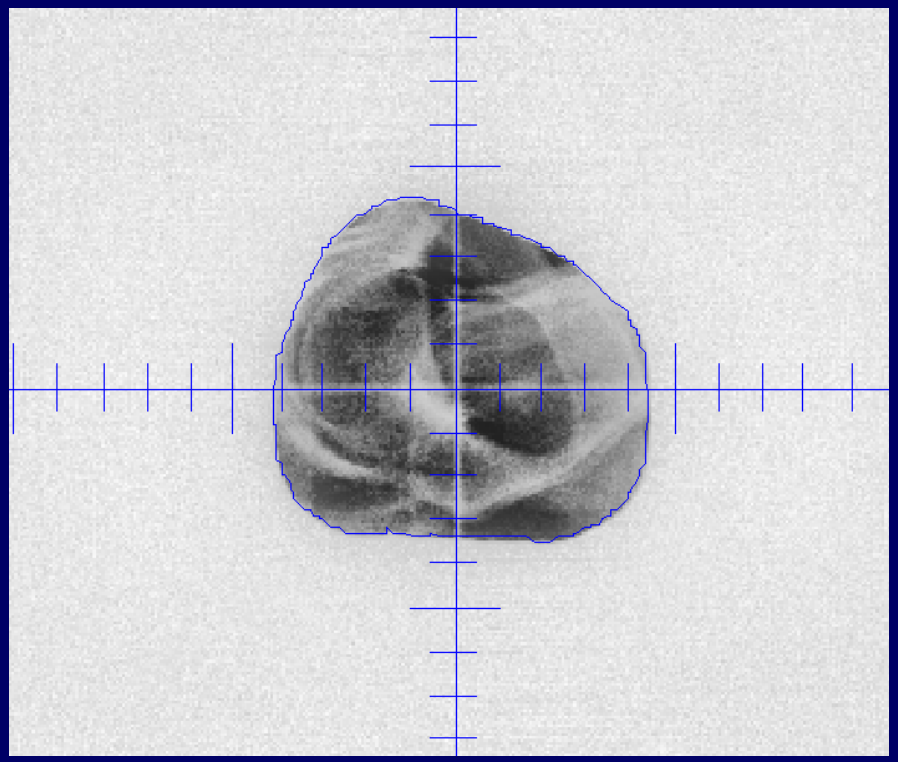




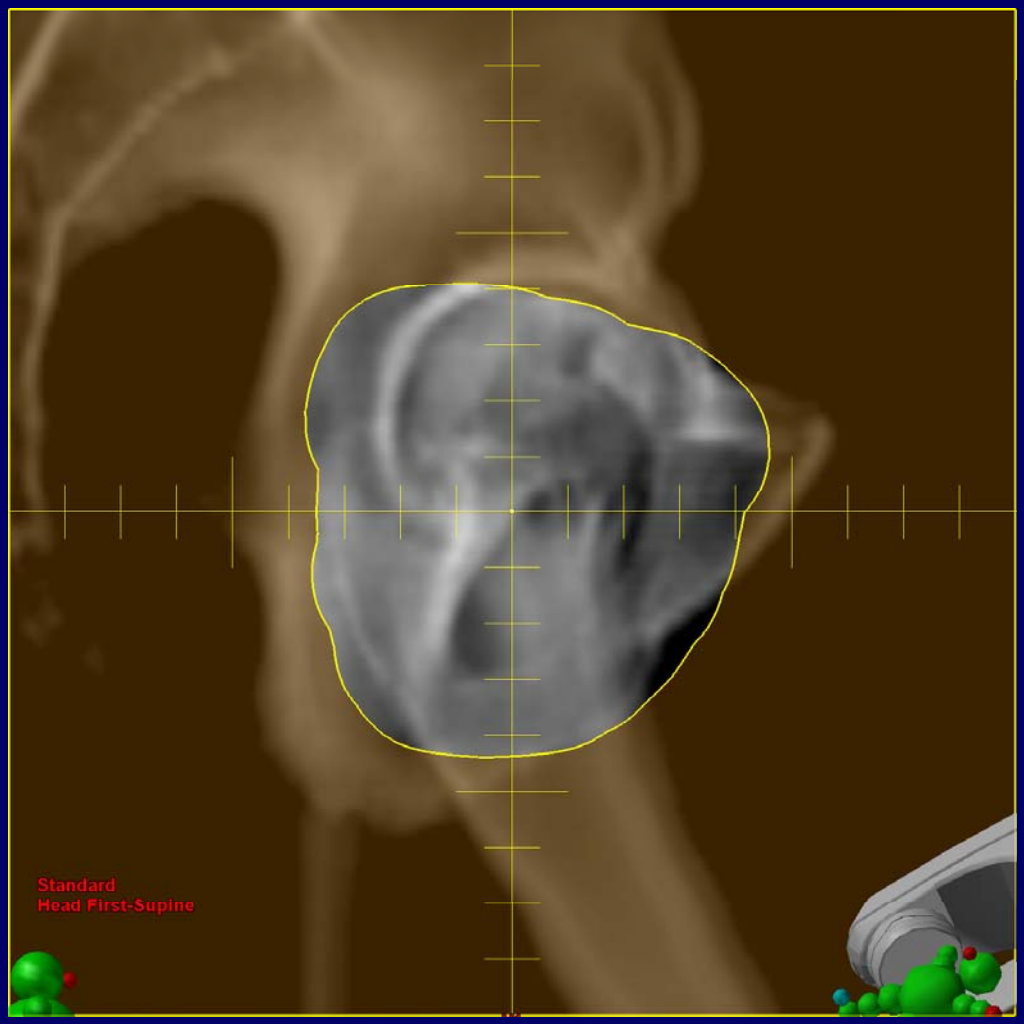
REFERENCE IMAGE

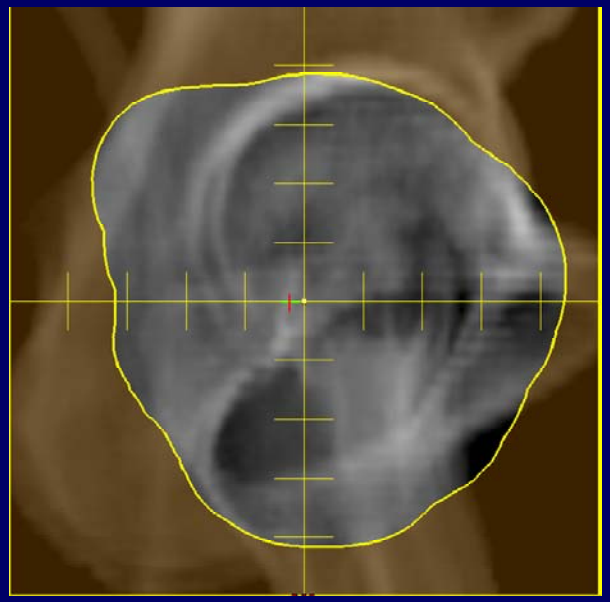
DAILY IMAGE





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

PTC-H initial clinical experience

- May 4, 2006 first patient treated at PTCH
- **~340** prostate cancer patients have completed Rx
  - cT1-2, Gleason 6-7, PSA <20 ng/ml
  - ER balloon tolerated well
- 255 men have minimum 3-month FU evaluation
  - No PSA failures
  - 7 patients had Grade 2 rectal bleeding (~2.7%)

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

THANK YOU