PTCOG 52
Proton Therapy for Prostate Cancer

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Disclosures

- No relevant financial disclosures

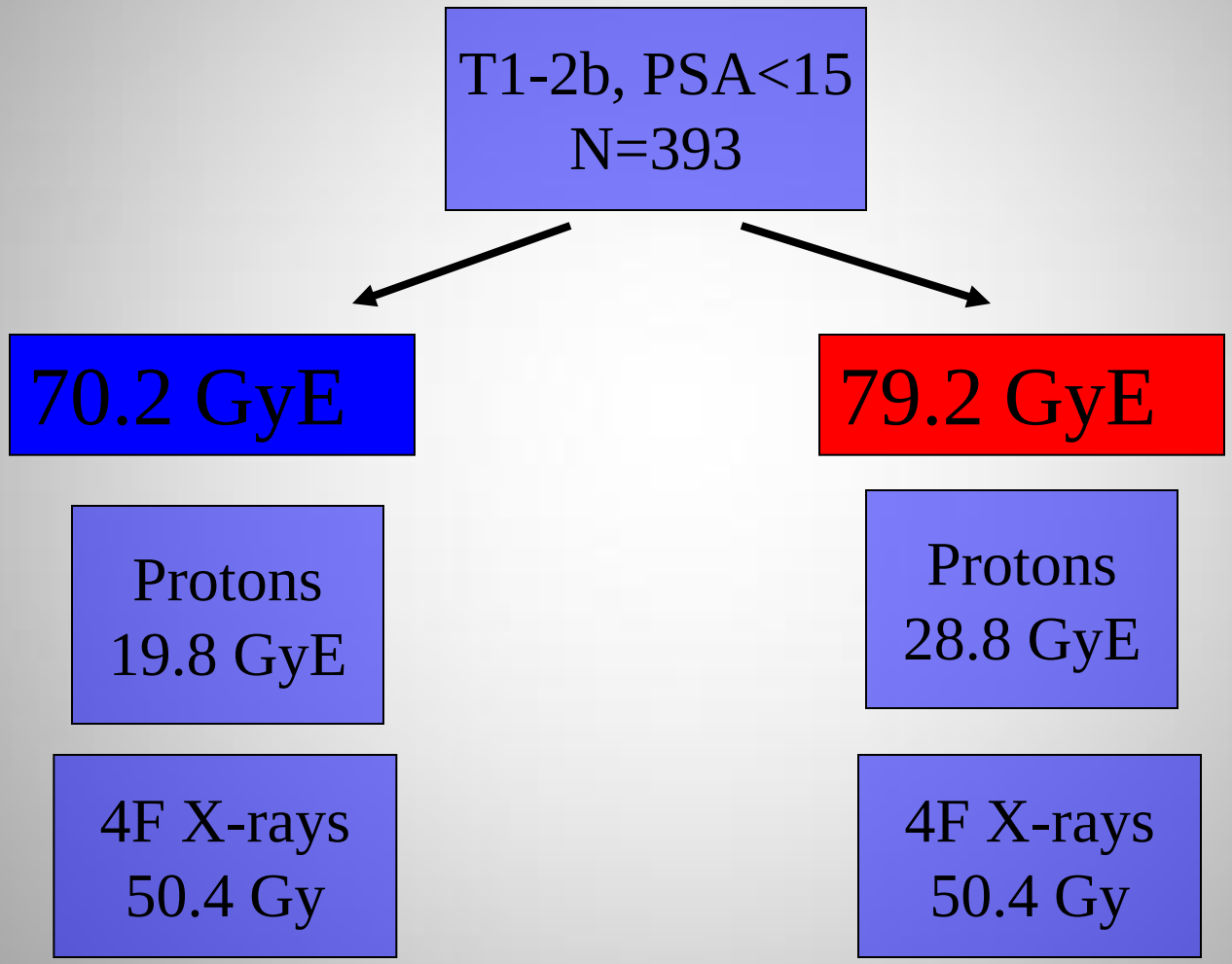
- This presentation will not discuss off-label or investigational treatments

Take home points

- Higher radiation doses yield higher PSA control rates
- Do not use too tight of a margin
- Proactively position the patient and target
  - Minimize inter- and intra-fraction variation
- Opposed lateral beams are relatively forgiving
- Do not treat more of seminal vesicles than needed

PROG 95-09

PROTON-photon randomized trial



JAMA 294, 2005

MGH Perineal boost
Limited beam energy…4x per week

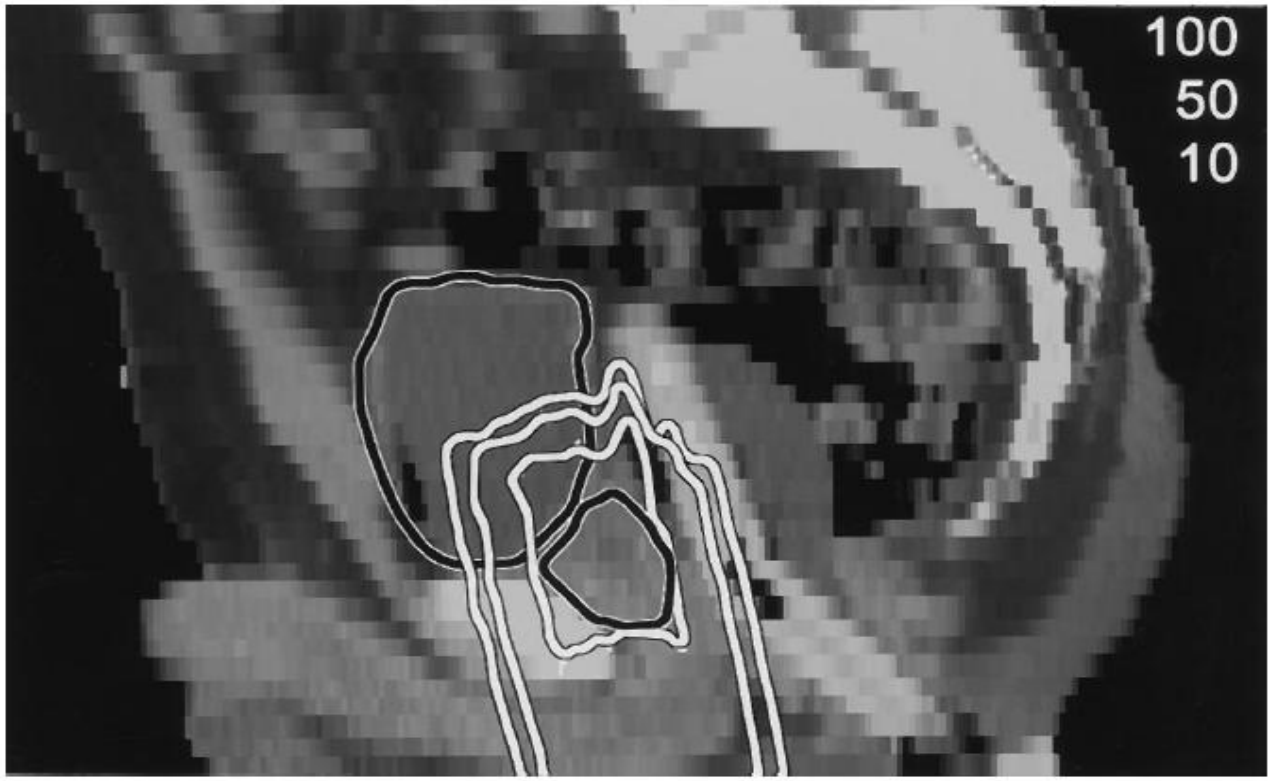
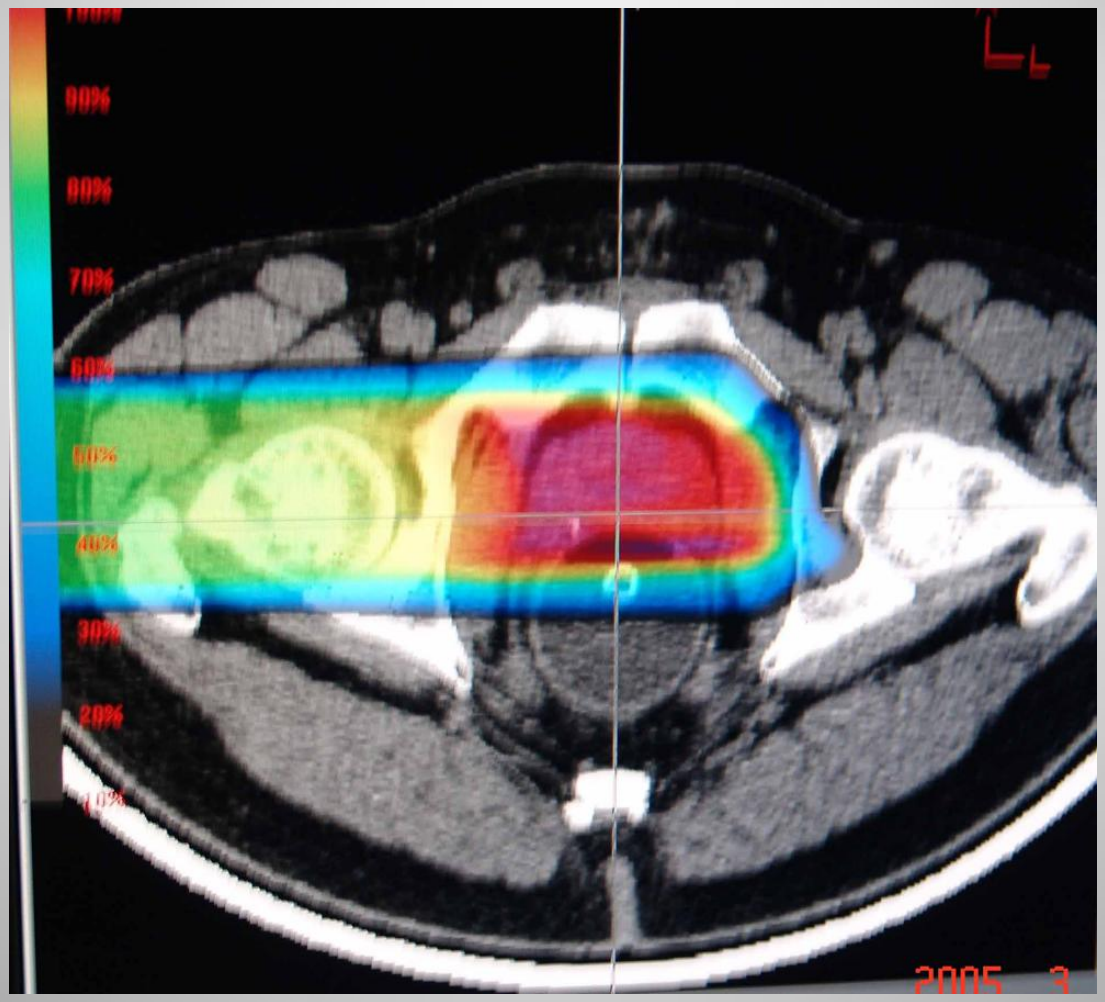


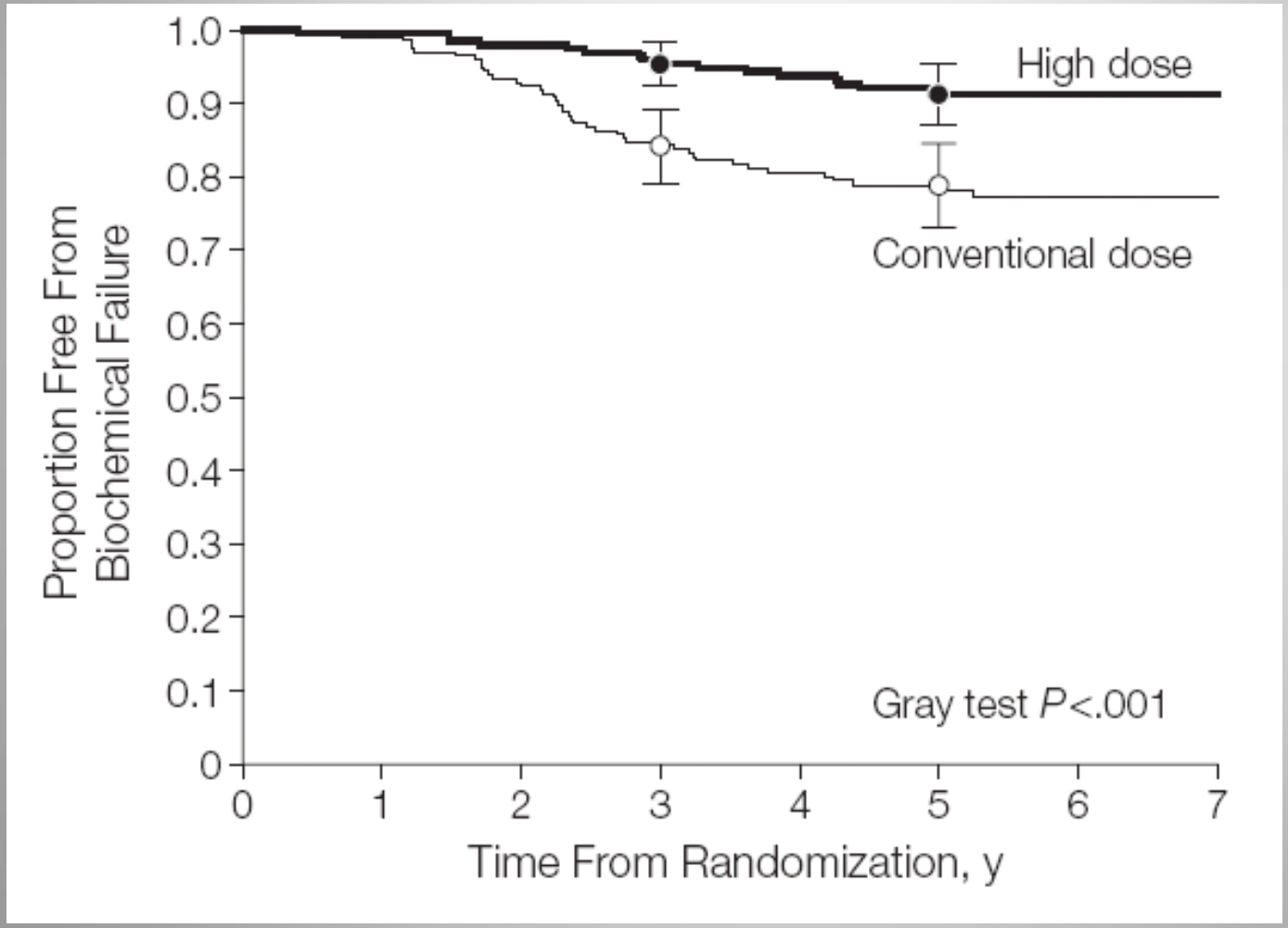
FIG. 1. Sagittal CT reconstruction shows perineal proton boost technique and how beam high dose region incorporates prostate, prostatic urethra and bladder neck.

Journal of Urology 167:123, 2002

LLUMC- one field a day



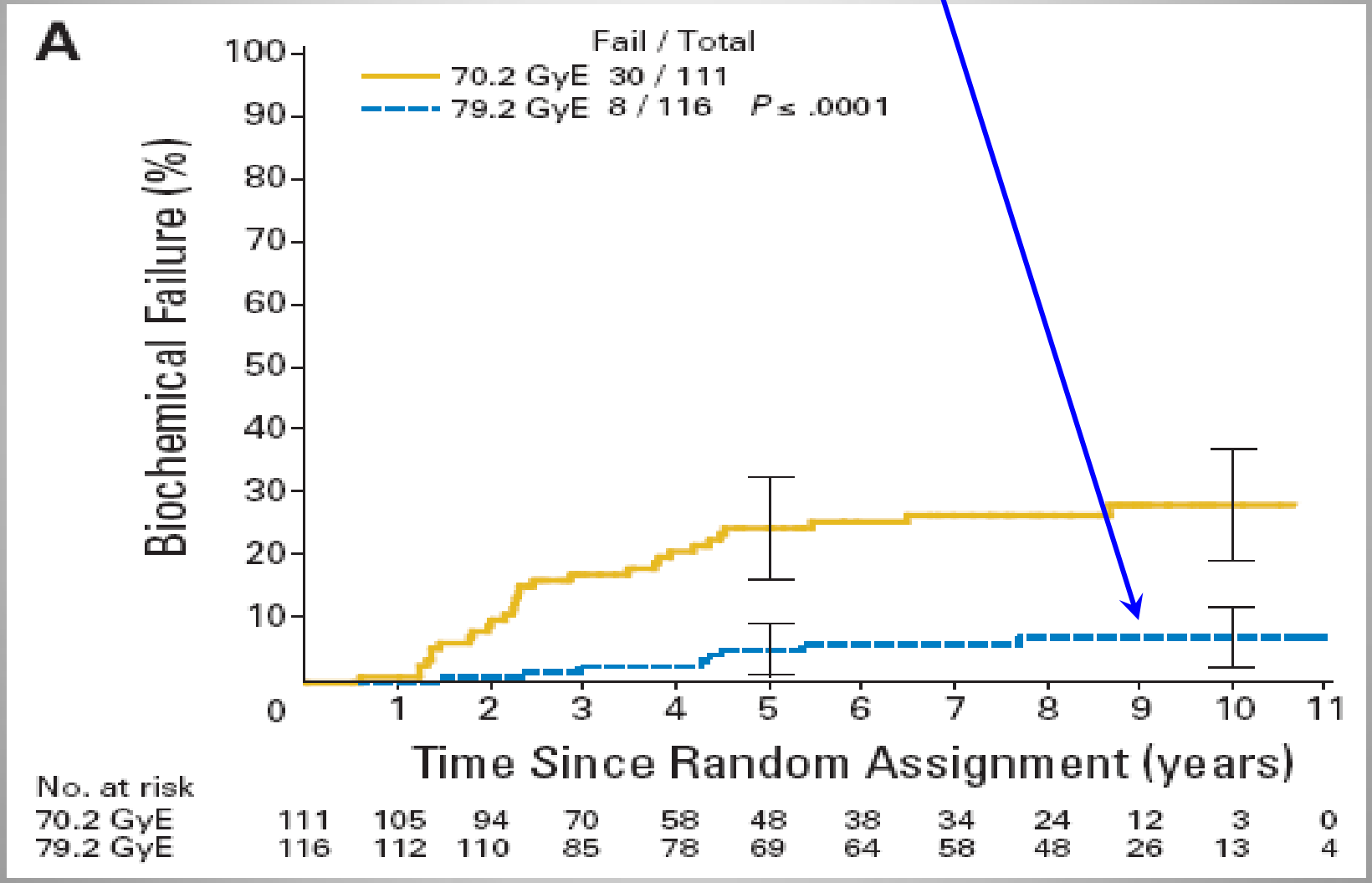
Proton-photon trial: PSA-Failure free survival *CORRECTED* calculation (JAMA 299, 2008)



92% PSA-FFS

PROG update: Low risk PSA control ~95% w/ median FU 9 years

J Clin Oncol March 2010



PROG 9509

J Clin Oncol 2010

- Difference in bNED survival between arms persists with median follow-up of 9 years
- No difference in Gr≥3 GI/GU morbidity between arms using data from validated patient questionnaire
- Fewer patients in high dose arm required salvage hormones

Comments

- PROG study has the best PSA control from any prospective external beam trial

- Proton technique was not optimal and used simple beam arrangement (one beam a day)

CLINICAL INVESTIGATION

MULTI-INSTITUTIONAL PHASE II STUDY OF PROTON BEAM THERAPY FOR ORGAN-CONFINED PROSTATE CANCER FOCUSING ON THE INCIDENCE OF LATE RECTAL TOXICITIES

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Prospective study of 151 men treated 2004-2007

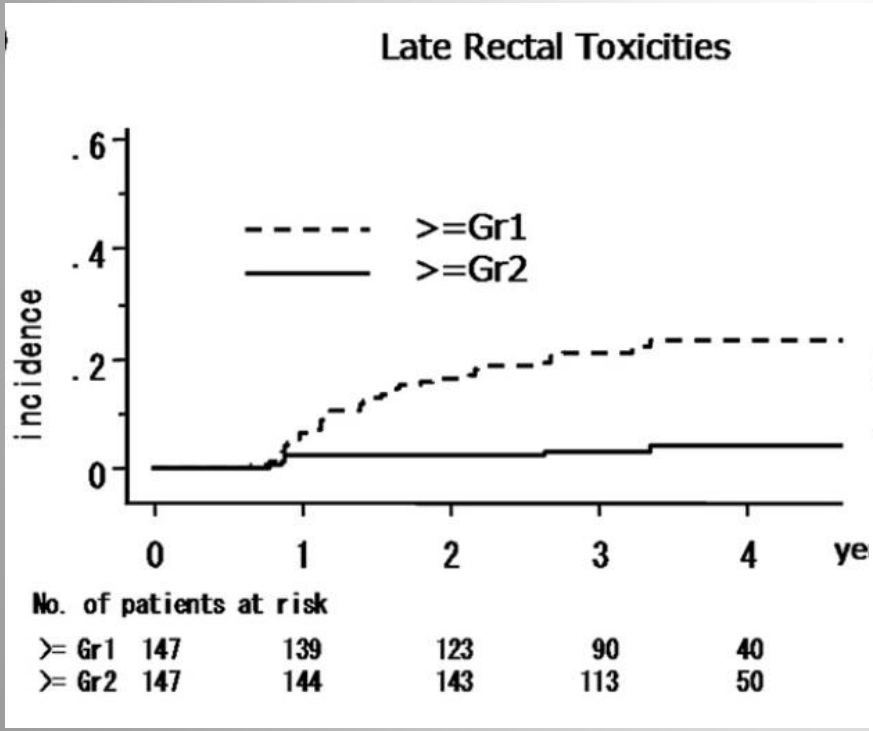
74GyE (2GyE/fxn)

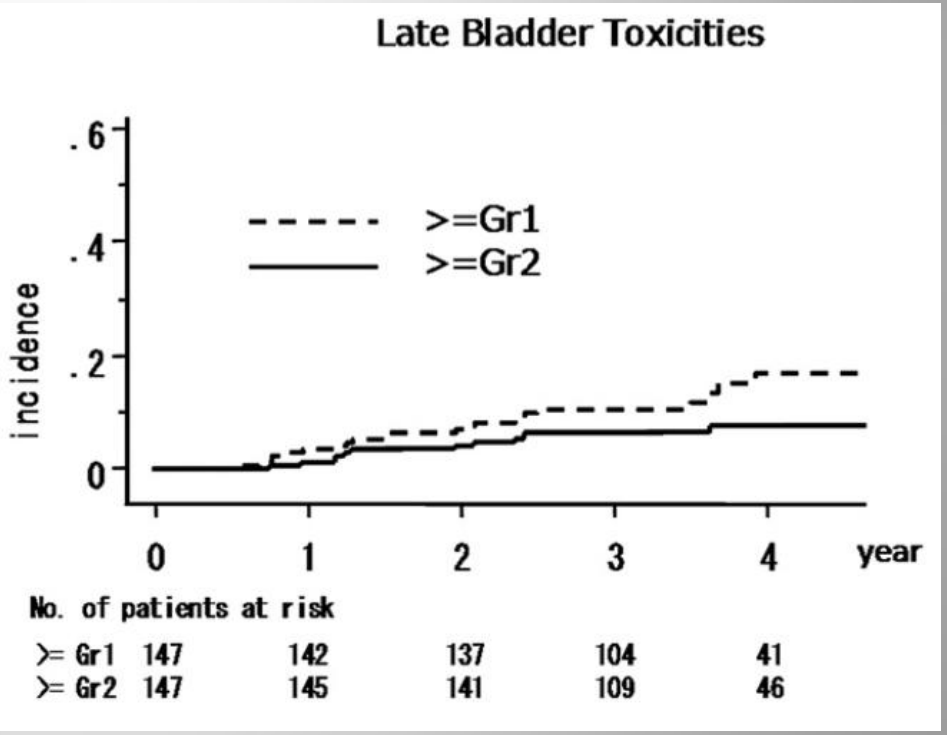
Median FU 43.4 months

CTC v2.0

4% Grade 2 rectal 7.8% Grade 2 bladder

No Grade 3





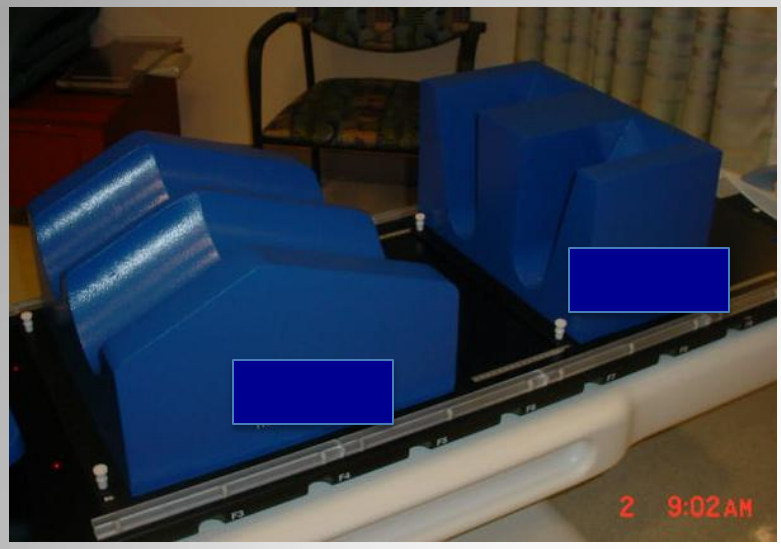
Nihei et al. IJROBP 2011

Grade 2+ side effects from **prospective** studies

Study	Grade ≥2 GI	Grade ≥3 GI	Grade ≥3 GU
MDACC X-rays 70 vs. 78Gy	13 vs. **26%**	1 vs. **7%**	5 vs. **4%**
Dutch X-rays 68 vs. 78Gy	27 vs. **37%**	5 vs. **4%**	13 vs. **12%**
PROG Protons 70.2 vs. 79.2Gy	9 vs. **18%**	1 vs. **1%**	2 vs. **1%**
Japanese Protons 74GyE	4%	0%	0%

Protons have benefited in technologic advances (just like x-ray therapy)

- Imaging
- Treatment planning (software)
- Treatment delivery systems
- Intensity modulation
- Inverse planning
- Immobilization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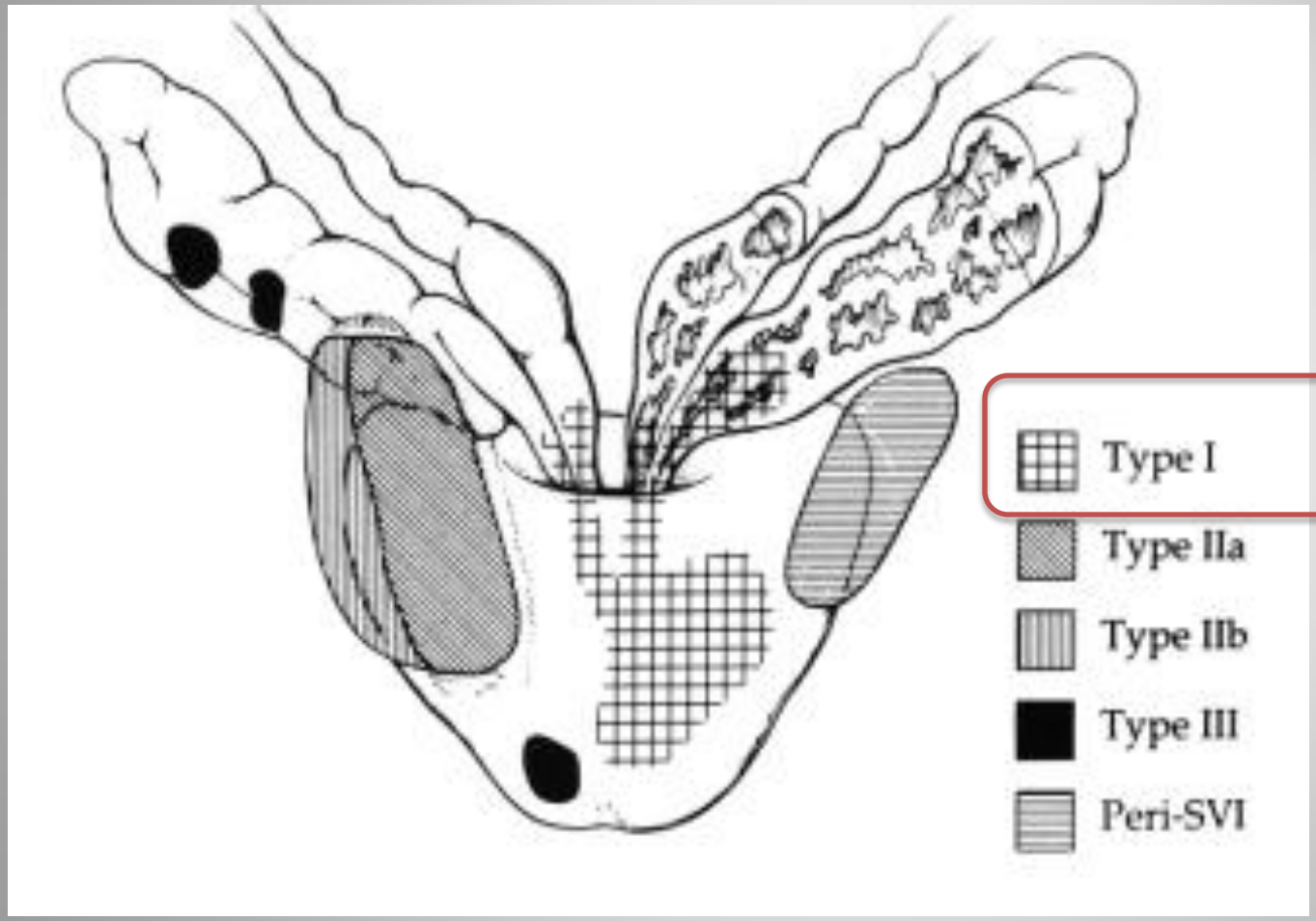
Proton therapy for Prostate Ca MDACC technique

- Supine
- ER Balloon (2 sizes: 80cc vs. 60cc)
- Bony and fiducial alignment
- 2-fields every day (opposed lats)
- CTV = Prostate +/- portion of SV
- 2 CGE x 39 = 78 CGE to “PTV”
  - Mean dose to CTV ~80-81 CGE

MDACC prostate EBRT recommendations

- Low risk
  78 Gy (2 Gy) PTV
  (>80 Gy CTV)
- Intermediate risk
  Prostate & “proximal” SV
  6mo HT for select pts
- High risk & T3
  Prostate & most of SV
  (Select pts LN)
  2 years HT

Types of seminal vesicle invasion:
Type I direct invasion most common & worst prognosis



Most common w/ worst prognosis

Least common w/ best prognosis

Ohori et al. Am J Surg Path, 1993

Estimating risk of SVI

- SVI is rare in modern era (~5%) for T1-2
- Risk based stratification (pT3b may be >30% in higher risk patients)
- Gleason score, PSA, T-stage, % (+) biopsies, MRI findings

- Updated Partin tables
- Kattan nomogram

Cover 2.0-2.5 cm of SV (~60%) in CTV

- N=344 RP specimens
- 15% had SVI
- Median SV length 3.5 cm (0.7-8.5 cm)
- Median length of SVI 1 cm

  7% had SVI >1cm

  1% >2cm or ~60% of SV

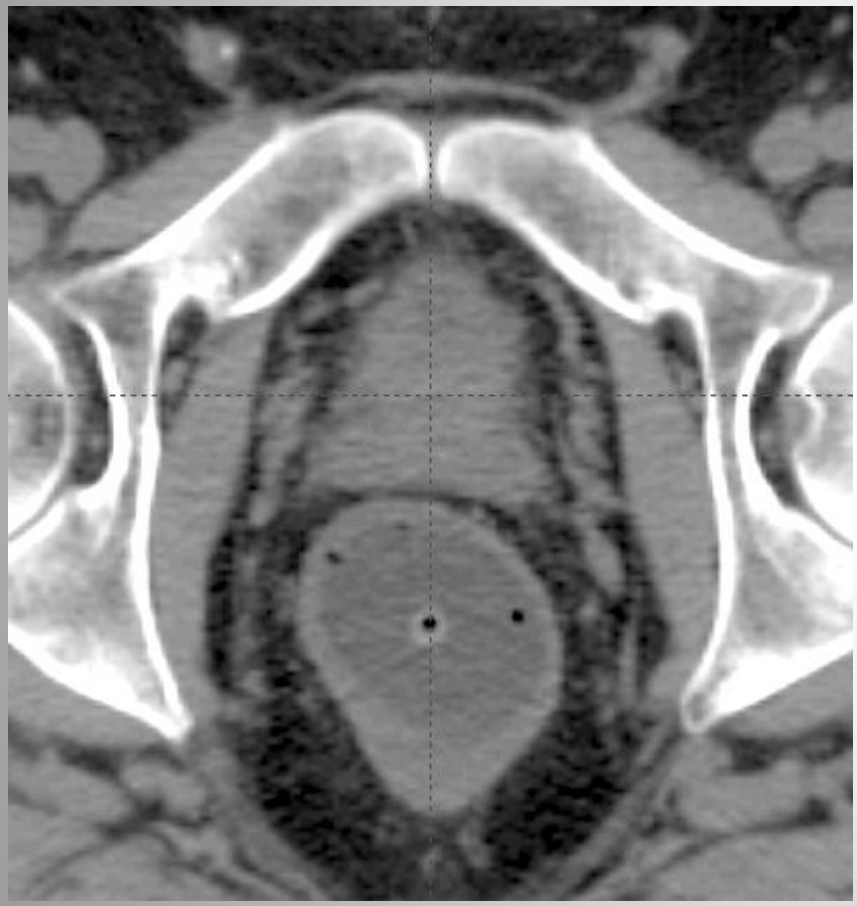
  Less than 4% had >2cm SVI (even for higher risk)

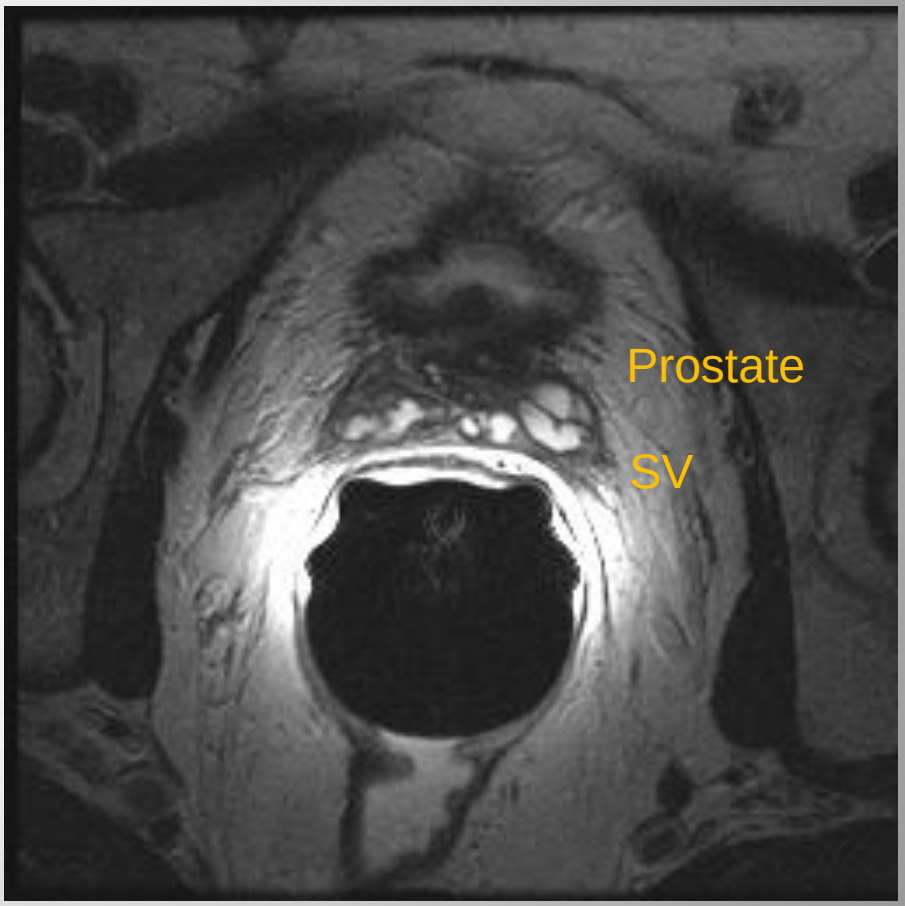
- Low risk 1% (T1-2a, Gleason 6, PSA <10)
  - 1 factor elevated 15%
  - 2 factors elevated 38%
  - 3 factors elevated 58%

Kestin et al. Int J Radiat Oncol Biol Phys 54, 2002

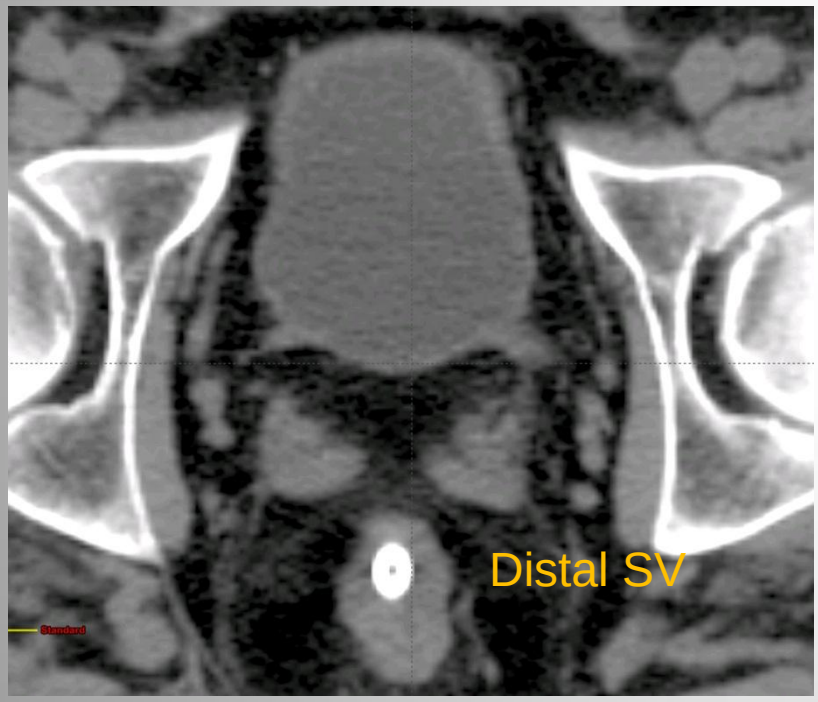
CT vs. MRI

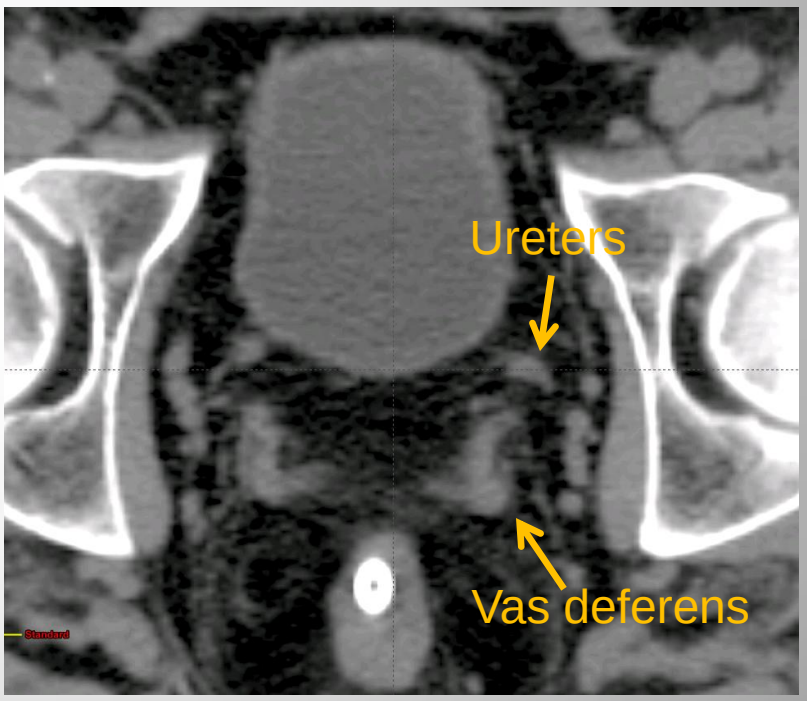
This has implications for SV length

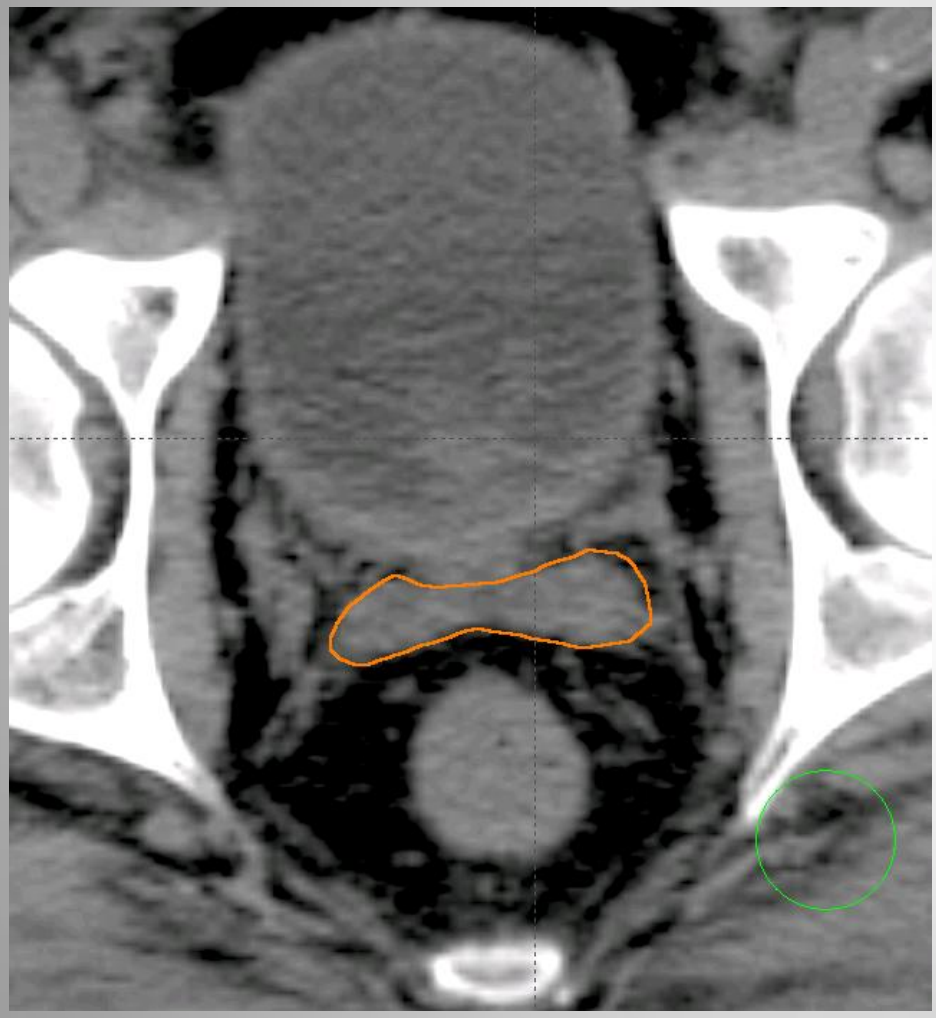


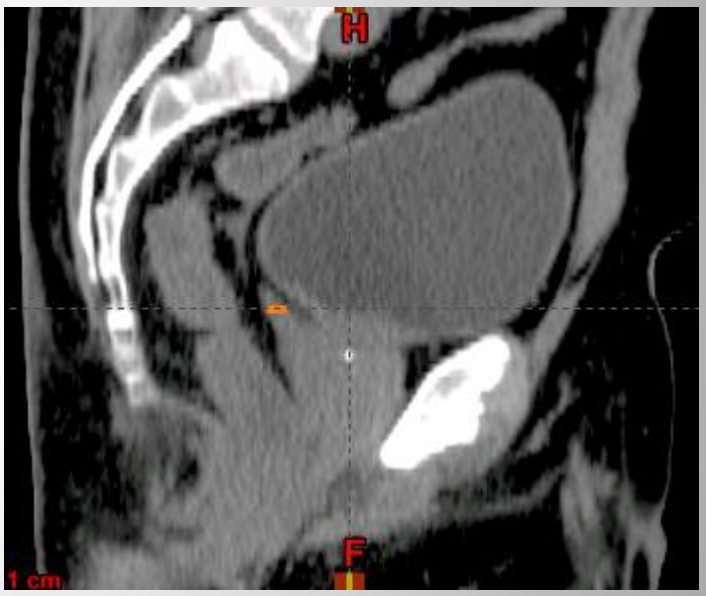


Distal SV vs. Something else





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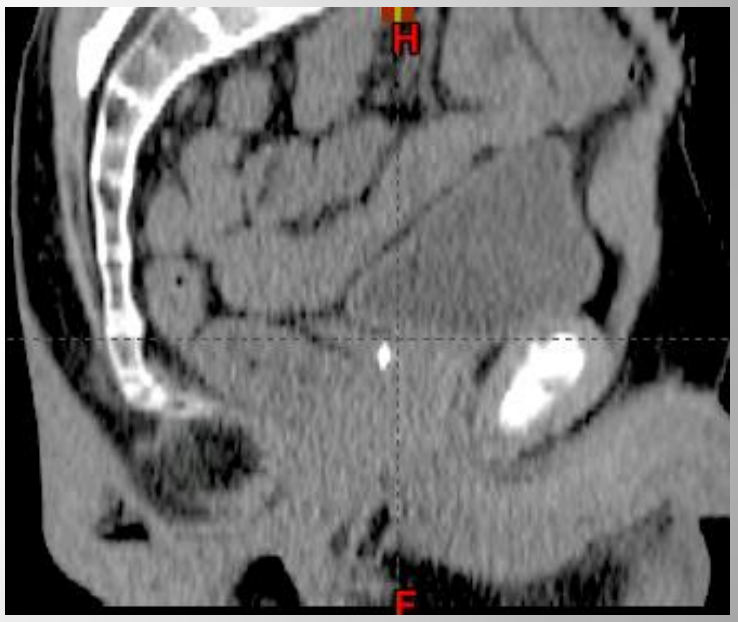
1 cm

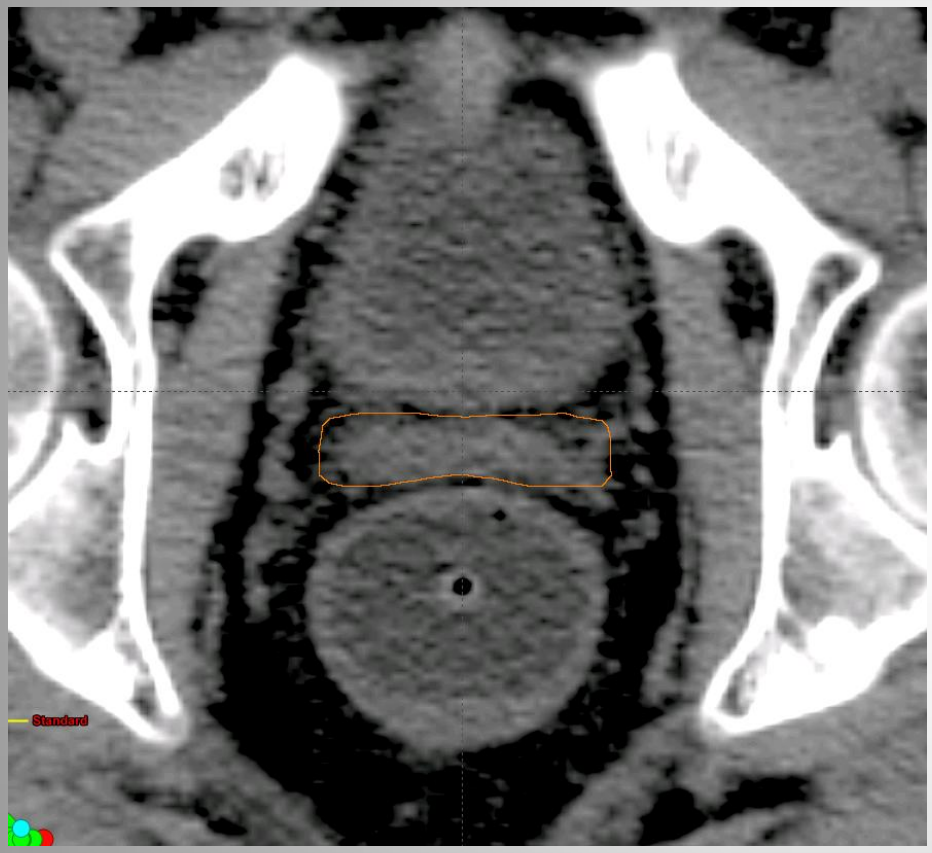


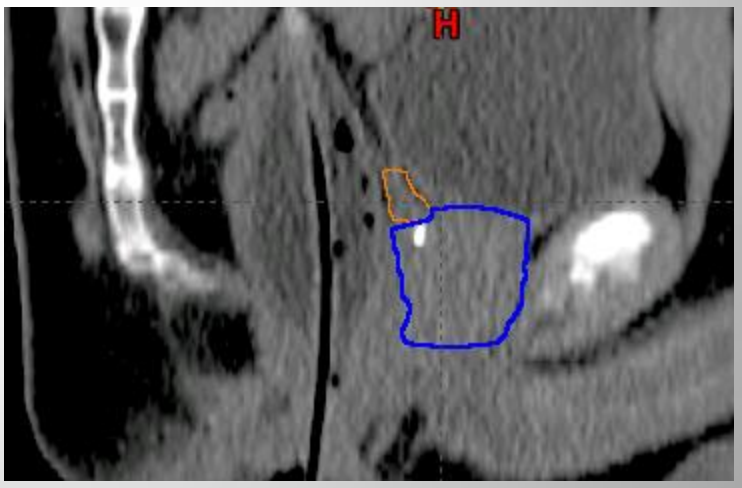
OPTIONS:

Decrease CTV...Not just superiorly but also laterally (remember type I SVI)

Decrease dose…Total dose or just SV followed by prostate boost

ERB…Does not always work....sometimes still have “droopy” SV


Standard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Planning parameters

Right & left lateral beams (daily)

- Improved conformality
- Potentially more forgiving and robust
  - Geometrically and biologically (RBE)
- Trade off is patient throughout

First 179 pts received 75.6 CGE (1.8CGE/fxn)

Now 78 CGE (2 CGE/fxn) to CTV + margin

- Usually prescribe to 98-96% isodose line

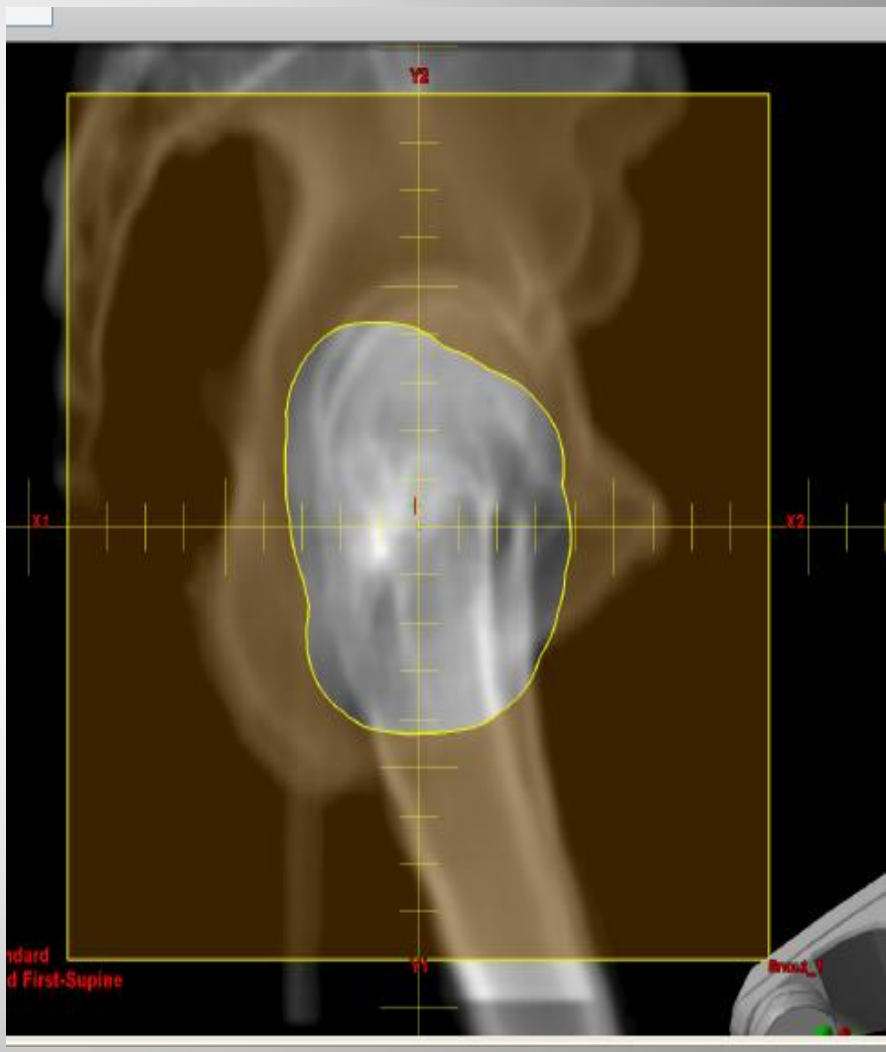
Proximal and Distal Margins for passive scattered planning

- Setup uncertainty <5mm
- Distal margin = (0.035 x distal CTV radiological depth) + (3mm)*
- Proximal margin = same (~ 1cm)
- Smear ~0.8-0.9 cm

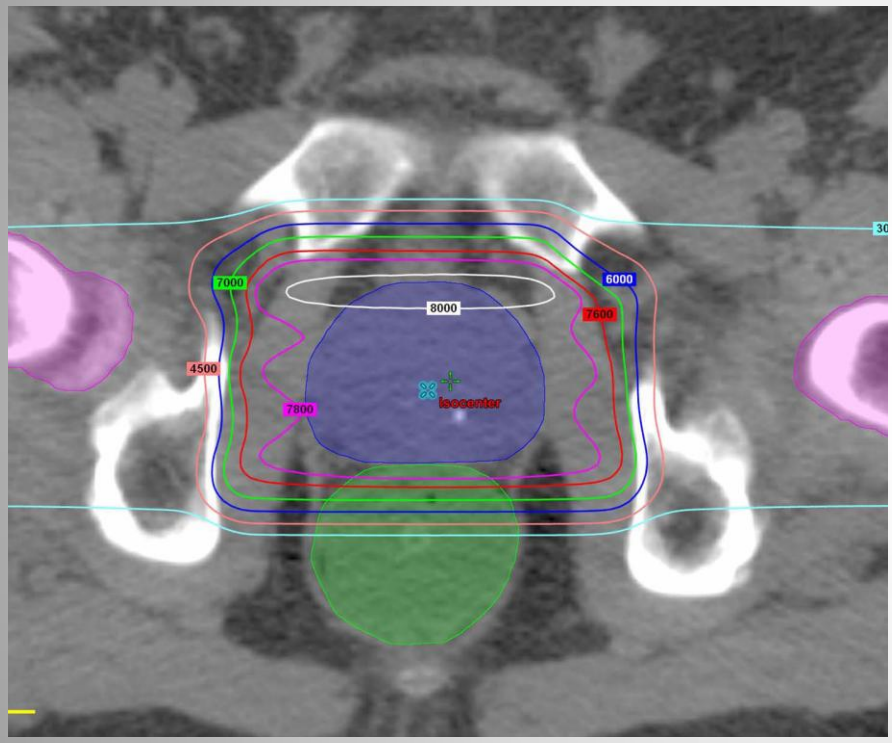
(*Beam range uncertainty)

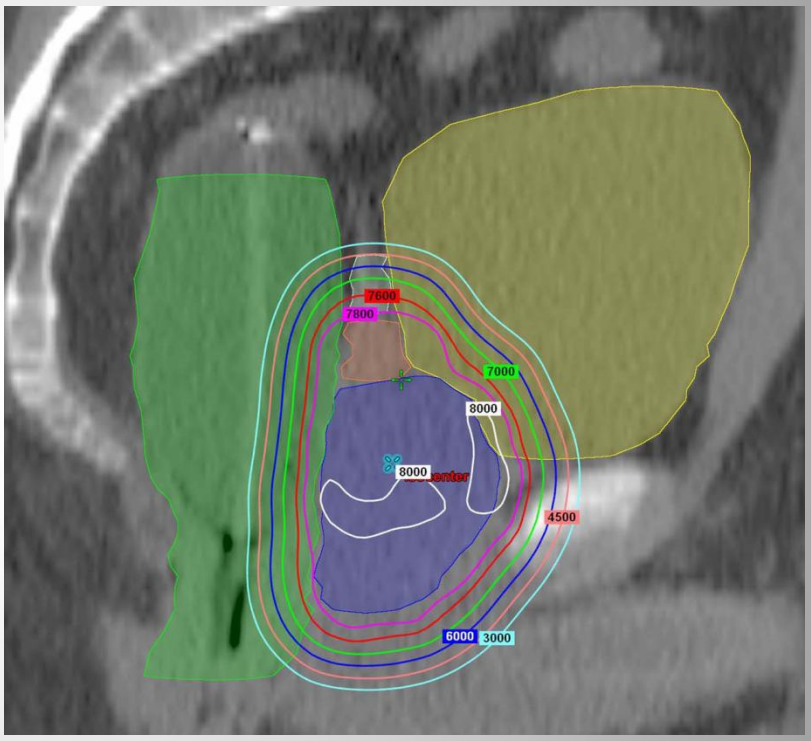
Lateral Margin

- LM = setup uncertainty + penumbra
- Setup uncertainty = 0.5cm
- 225-250 MeV beam penumbra (95-50%) = 1.0-1.2cm
- LM = 1.2-1.7 cm



Two opposed lateral beams

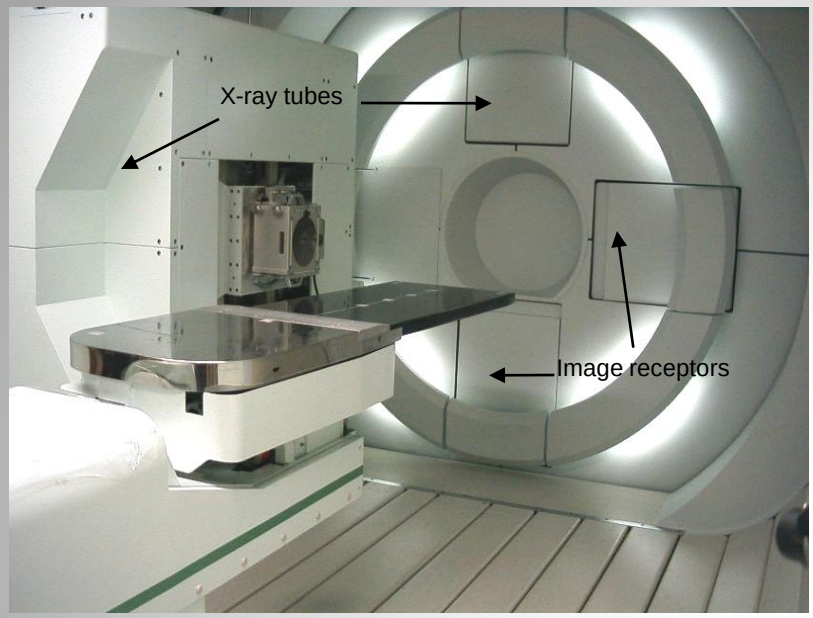


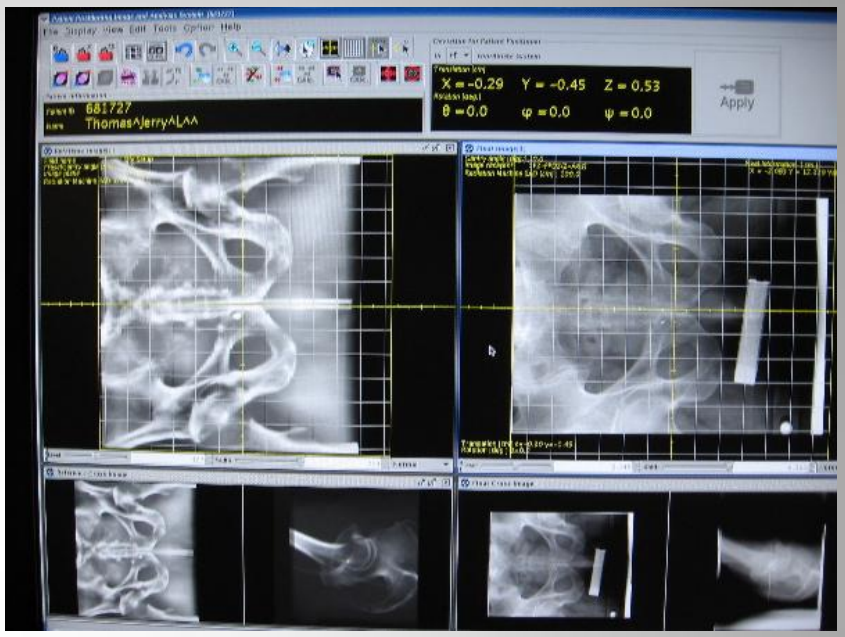


Rectal DVH V70 <12%

Anterior rectal wall V70 <40%

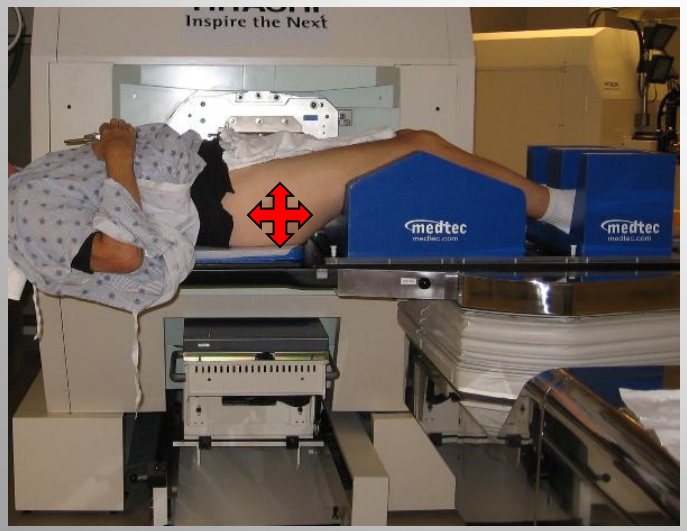
Simultaneous orthogonal pairs



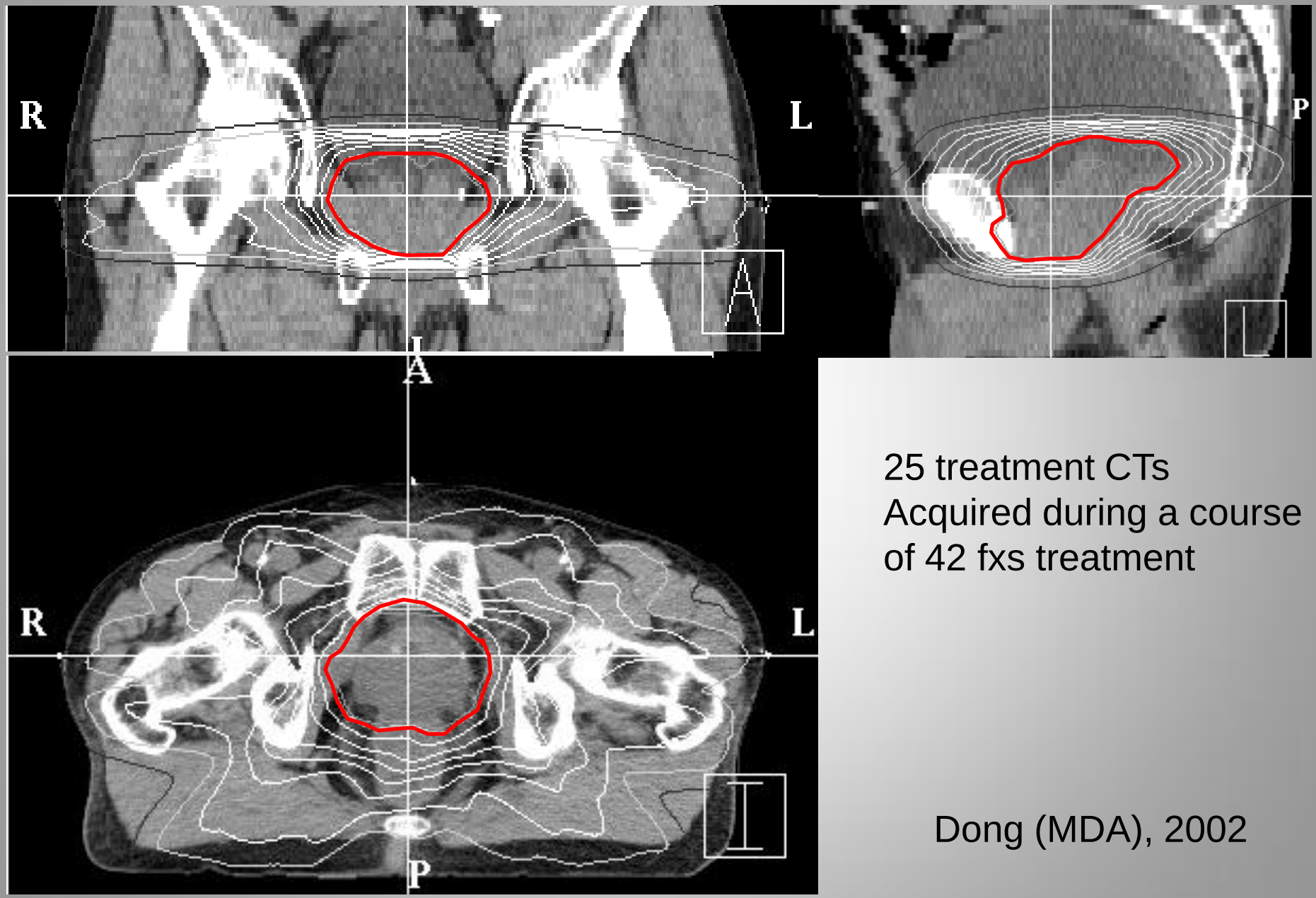


Positioning Image Analysis System, 'PIAS'

Hitachi



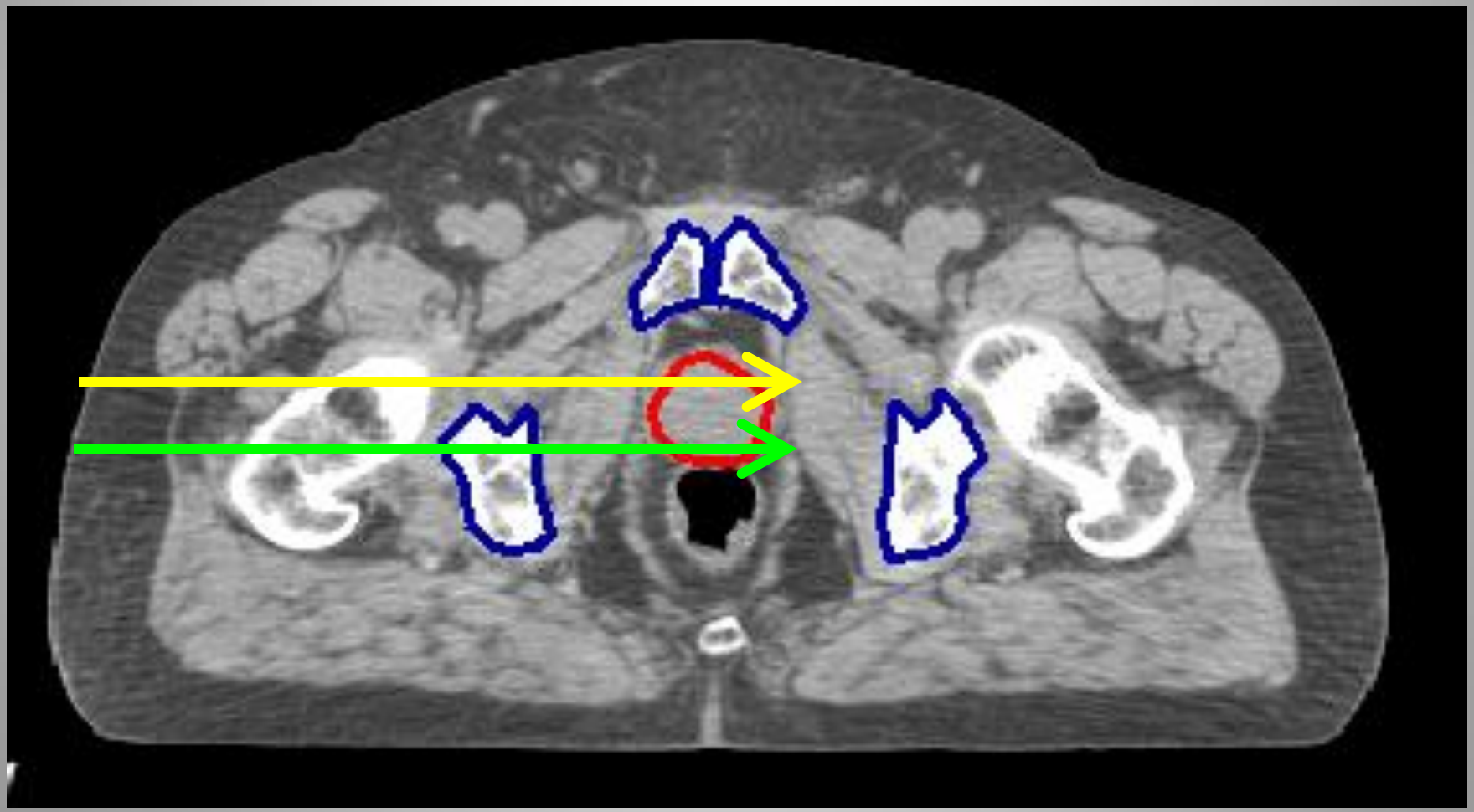
Dancing prostate & hips using vacuum bag



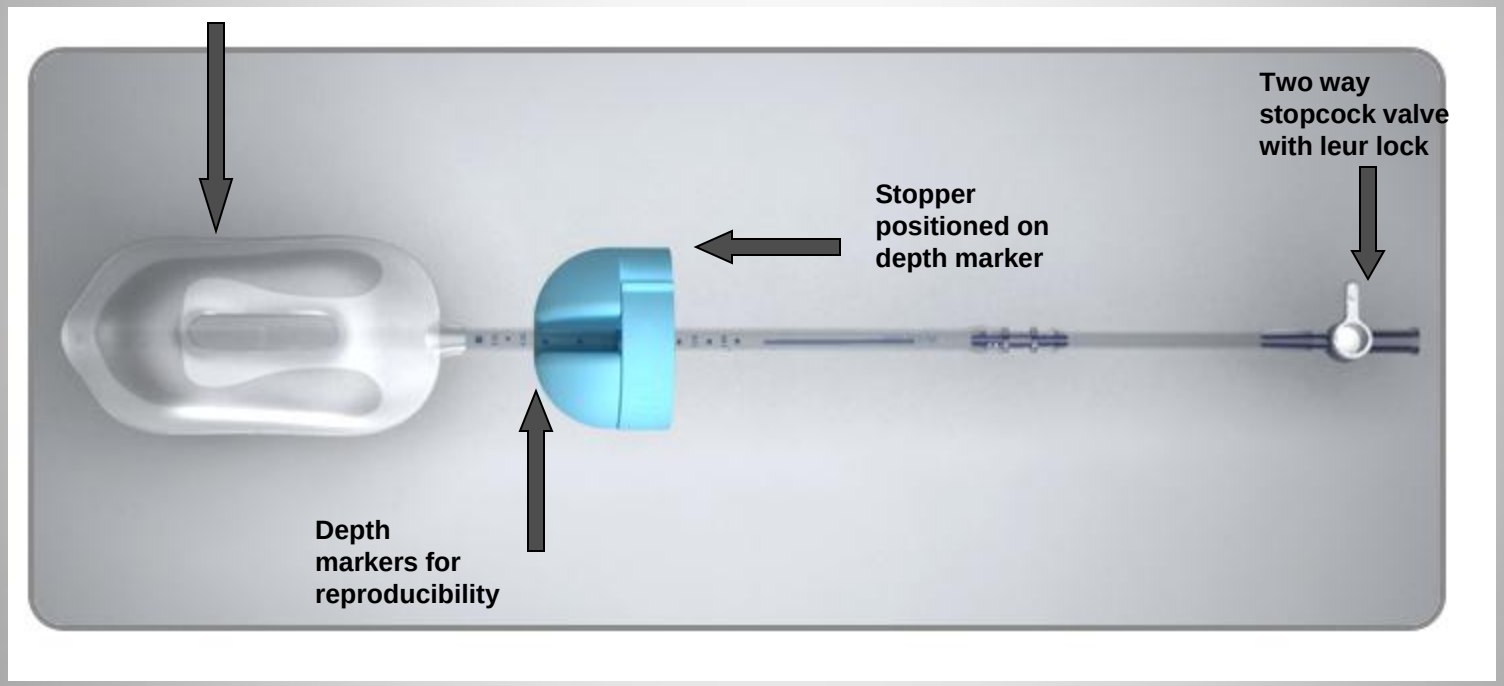
25 treatment CTs
Acquired during a course of 42 fxs treatment

Dong (MDA), 2002

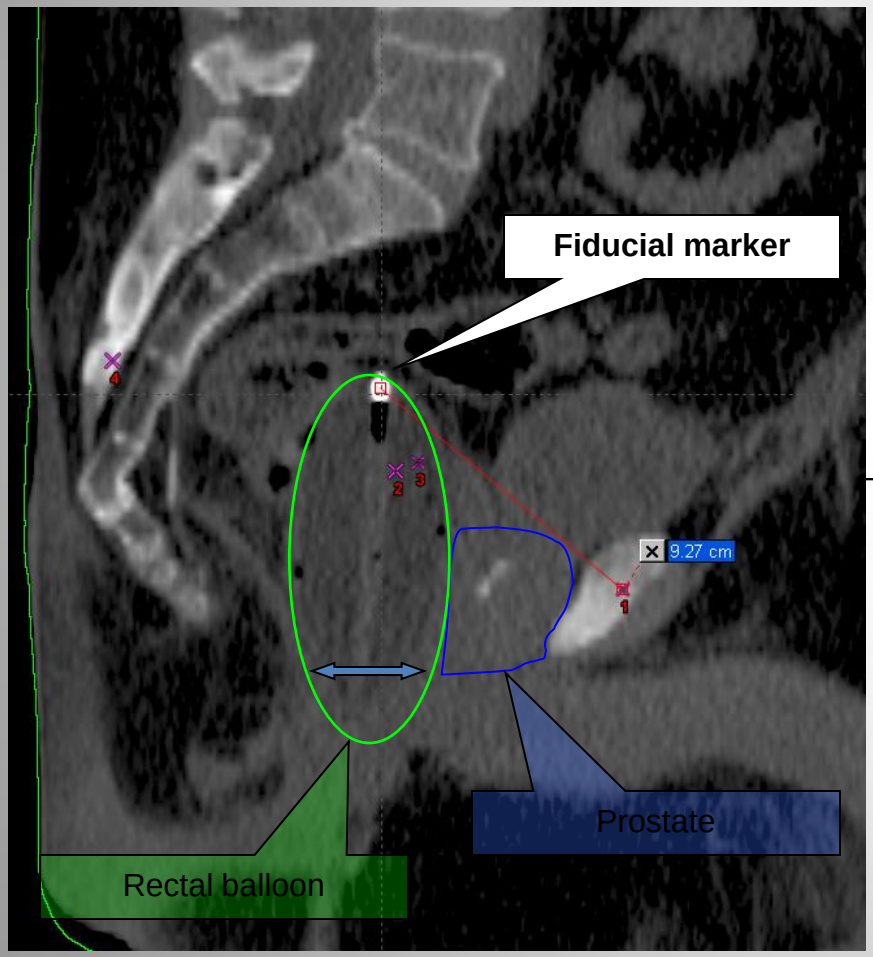
Range depends on radiologic path length

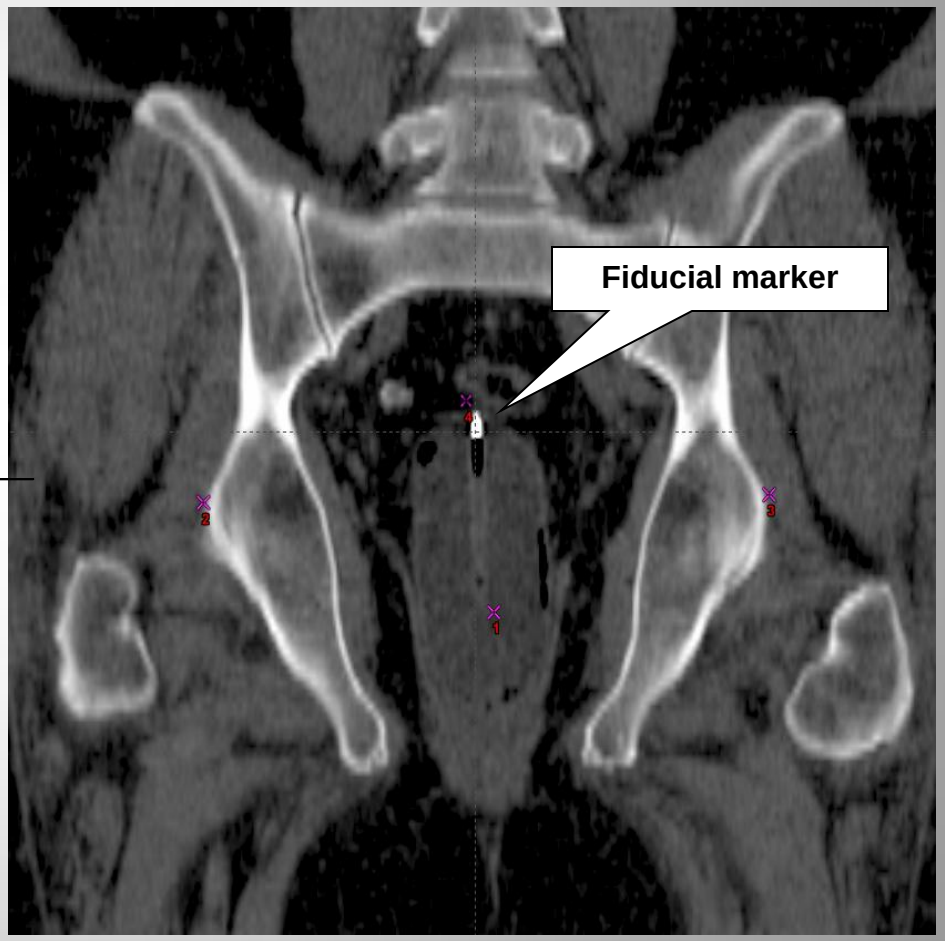


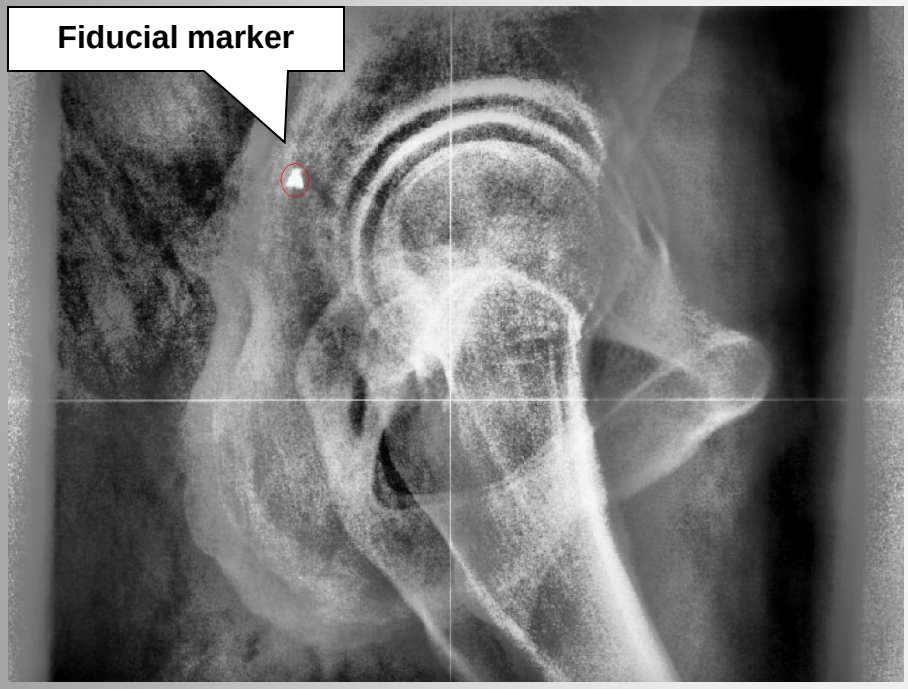
Gas-release double-ported ERB

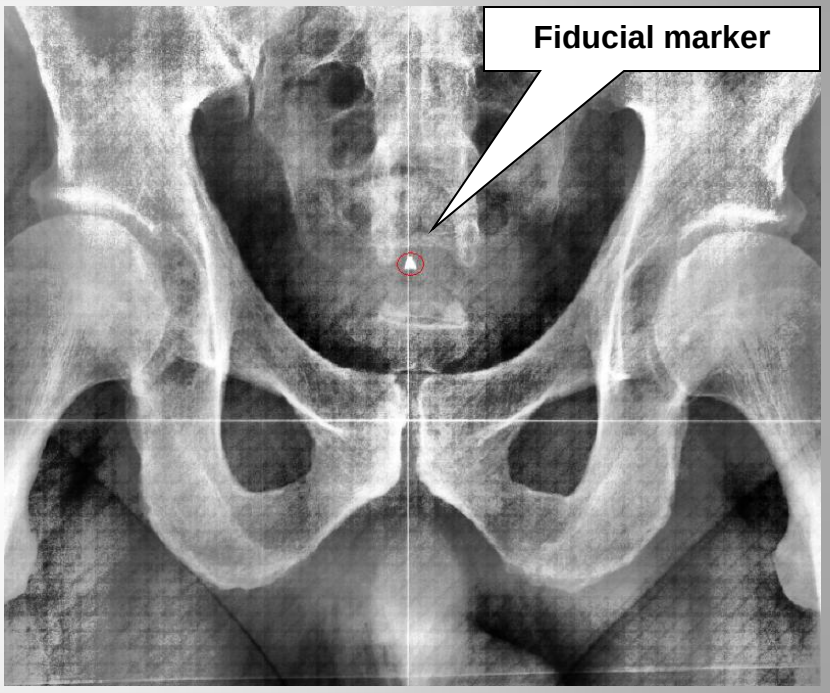


Sagittal and Coronal






Fiducial marker


Fiducial marker

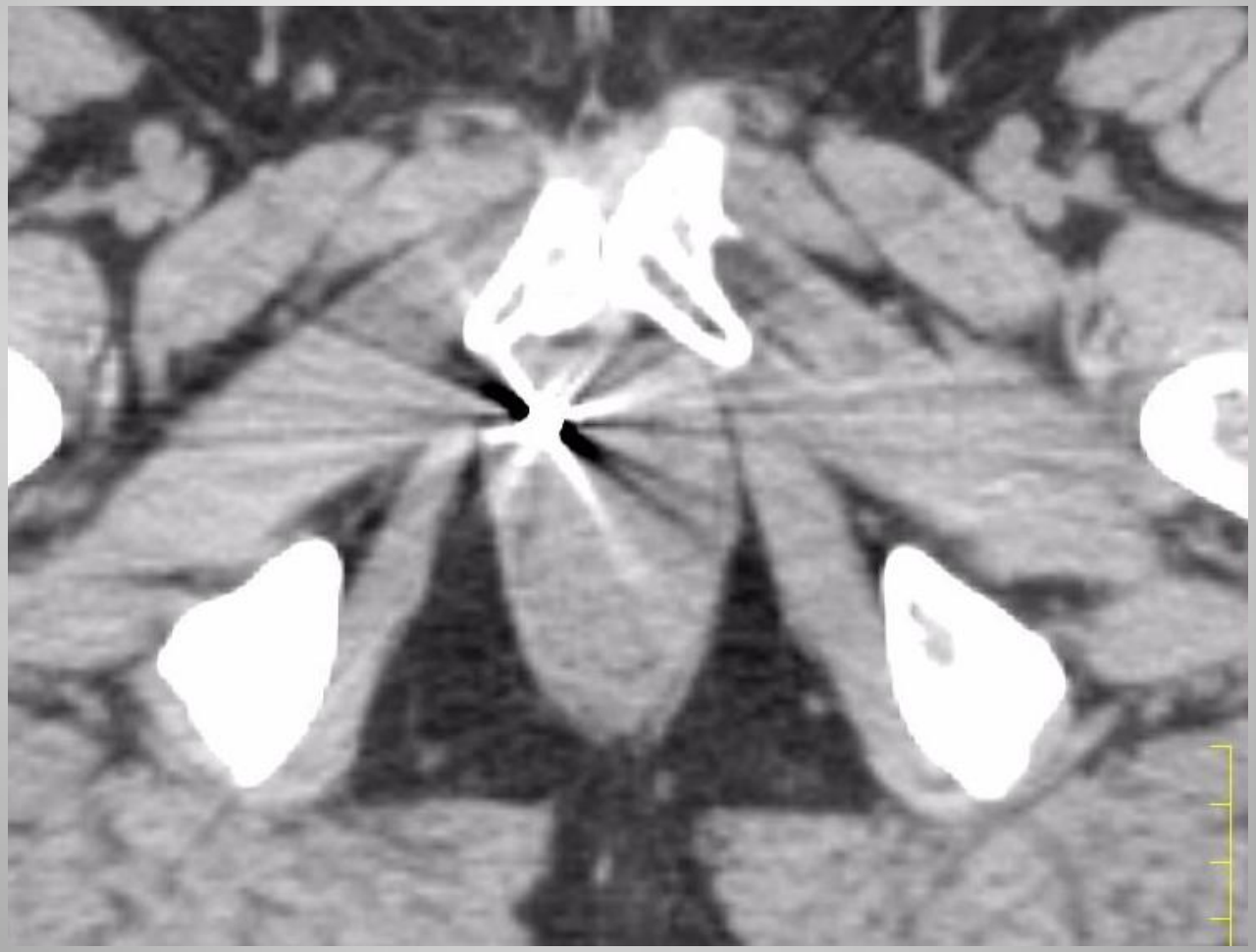
Fiducial markers

Fiducial markers and protons

- Increases accuracy
- Faster alignment than bone for RTT's
- Use lowest density material that is still visible
- Implant markers 5-7 days before simulation
  - If less time, consider verification CT 1st week of Rx
- Two markers (base-apex) w/ ERB is sufficient
- Do NOT orient long axis of markers parallel to beam path
- Investigate & correct large shifts between markers and bone

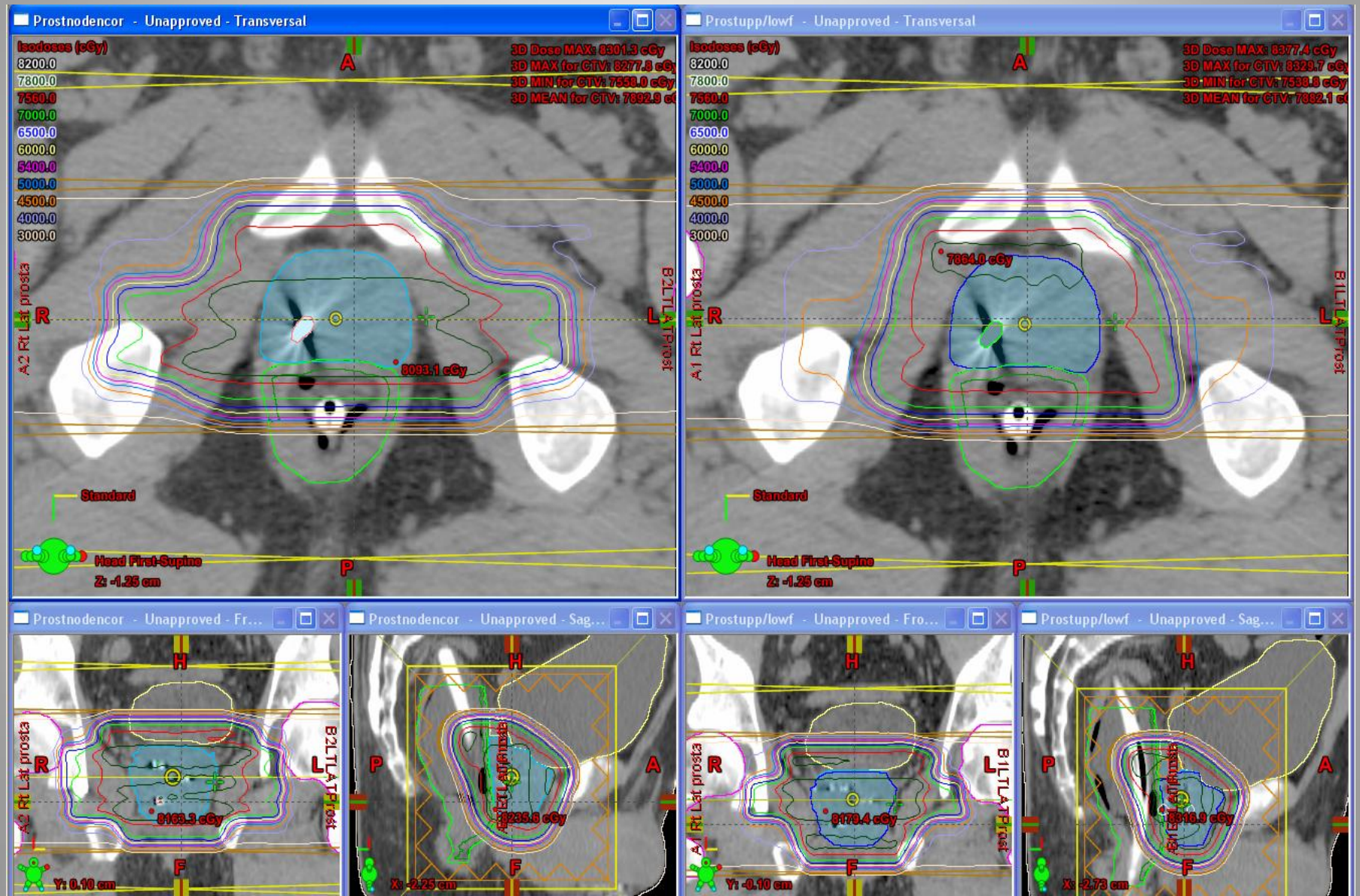
Gold fiducial:

CT numbers, Volume, Dose shadowing

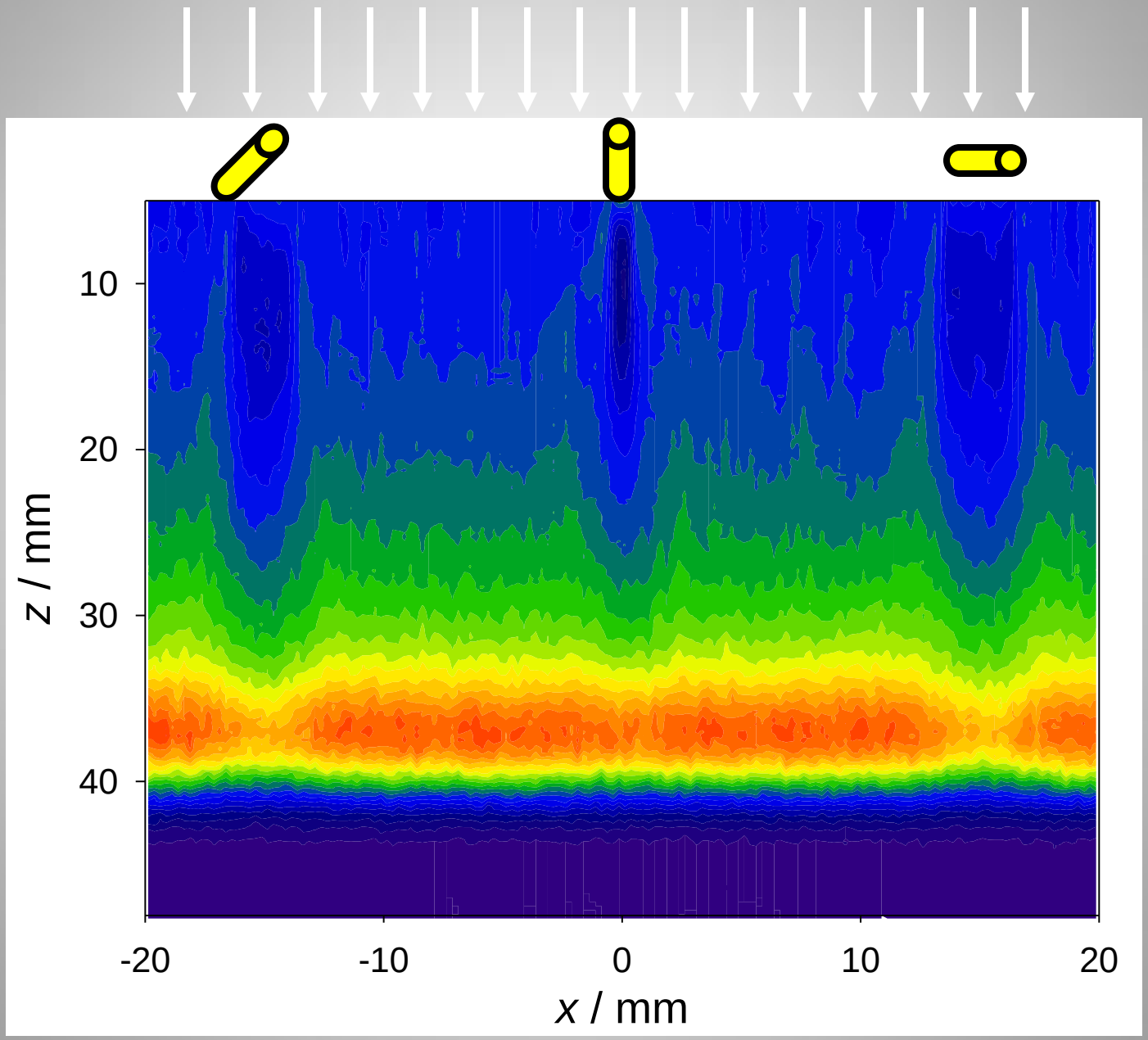


All 3 **large** fiducials to 3000 HU

No fiducials (over-ridden to tissue density)



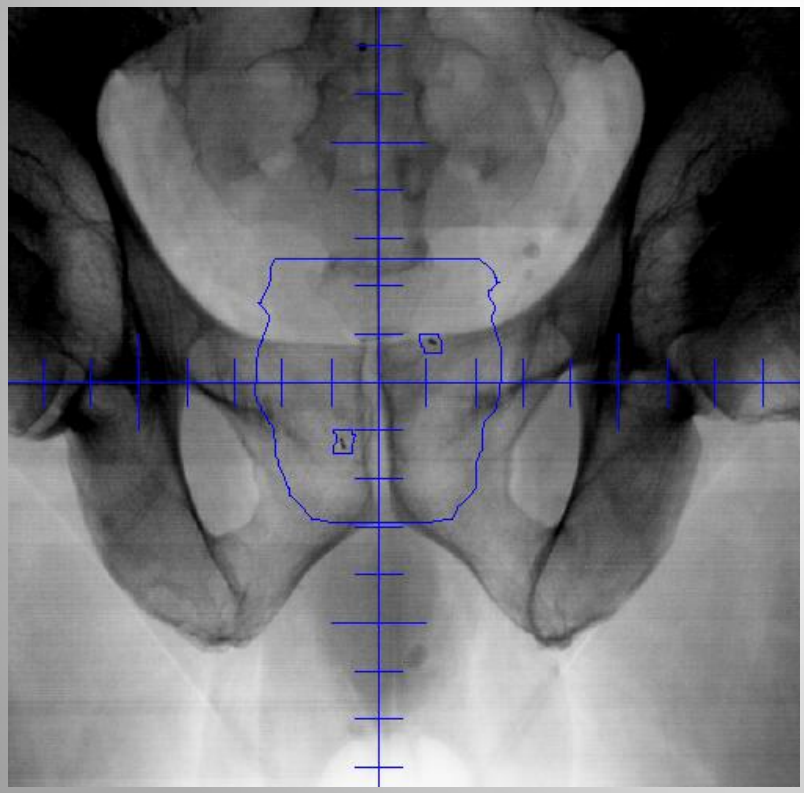
Newhauser et al: Dose Perturbations from Au Cylinders

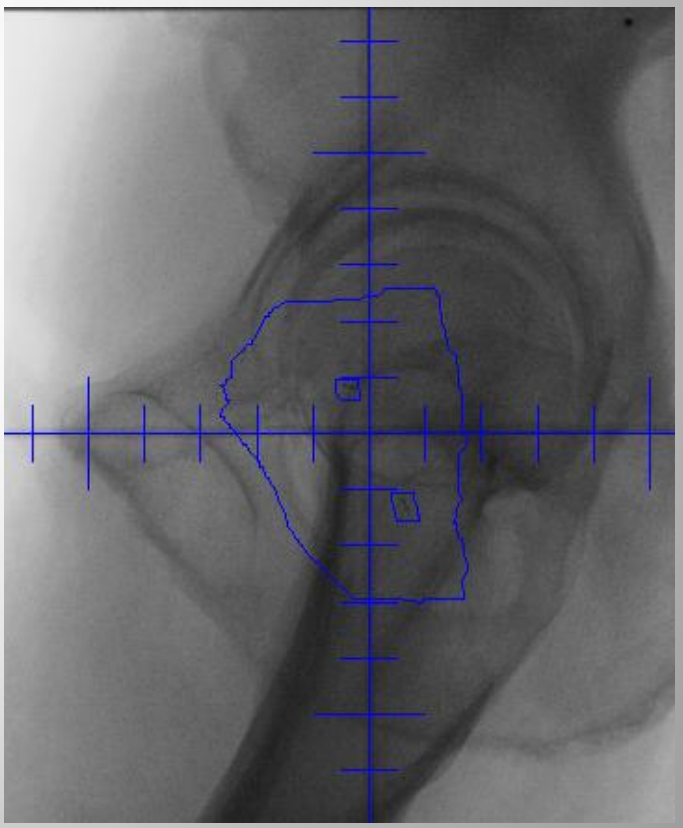


Ca^{++} vs. Carbon-coated ZrO_2

IGRT carbon-coated ZrO_2

May need to collimate kV imager for better visibility



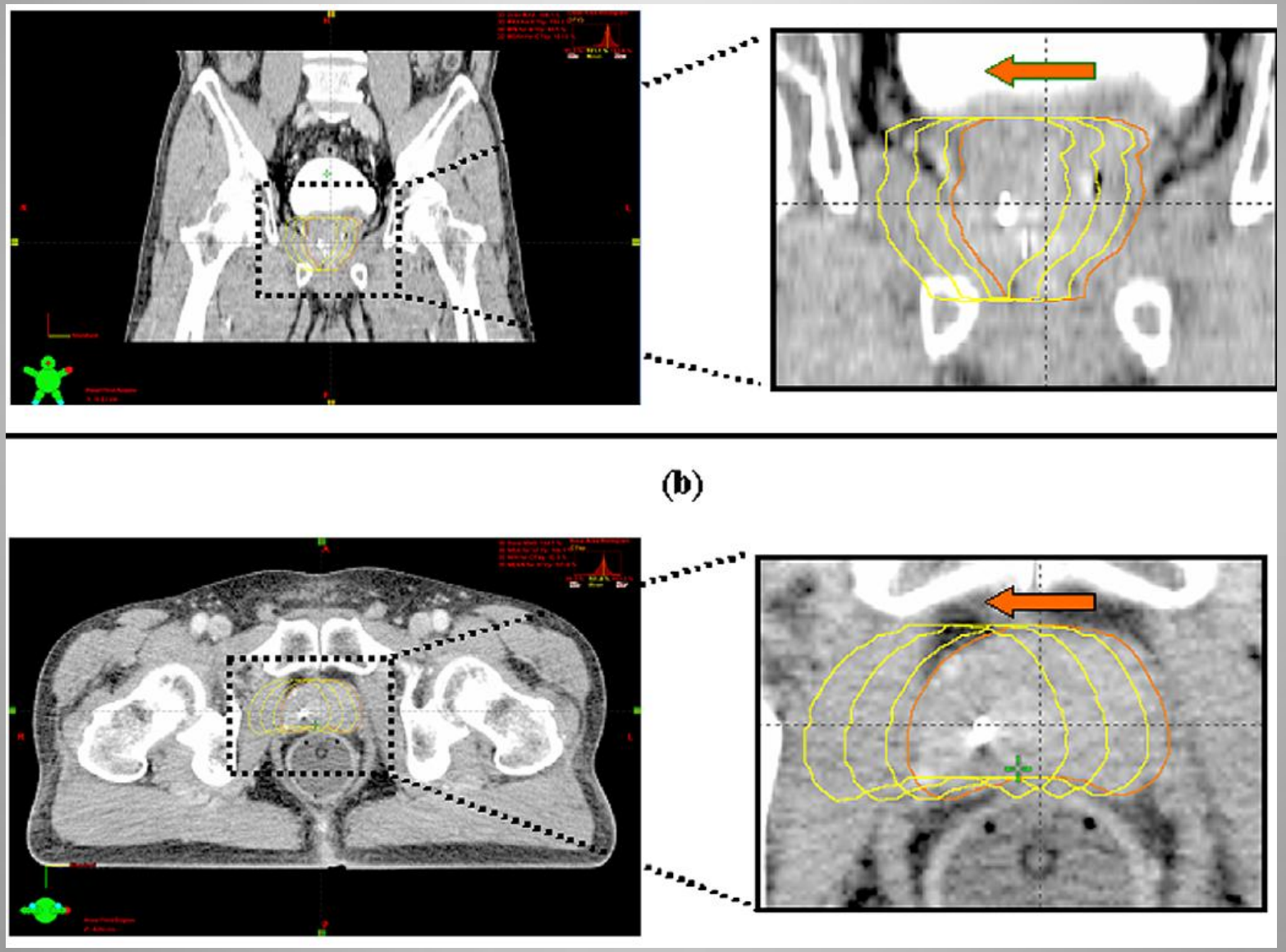


Translational shifts < 6mm and rotational shifts <5º do **not** significantly impact CTV coverage

- UF-Vargas et al. IJROBP 71, 2008
- NCC Korea-Yoon et al. IJROBP 71, 2008
- MDACC- Sejpal et al. IJROBP 2010

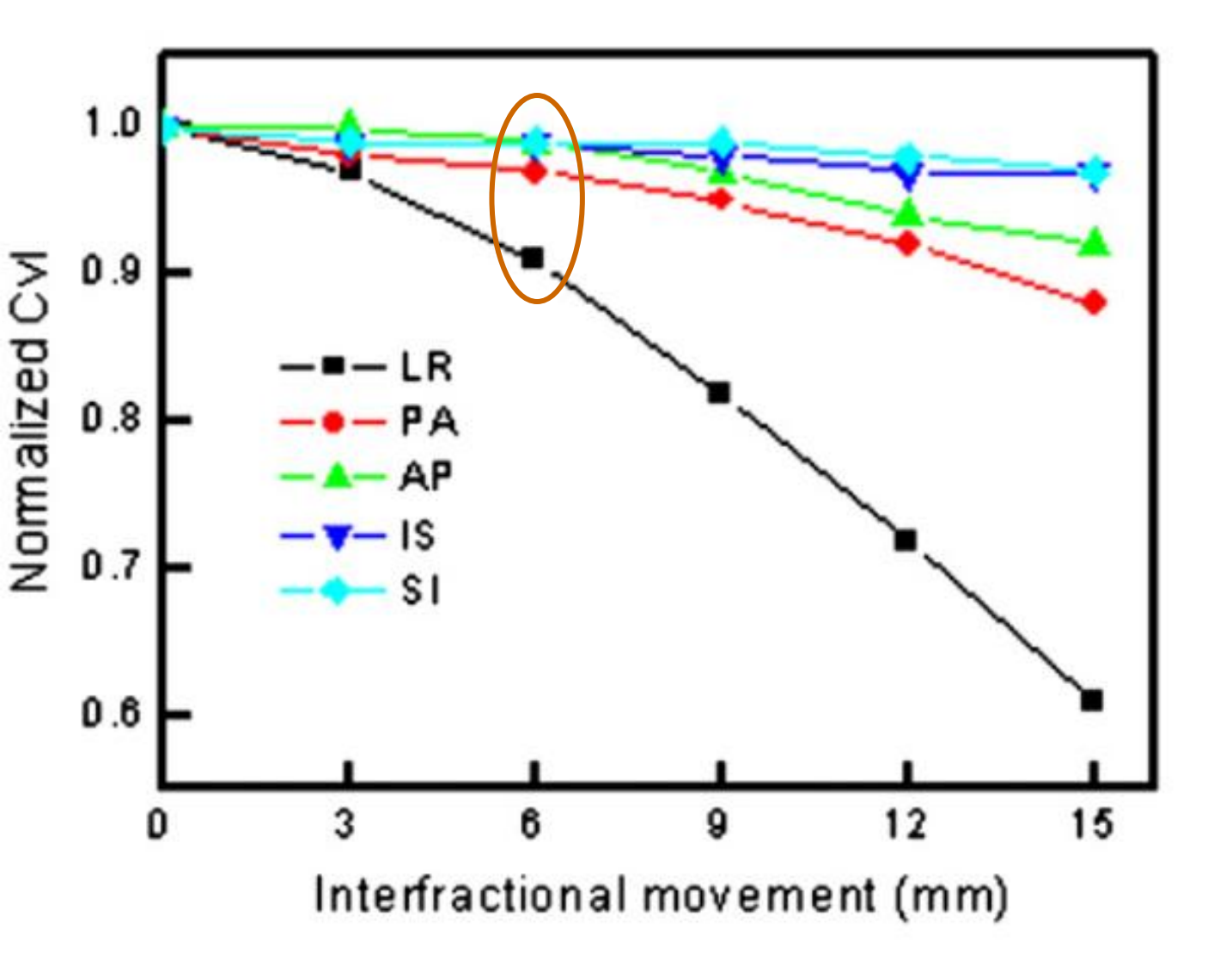
Virtual shifts

Yoon et al. IJROBP 71, 2008



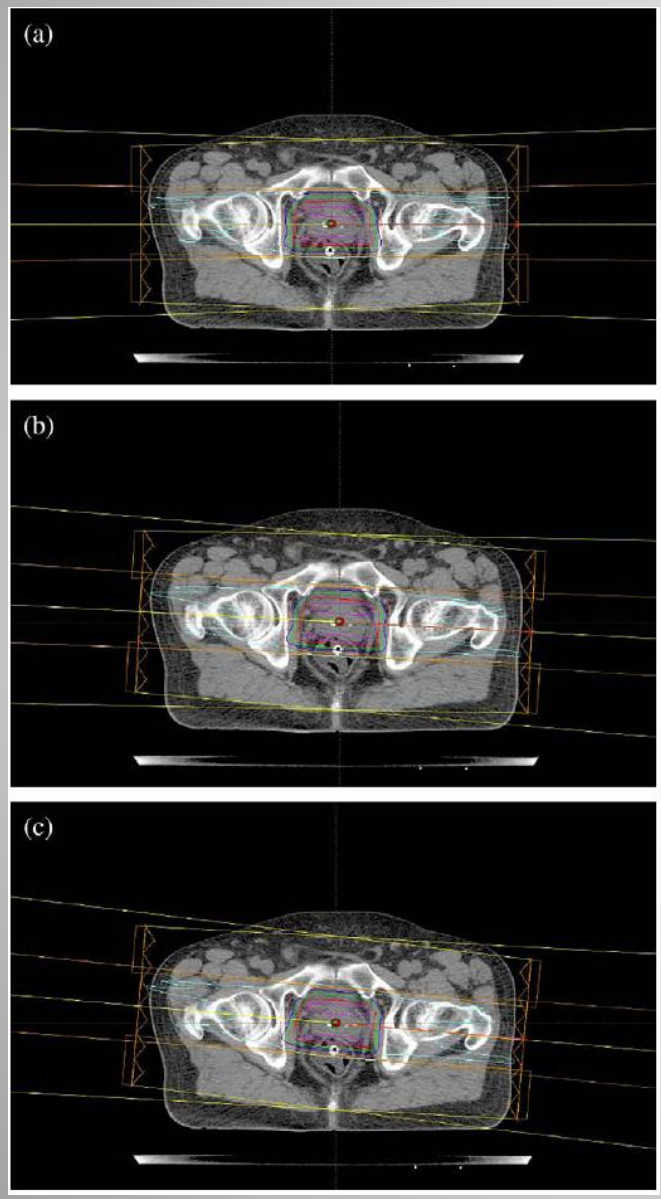
Yoon et al. IJROBP 71, 2008

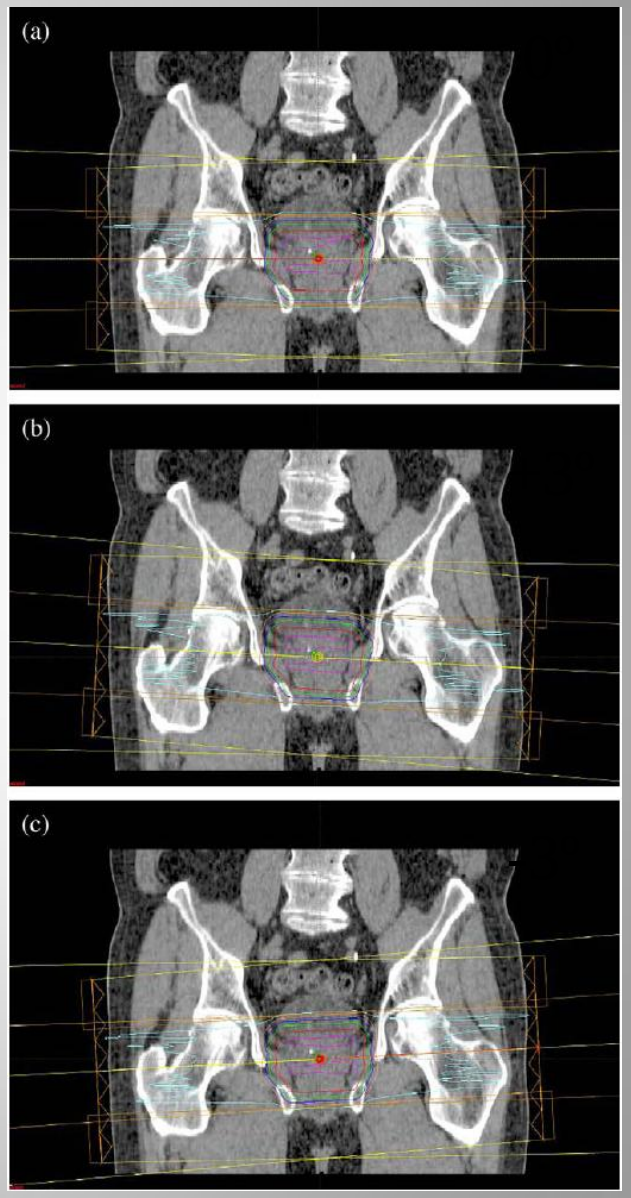
Coverage maintained well for shift up to 6mm



LR shifts >5mm occur <2.5%

How important is rotation?





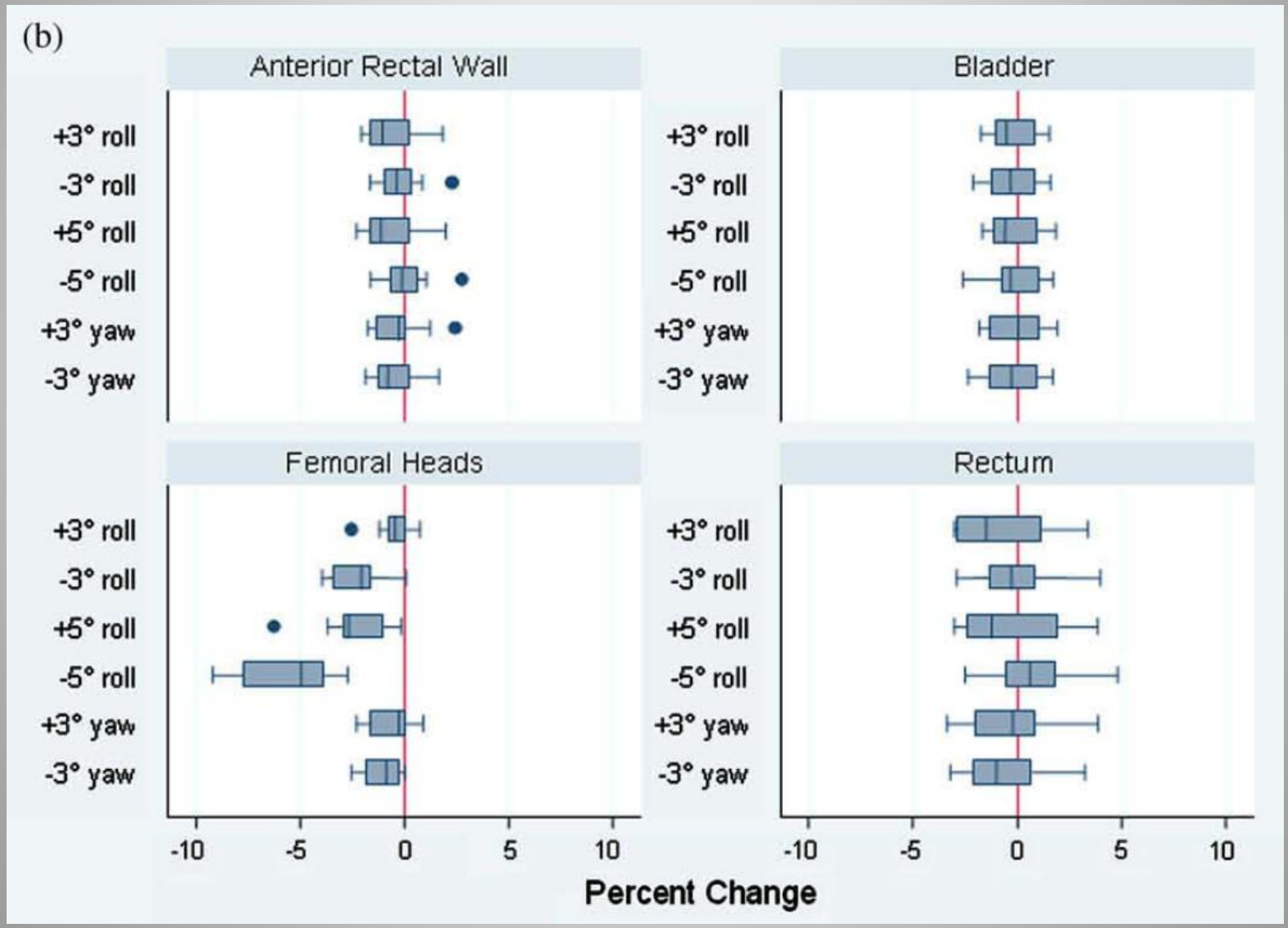
Worst case scenario is underdosing by 0.06 GyE (<0.08%) [Sejpal et al. IJROBP 2009]

Table 4. Mean change in dose to CTV across all six scenarios compared with control plan

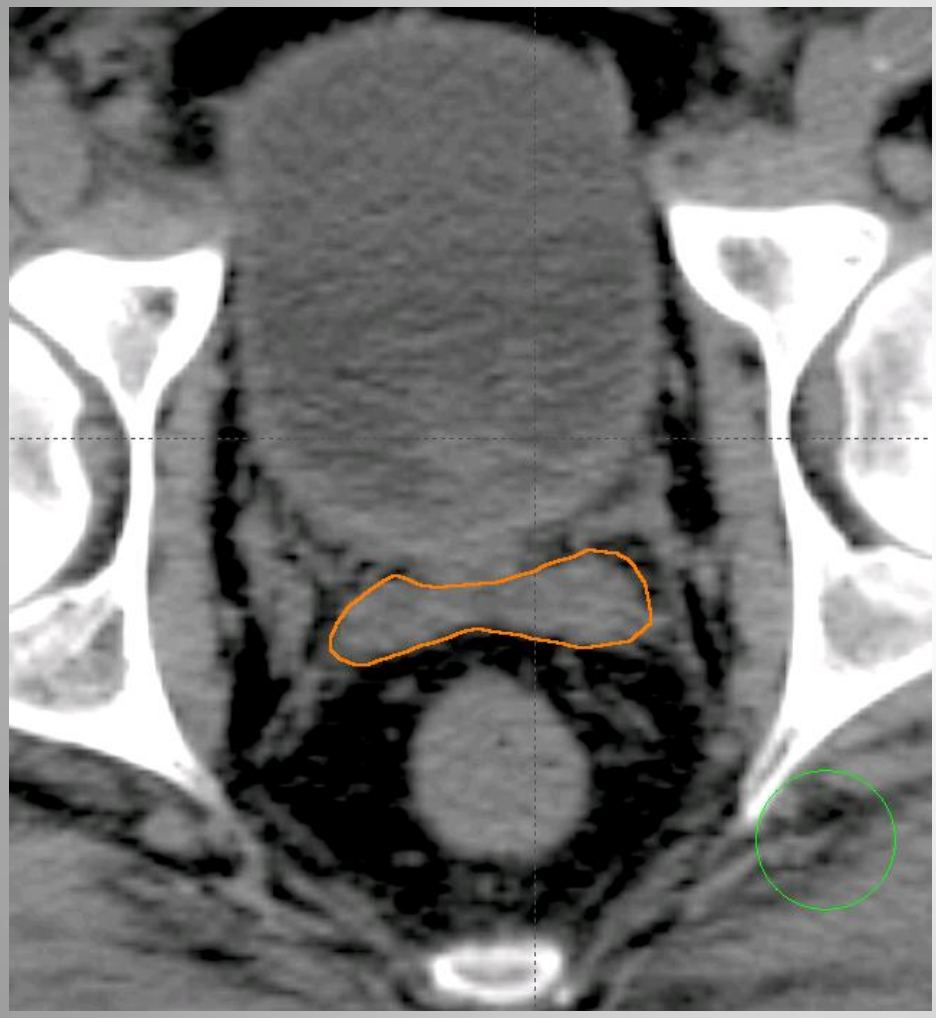
		Dose to CTV (CcGE)			
Variation	Patients (n)	Mean	SD	Minimum	Maximum
Control	10	0	0	0	0
+3° roll	10	+1	(0.3)	(−1)	(+1)
−3° roll	10	−1	(0.9)	(−1)	(−3)
+5° roll	10	0	(0.4)	(−4)	(0)
−5° roll	10	−1	(2.3)	(+1)	(−6)
+3° yaw	10	+2	(0.5)	(−1)	(+2)
−3° yaw	10	+2	(0.4)	(0)	(+2)

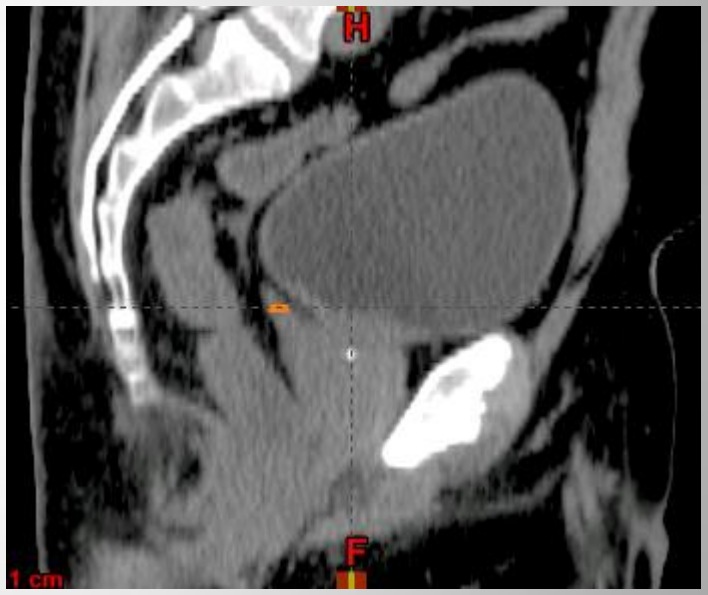
Abbreviations as in Table 3.
Data in parentheses are SDs.
Change in mean dose given for full treatment course of 7,600 CcGE delivered in 38 fractions.

If you make systematic error every fraction, change in normal tissue dose <5%

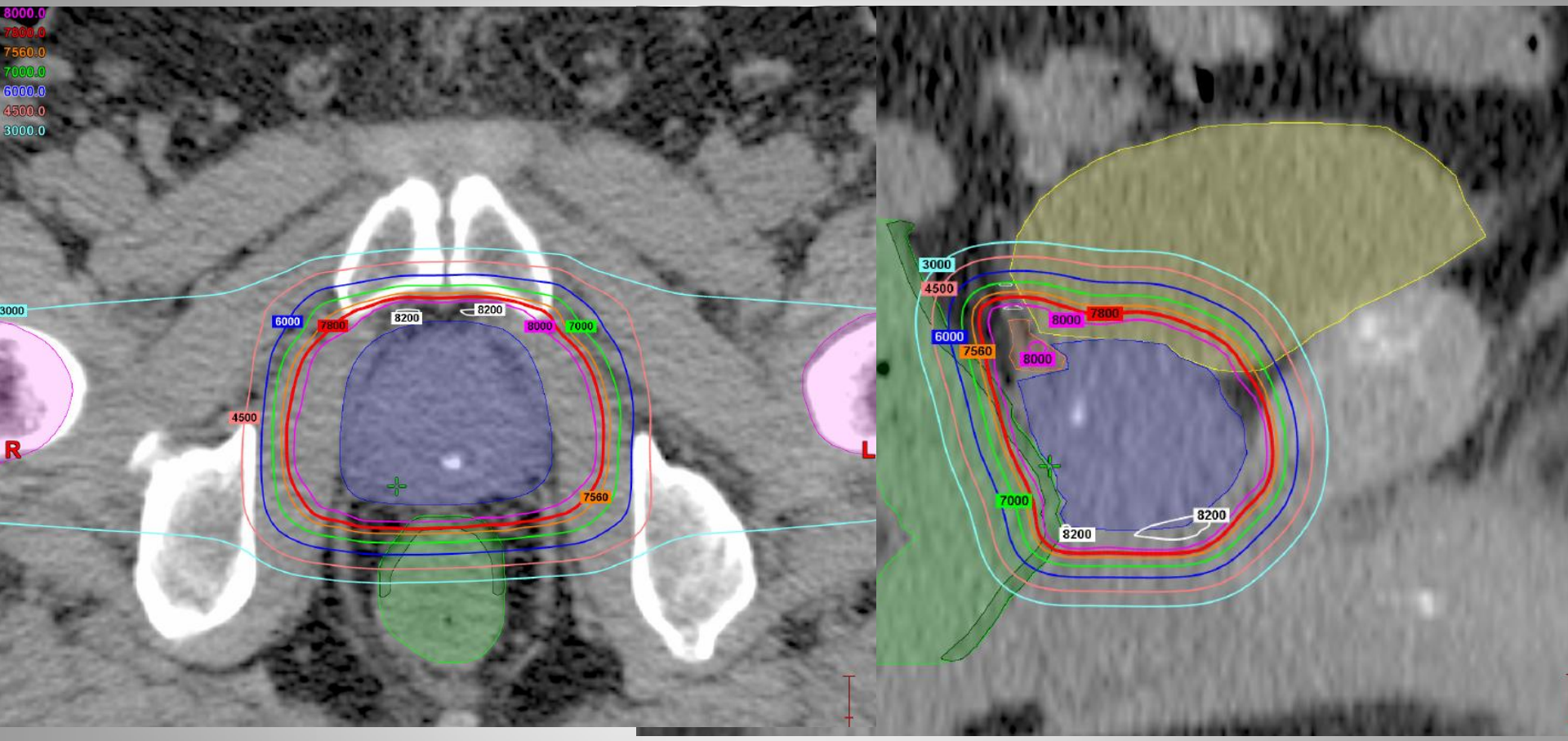


Does every patient need ERB?





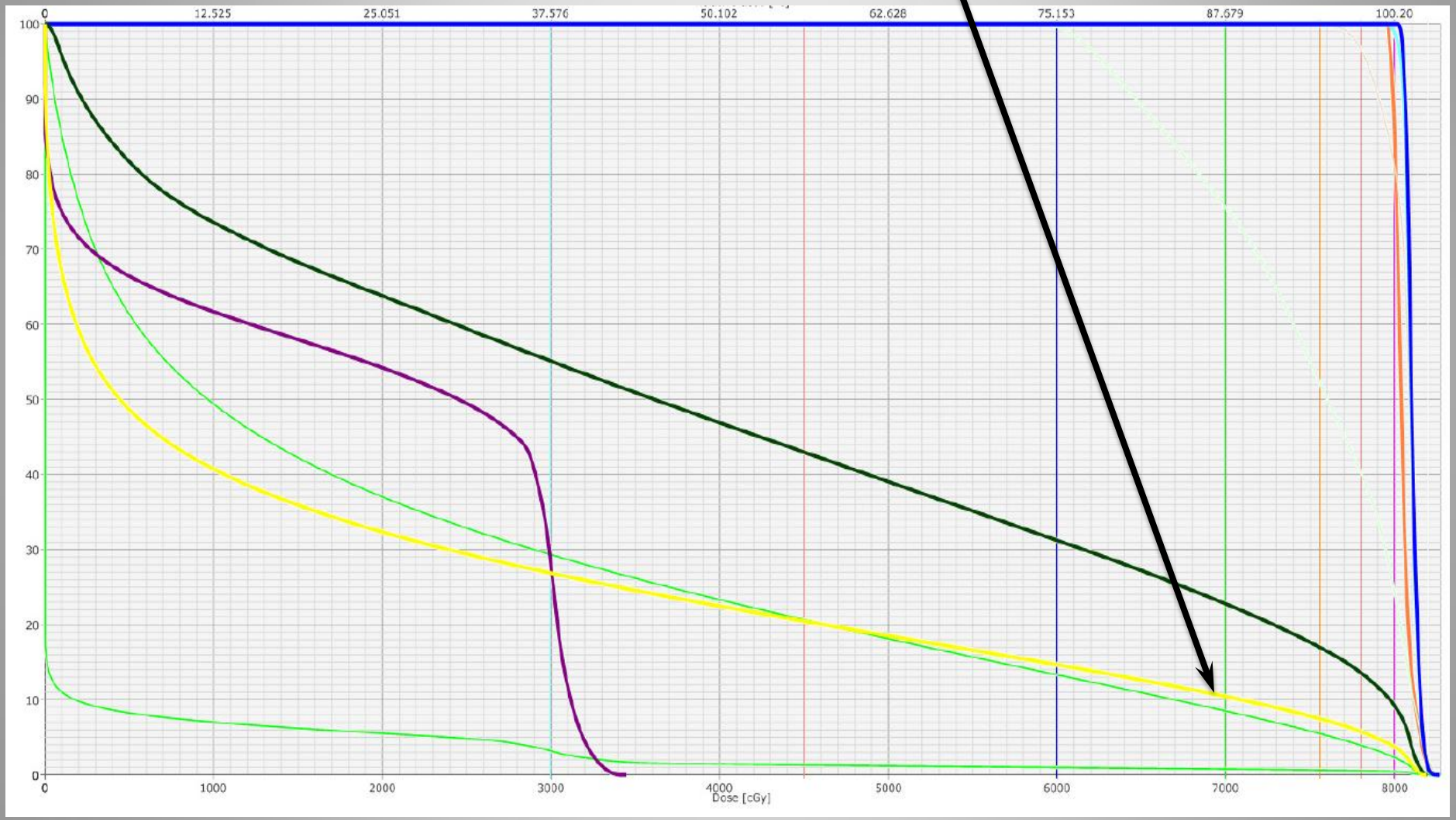
Treating without ERB w/ fiducials



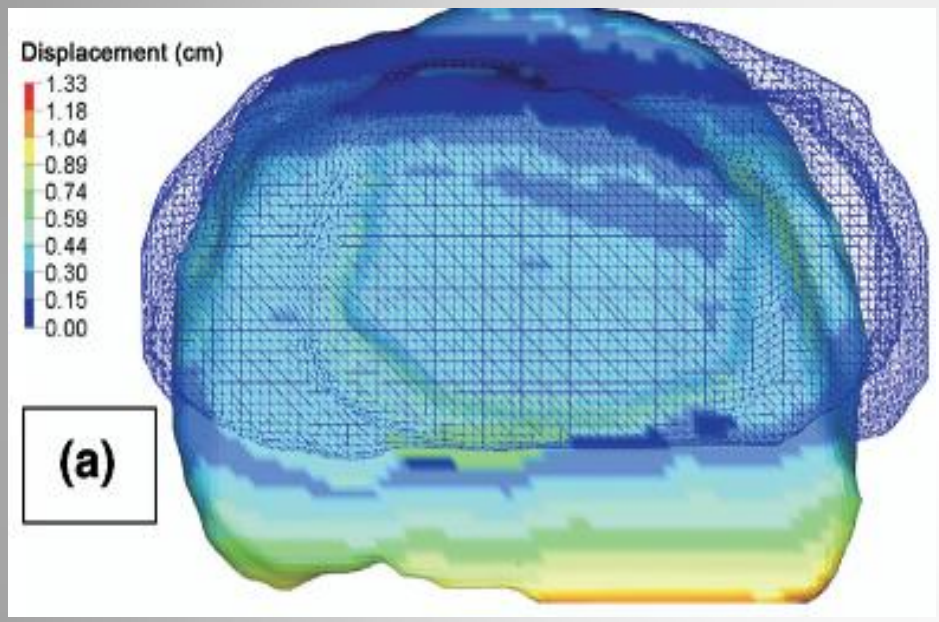
Patient anatomy: Posterior angulation of rectum, peri-prostatic/rectal fat

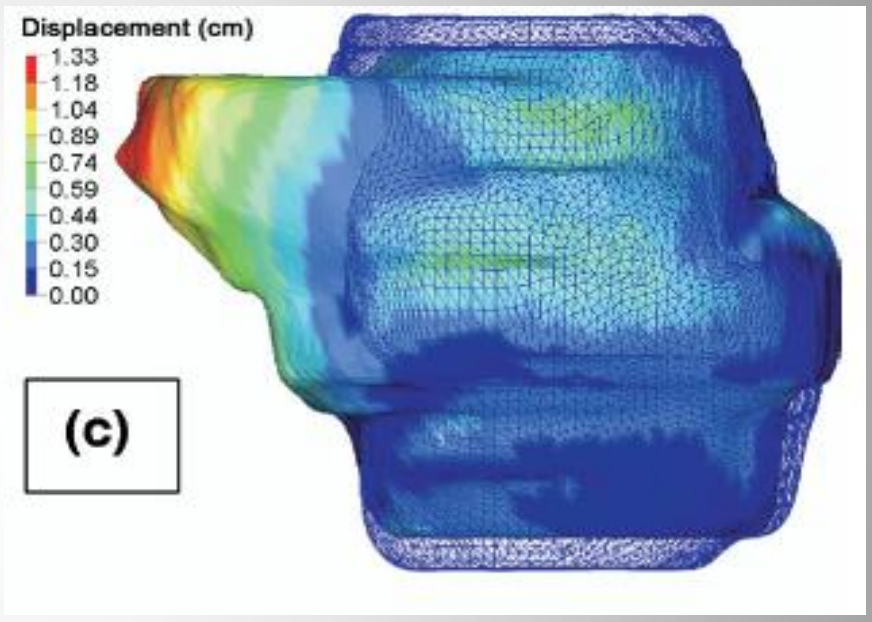
Patient compliance on rectal emptying (intervene if rectal gas on kV imaging

Treating without ERB DVH
Rectal V70 = 8% (light green)



But use caution…fiducials are not perfect: Fiducials vs. MRI





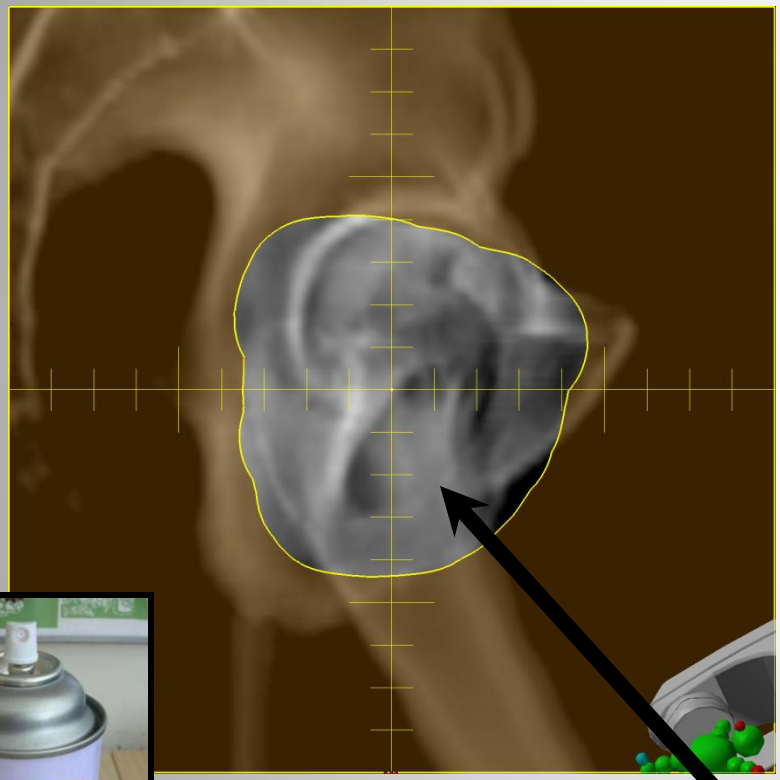
Max prostate deformations after translational matching of fiducials: 6mm x-direction, 13mm in y, 7mm in z

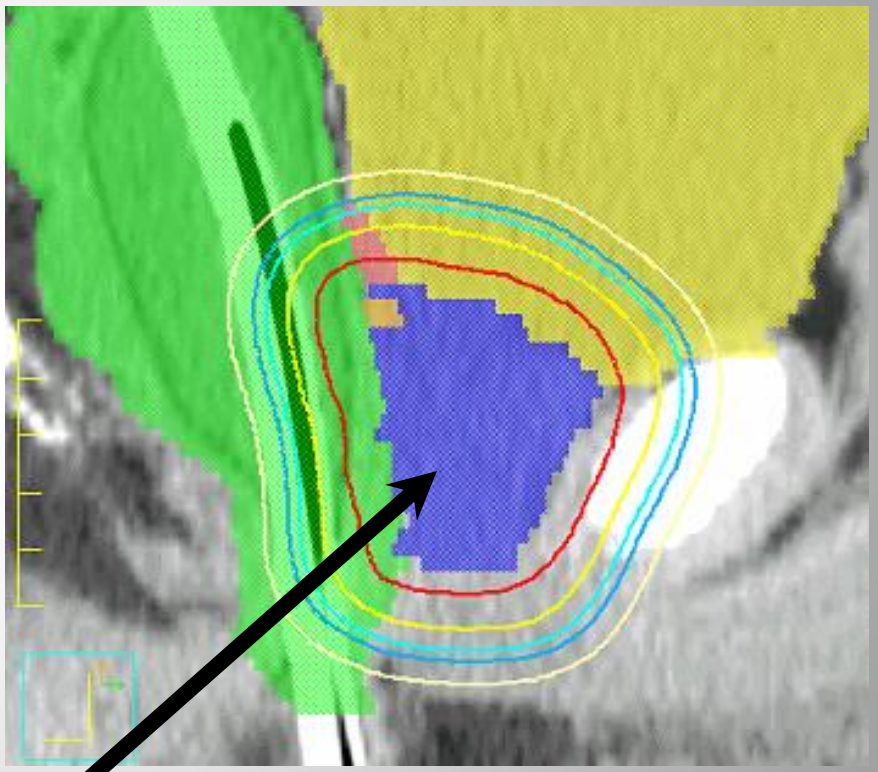
[Nichol et al. IJROBP 67, 2007]

Spot scanning (aka pencil-beam scanning)

“Conventional” proton therapy

(Right lateral beam’s eye view)





Prostate

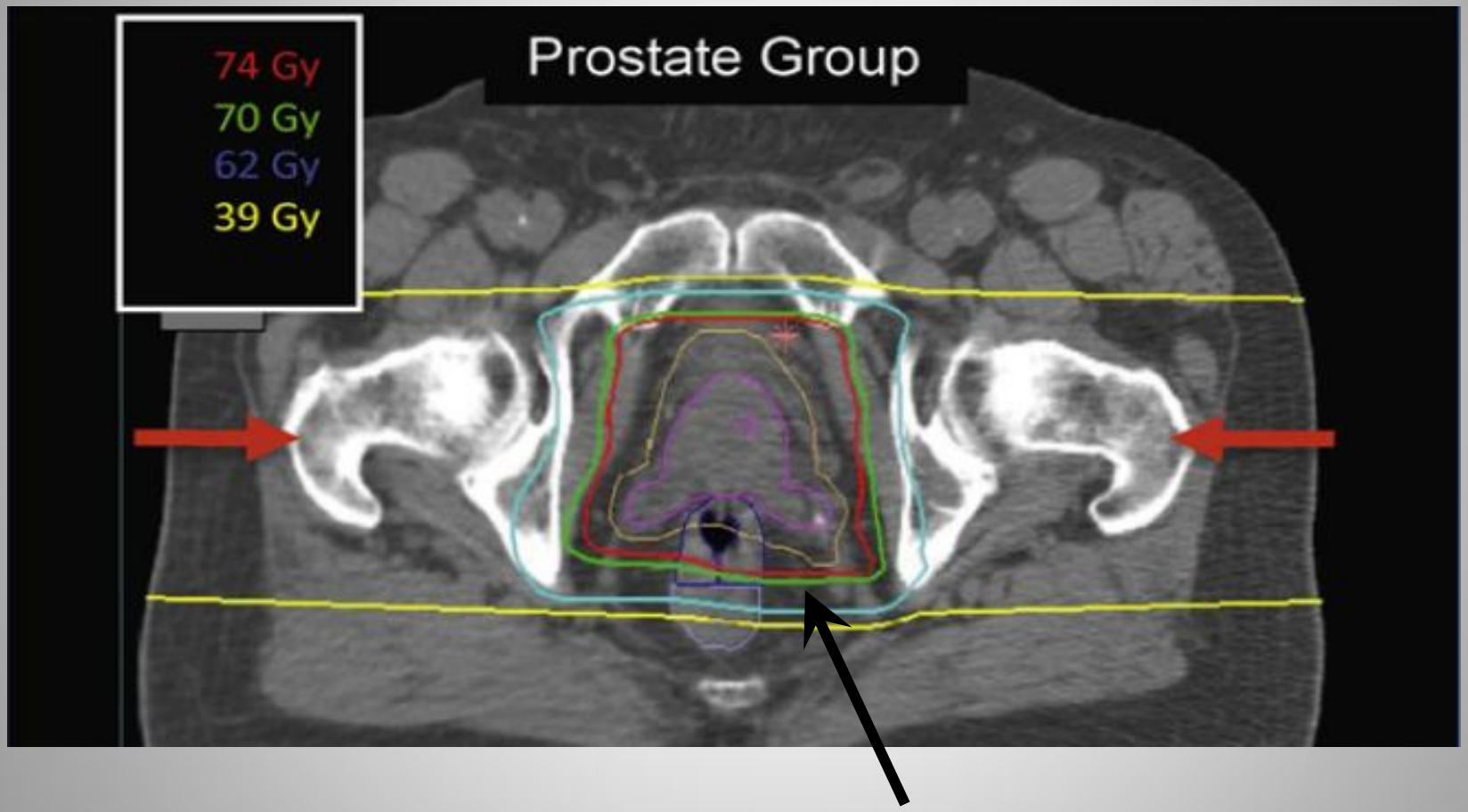
Advantages of Pencil Beam Scanning

- Improved **conformality**…especially concave structures
- Less hardware…fewer patient specific devices
- More beam angles are feasible
- Sparing of healthy tissues proximal to the target
- Intensity modulated proton therapy (IMPT)
- More flexibility for concomitant boost techniques (e.g. SV to 70.2 GyE @ 1.8 and prostate 78 GyE @ 2 GyE in 39 fractions)
- Fewer neutrons

Proton therapy planning & delivery

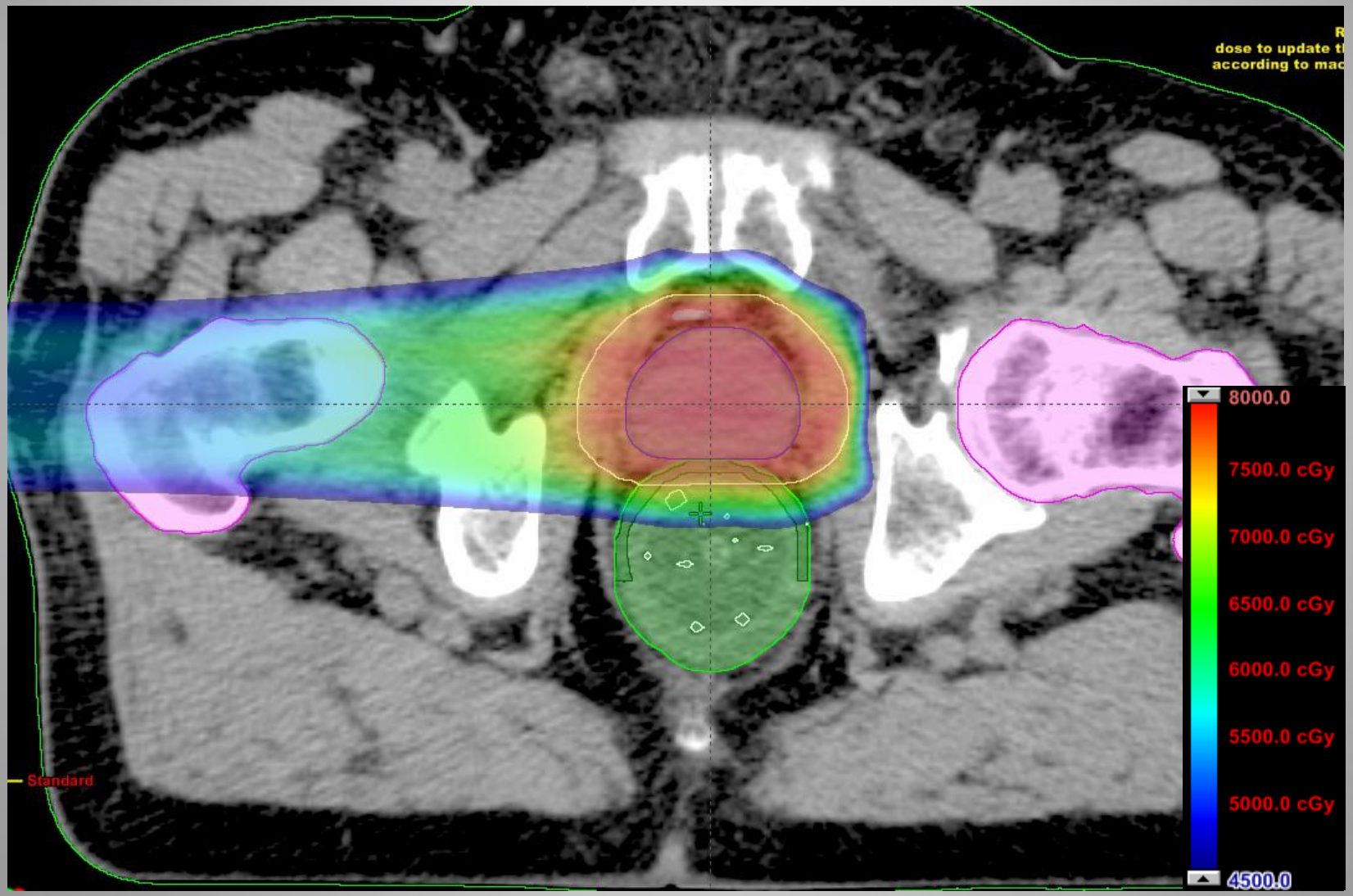
- Passive scattered (most common)
- Spot-scanning (SFUD): Each field covers target
- Spot-scanning w/ constraints: SFUD w/ more inverse planning
- Multi-field optimized intensity modulated proton therapy (MFO-IMPT): Most conformal but most complicated

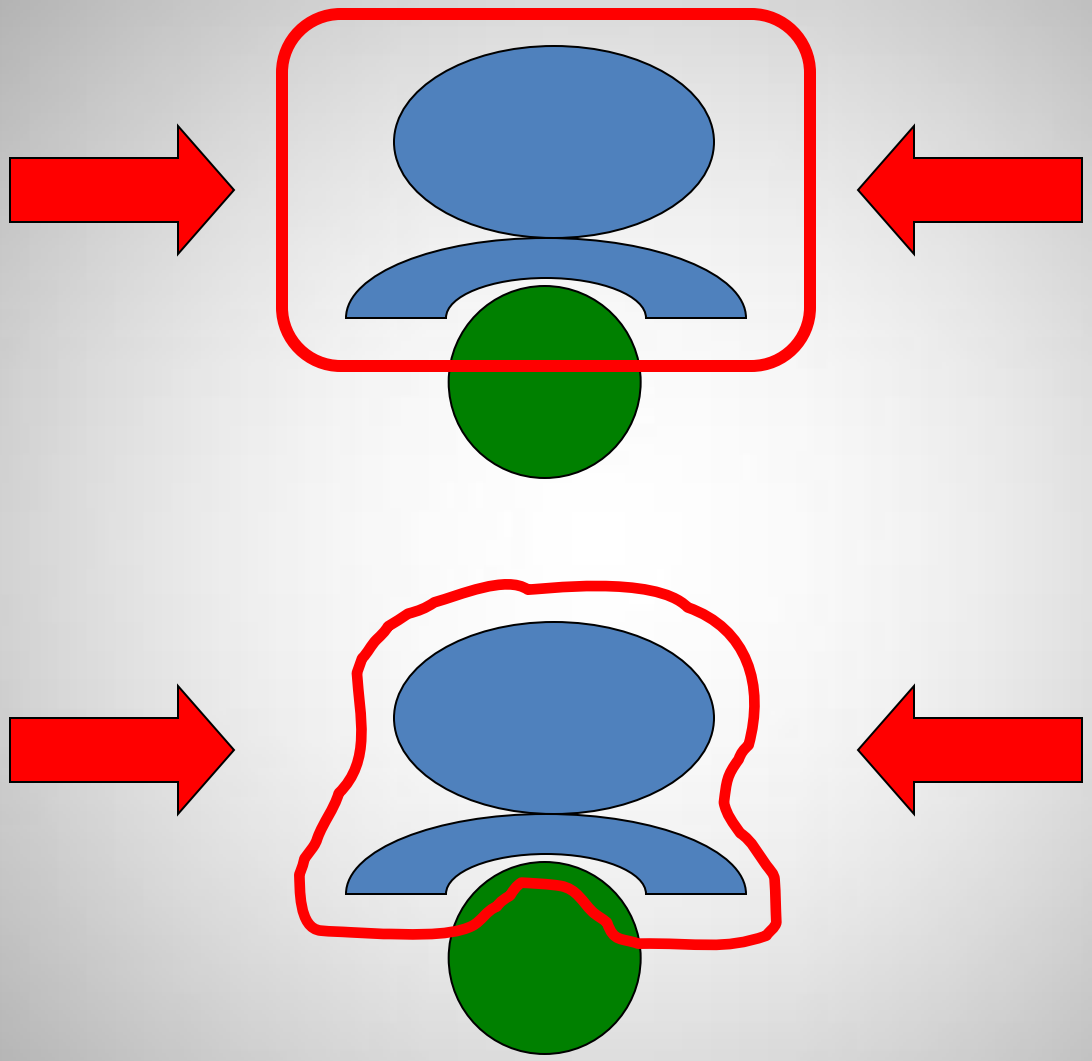
It’s not magic…it’s still radiation



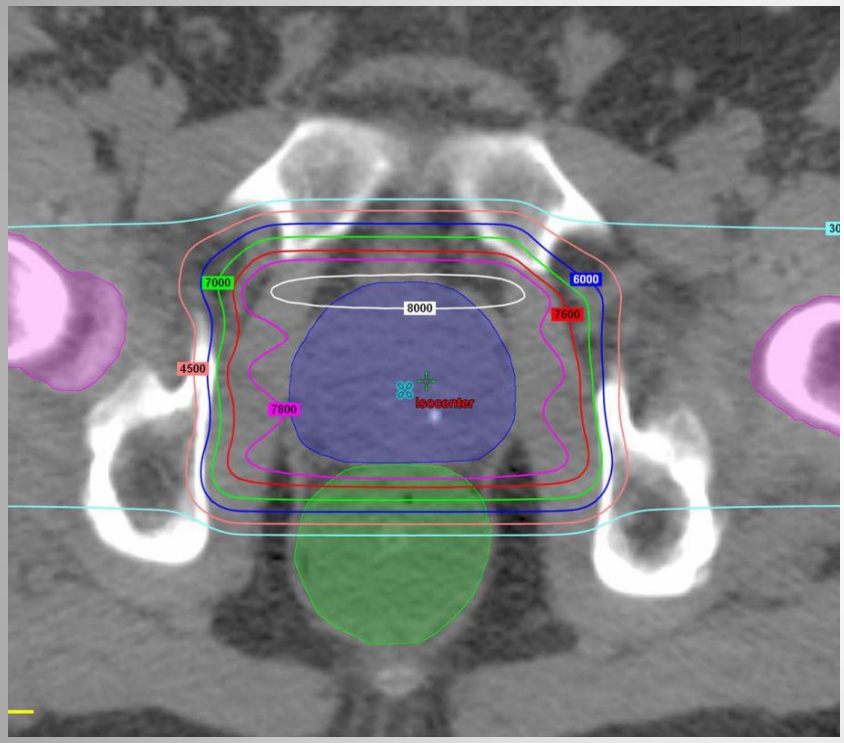
Half the rectum is getting 74Gy!!

SINGLE right scanning beam

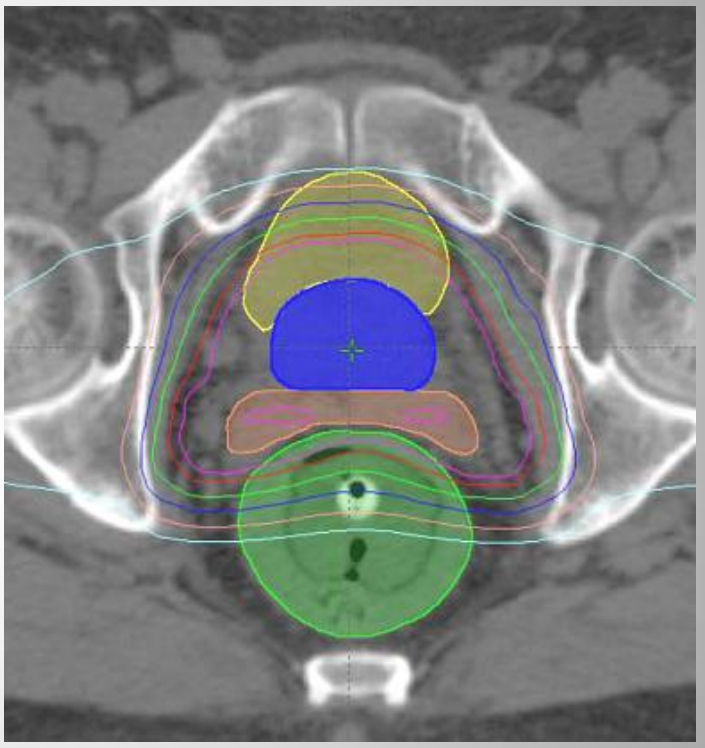




Two opposed lateral fields



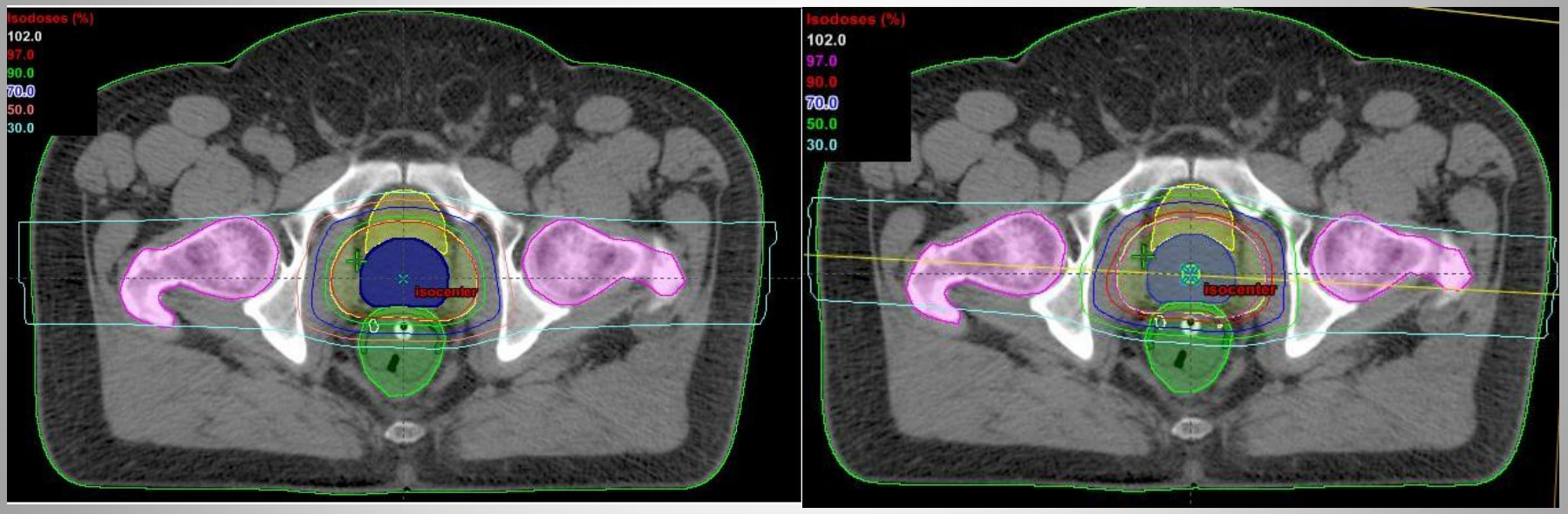
Passive



Spot-scanning (SFUD)

How robust are the spot scanning plans?

0 º **3 º**



Meyer et al. IJROBP 2010

CTV dose was >99% of prescription for rotations (3-5º) & shifts (3-5mm) (Meyer et al. 2010)

Means of the percentage differences between the ten control and test cases

	+3° rotation	-3° rotation	+5° rotation	-5° rotation
CTV				
Minimum	-0.4 (0.5)	-0.6 (0.5)*	-0.9 (1.0)	-1.1 (0.6)*
Maximum	0.2 (0.3)	0.5 (0.4)	0.4 (0.5)	0.5 (0.5)
Mean	0 (0)	0 (0.1)	0 (0.1)	0 (0.1)

Data in parentheses are standard deviations. *p<0.05

6b

	+3° yaw	-3° yaw	+5° yaw	-5° yaw
CTV				
Minimum	-0.1 (0.2)	-0.2 (0.6)	-0.3 (0.3)	-0.4 (0.7)
Maximum	0.1 (0.2)	0.3 (0.3)	0.3 (0.3)	0.4 (0.3)*
Mean	0 (0)*	0 (0)	0.1 (0)*	0 (0.1)

Data in parentheses are standard deviations. *p<0.05

6c

	+3 mm	-3 mm	+5 mm	-5 mm
CTV				
Minimum	-0.1 (1.2)	-0.4 (0.4)	-2.6 (1.4)*	-1.0 (0.7)*
Maximum	0.2 (0.2)	0.2 (0.3)	0.4 (0.3)*	0.5 (0.3)*
Mean	0.1 (0)*	-0.1 (0)*	0.1 (0.1)	-0.1 (0.1)*

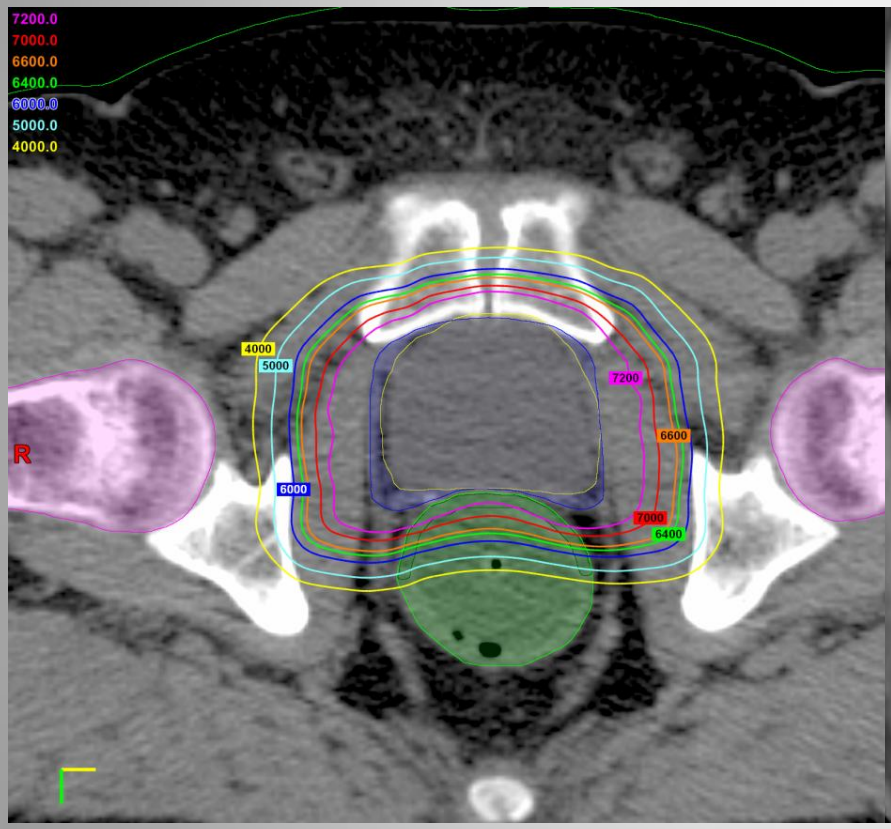
+ = anterior displacement; - = posterior displacement.
Data in parentheses are standard deviations. *p<0.05

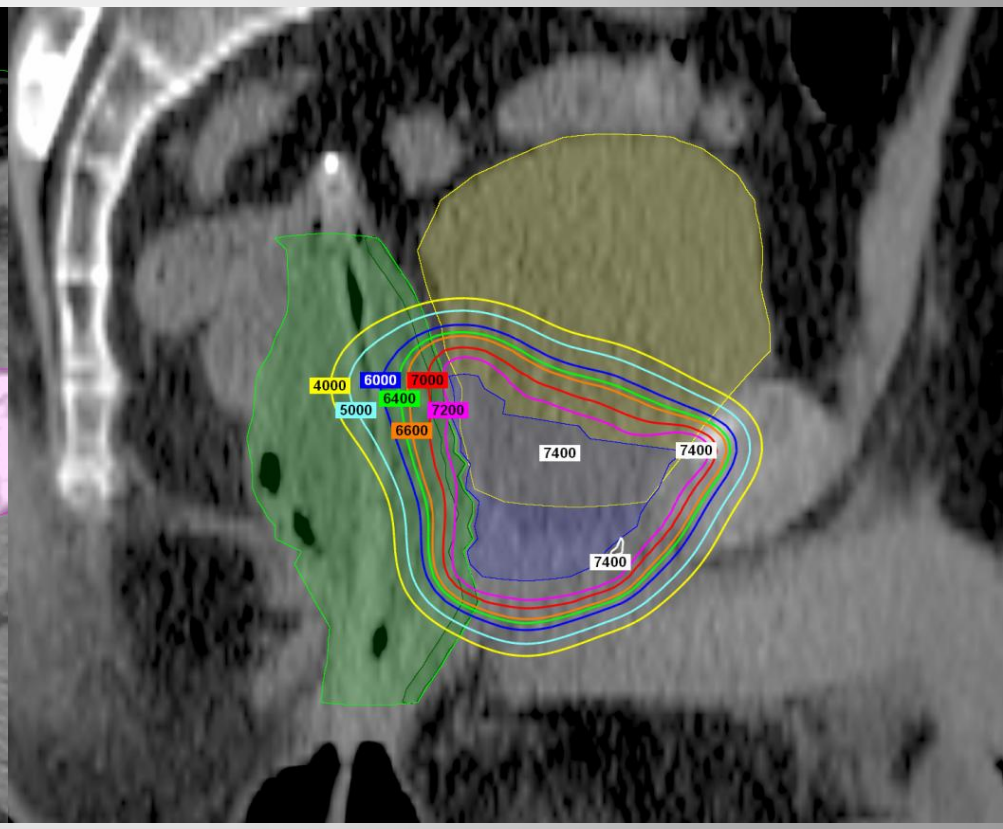
MD Anderson scanning beam technique (SFO) for prostate cancer

- Typically reserved for men with more advanced disease or challenging anatomy
- Cannot use classical distal & proximal margin formulas
- Use expanded volume to guide treatment planning: **Scanning Target Volume (STV)**
  - Considers setup and range uncertainty
  - Proximal & Distal margin 12mm
  - Anterior 6mm, Sup-Inf 5mm, Post 4mm

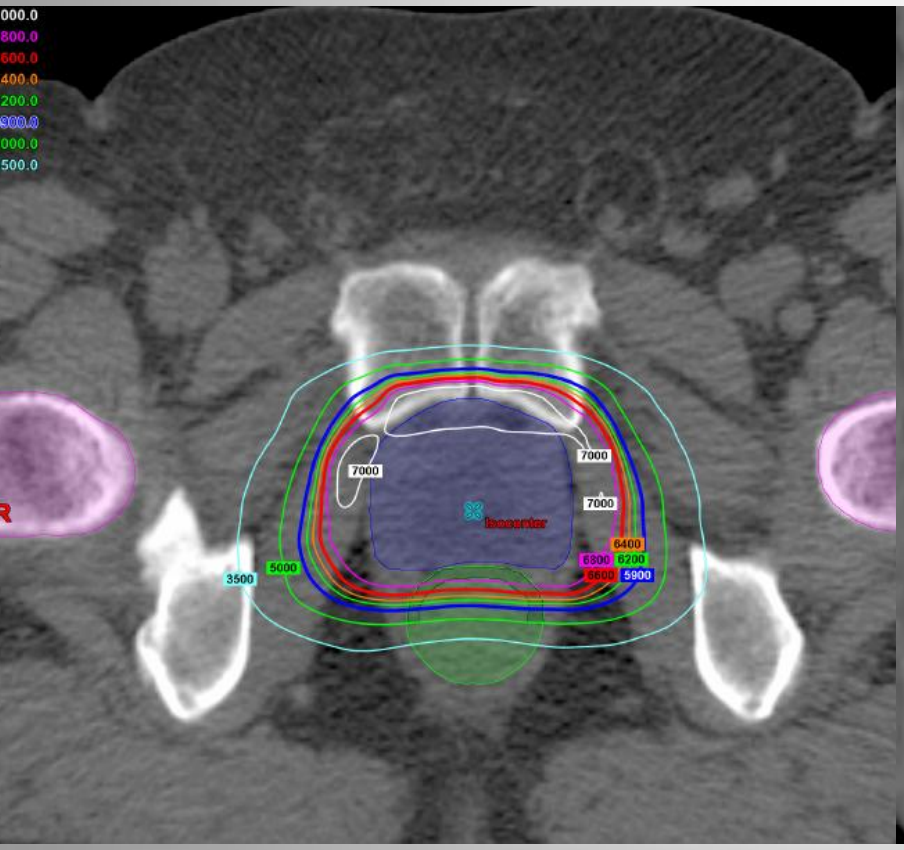
- >96% STV and 100% CTV covered by prescription
- Typically prescribing to 97-98% isodose line
- If plan too heterogenous, consider increasing STV margins and prescribing to lower isodose

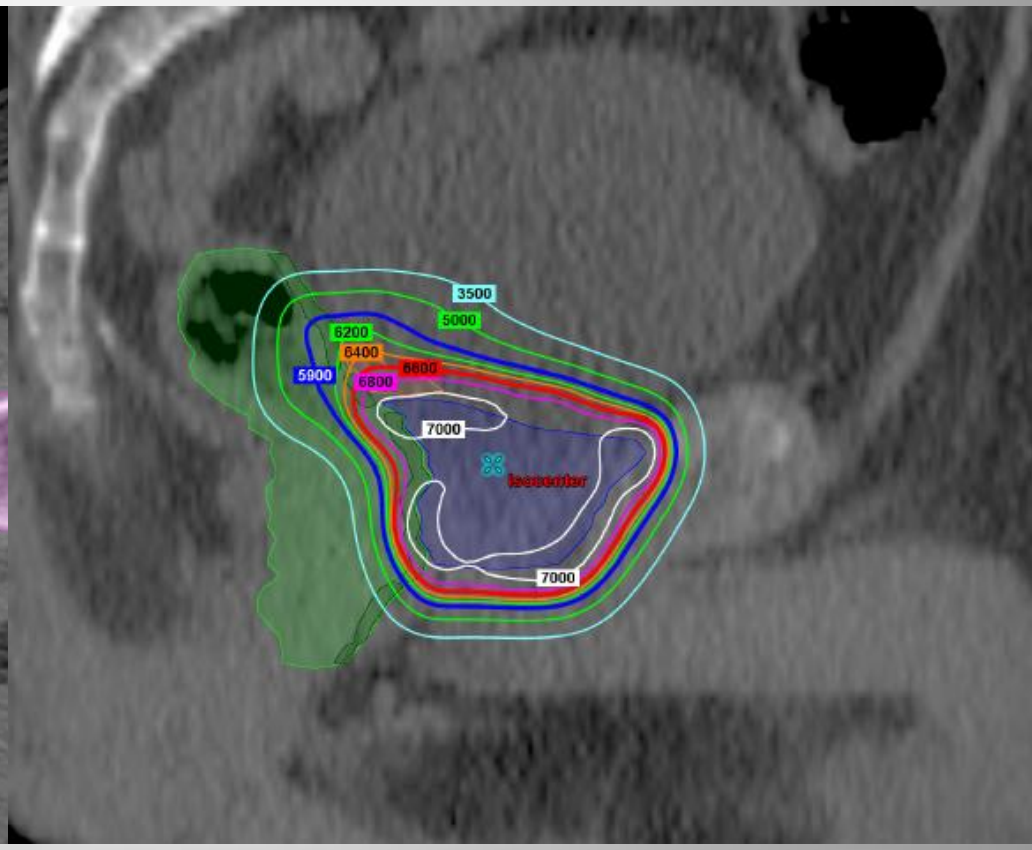
Postop w/ SFUD





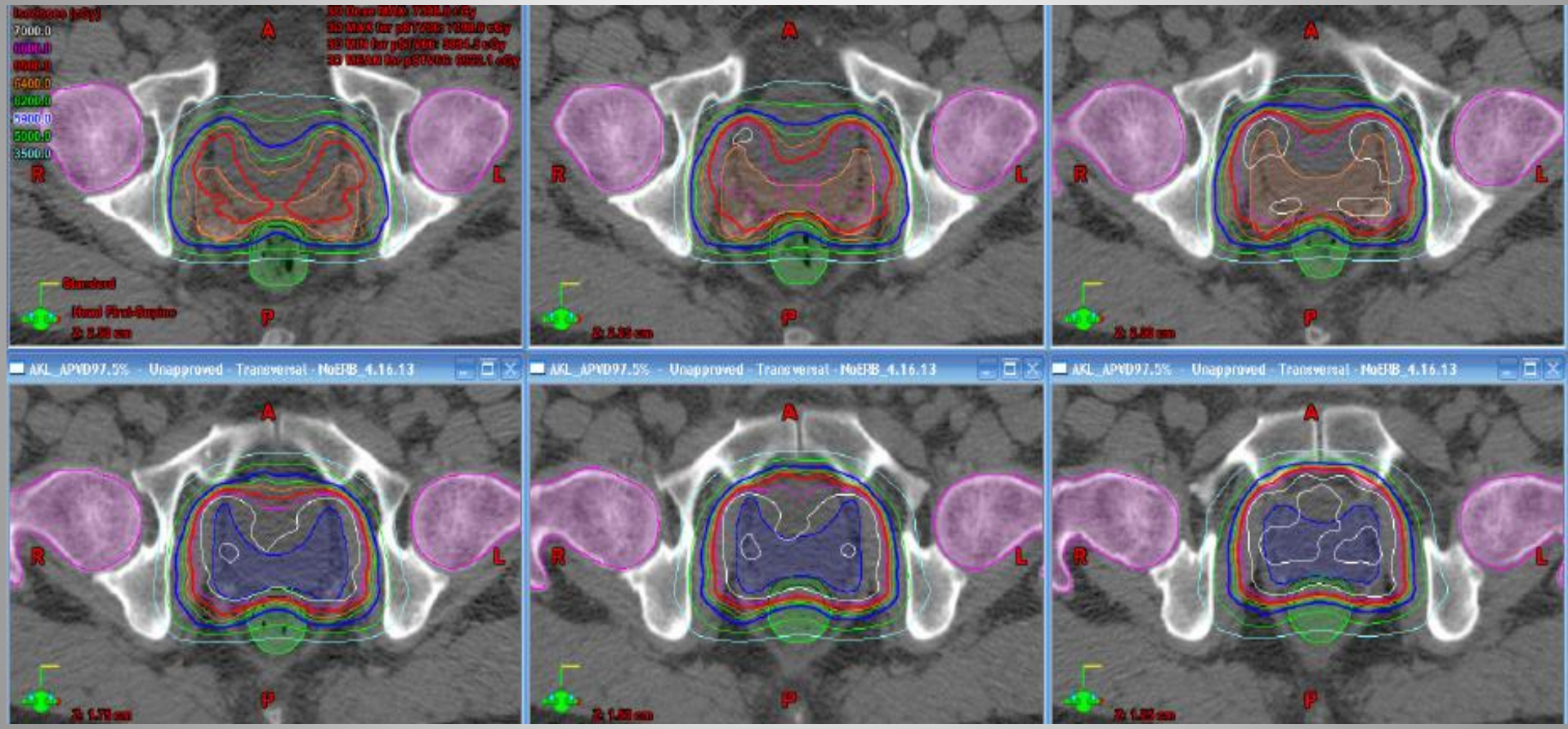
Postop w/ no ERB





Concomitant plans w/ SFUD:

Postop 66 GyE (red) to Prostate bed
SV beds concurrently 60 GyE (blue)



SFUD vs. MFO

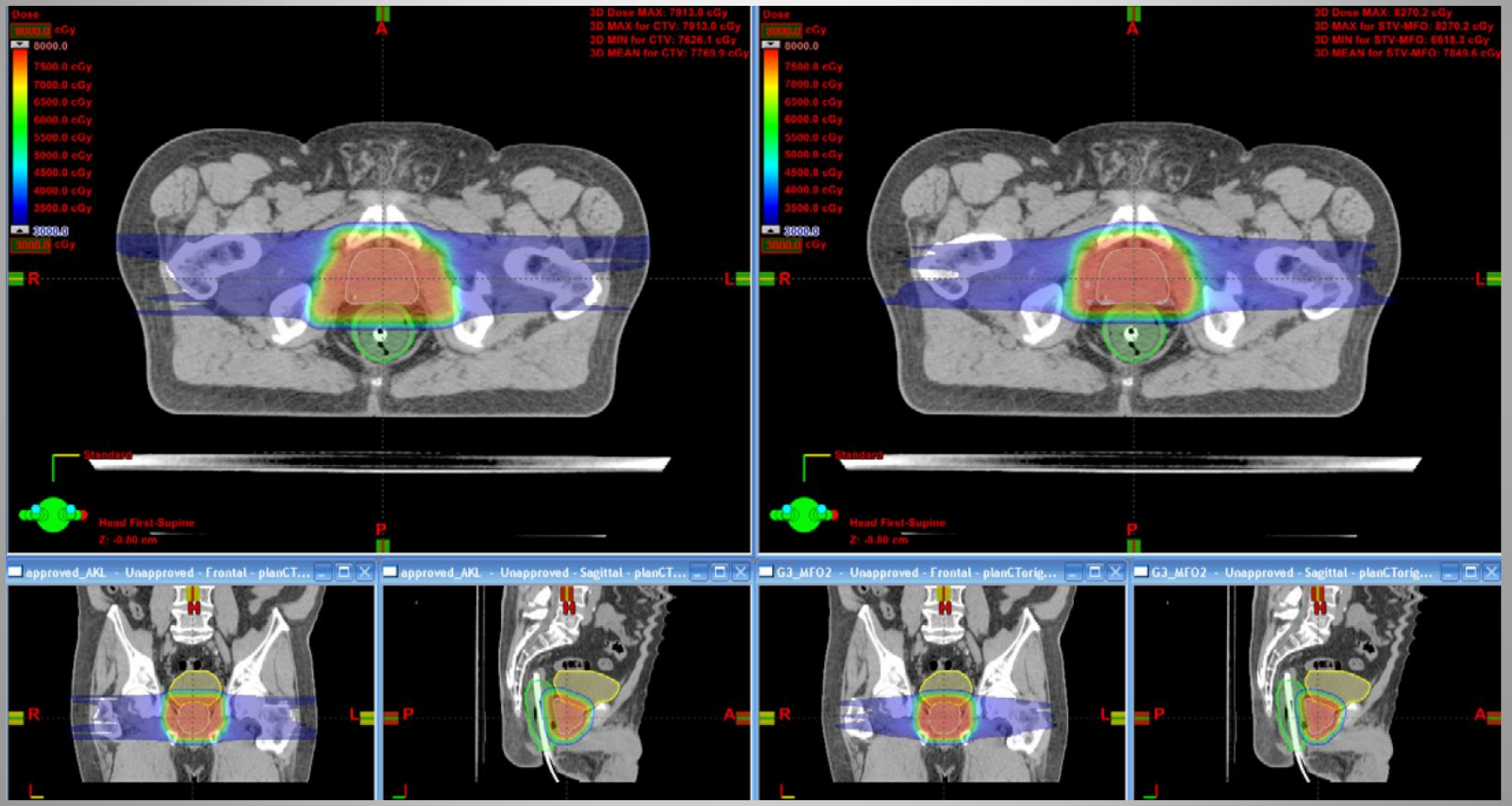
SFUD

- "Open Field" for simpler volume
- Uniform dose distribution or non-uniform dose
- Less sensitive to uncertainties
- Also can utilize normal tissue constraints
- Should use SFO plan if IMPT plan is not significantly better
- May need Range Shifter for shallow tumors (< 4cm)

MFO

- "Patch Field" for complex volume
- Uniform dose distribution or non-uniform dose
- More versatile to get a good plan
- But more sensitive to uncertainties
- Robustness of MFO is important
- QA is significantly more demanding

Scanning pencil beam is needed for Intensity Modulated Proton Therapy



Rectal DVH comparison: IMPT vs. PSPT

Rectum	IMPT	PSPT	P value
Mean V30	25.3 ± 2.0%	34.9 ± 4.3%	<0.01
Mean V40	20.3 ± 1.6%	29.9 ± 3.8%	<0.01
Mean V60	11.9 ± 1.2%	19.9 ± 2.7%	<0.01
Mean V70	7.5 ± 1.1%	13.3% ± 2.0%	<0.01

S. Choi et al. ASTRO 2011

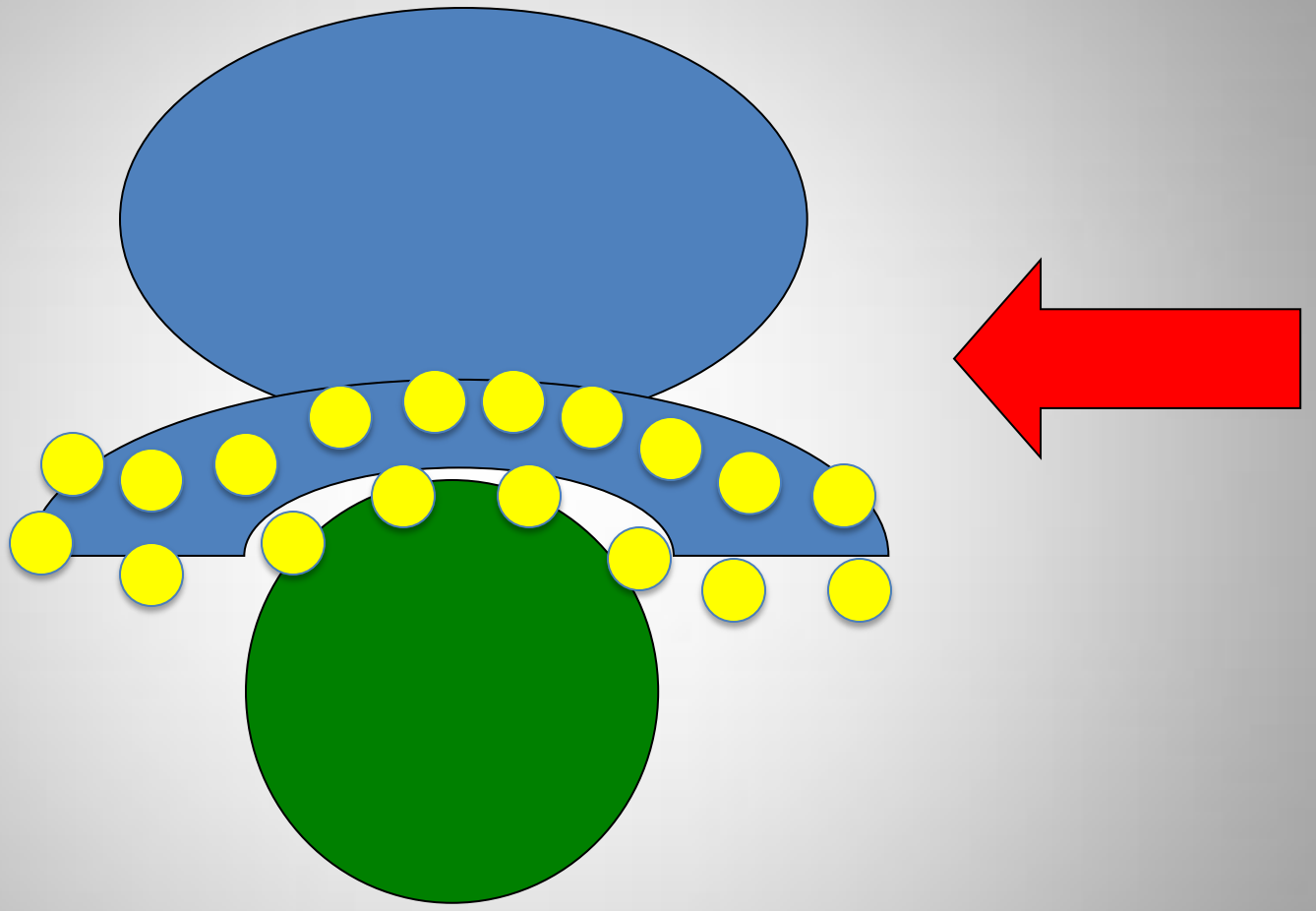
SFUD w/ mild inverse planning

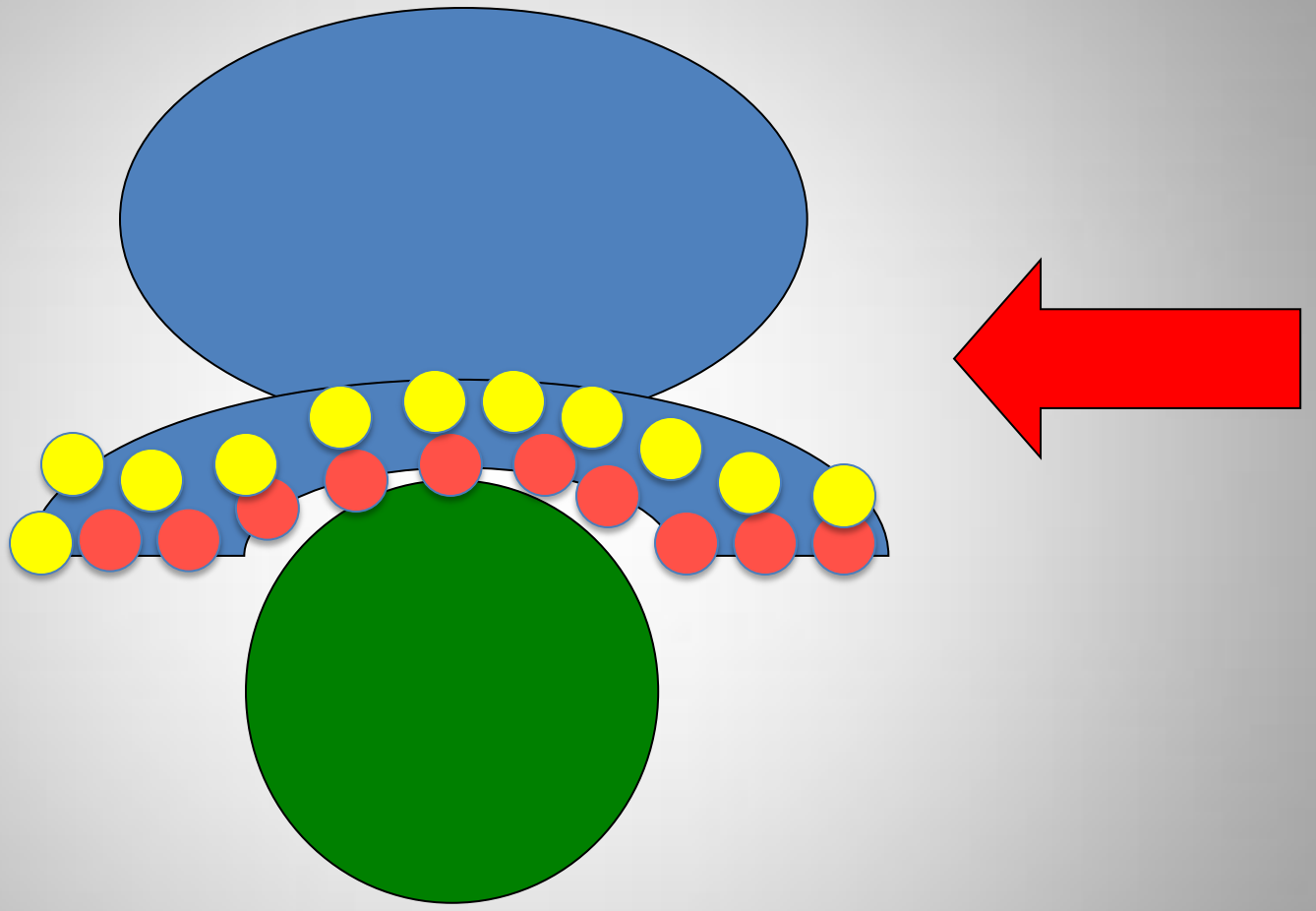
- MFO do give better plans but not always needed
- MFO more complex treatment planning, quality-assurance, and decreased robustness

- Instead of MFO, consider SFUD with normal tissue constraint (e.g. decrease rectal V30 by 5-10%)
  - Requires balancing STV coverage vs. dose heterogeneity

Rectal $V70_{Gy}$ (light green) and anterior rectal wall $V70_{Gy}$ (dark green) reduced by ~10%

Some spots may be outside STV



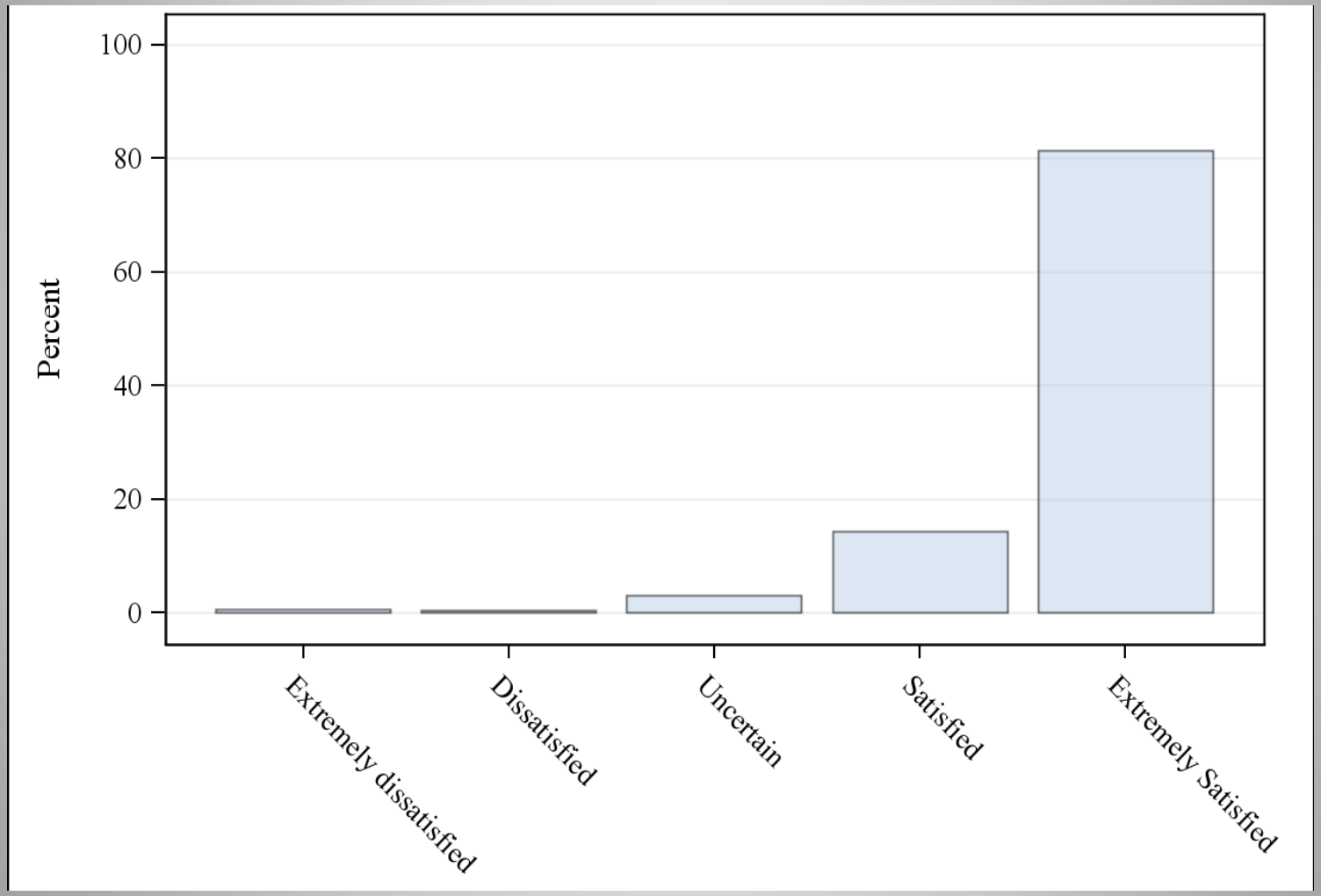


Patient satisfaction w/ protons

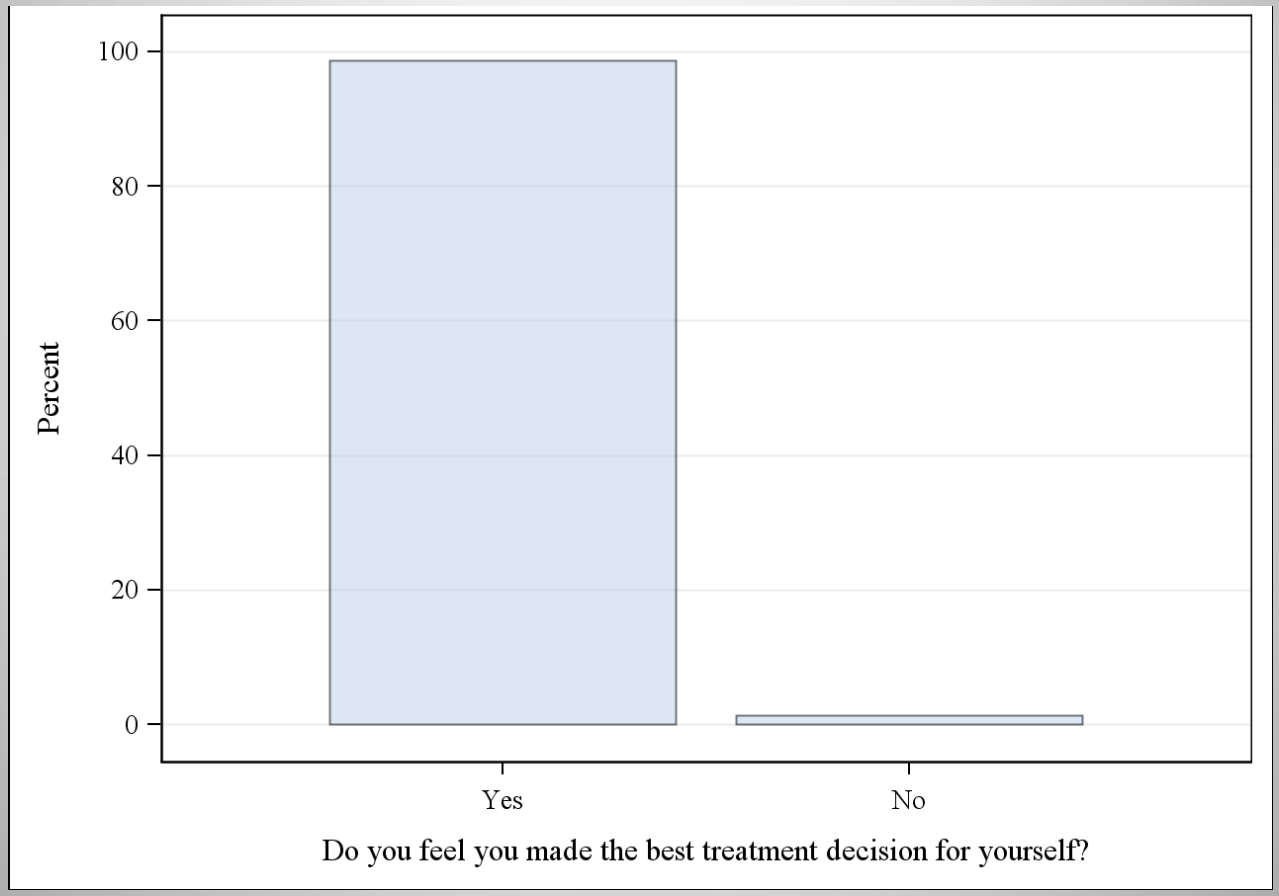
Survey of nearly 2000 men w/ prostate cancer treated with protons

Over 95% of respondents (n=1921) were “satisfied” or “extremely satisfied” with treatment

Overall, how satisfied were you with the treatment you received for prostate cancer?



Do you feel you made the best treatment decision for yourself?



Take home points

- Higher radiation doses yield higher PSA control rates
- Do not use too tight of a margin
- Proactively position the patient and target
  - Minimize inter- and intra-fraction variation
- Opposed lateral beams are relatively forgiving
- Do not treat more of seminal vesicles than needed

Thank you

Physicians

Physicists

Engineers

Therapists

Dosimetrists

Nurses

Pt Services Coordinators

Pt Access Specialists

Pt Access Coordinators

Billing

Administrative

IMRT or Protons?

The Proton plan delivers less scatter radiation dose to the pelvis compared to IMRT plan (axial view)

RED is high dose, **GREEN** is intermediate dose, **BLUE** is lower dose

Protons

IMRT

Prostate Ca
Second Solid Tumors After XRT
SEER 1973-1993

Second Cancer	6% ↑RR
≥ 5 years	15% ↑RR
≥ 10 years	34% ↑RR

Brenner et al, Cancer 2000

The longer you wait…the more 2nd cancers you get

	Latency 5–9 years	Latency 10–14 years	Latency ≥15 years	p-trend
Oral/pharynx	1·12 (0·99 to 1·27)	1·14 (0·95 to 1·38)	0·95 (0·74 to 1·22)	0·34
Rectum*	1·13 (0·94 to 1·35)	1·33 (1·03 to 1·70)	0·91 (0·64 to 1·27)	0·54
Larynx	1·57 (1·08 to 2·36)	1·04 (0·66 to 1·70)	1·29 (0·75 to 2·30)	0·45
Lung (non-small cell)	1·12 (0·98 to 1·27)	1·37 (1·12 to 1·65)	1·62 (1·23 to 2·09)	0·0079
Female breast	1·17 (1·05 to 1·30)	1·42 (1·24 to 1·62)	1·56 (1·34 to 1·81)	0·0013
Cervix (external beam)*	1·18 (0·79 to 1·75)	1·55 (1·00 to 2·40)	2·59 (1·84 to 3·68)	0·0032
Endometrium (external beam)*	1·30 (1·08 to 1·56)	1·99 (1·60 to 2·47)	2·18 (1·78 to 2·65)	<0·0001
Prostate (external beam)*	1·39 (1·29 to 1·50)	1·59 (1·41 to 1·80)	1·91 (1·53 to 2·38)	0·0031
Thyroid*	0·89 (0·49 to 1·55)	1·03 (0·47 to 2·14)	1·21 (0·64 to 2·17)	0·47

10-14y RR 1.6, >15y RR 1.91

de Gonzalez et al. Lancet Oncol, Mar 2011

Doses >5Gy associated w/ increased risk of 2nd cancers for pelvic RT

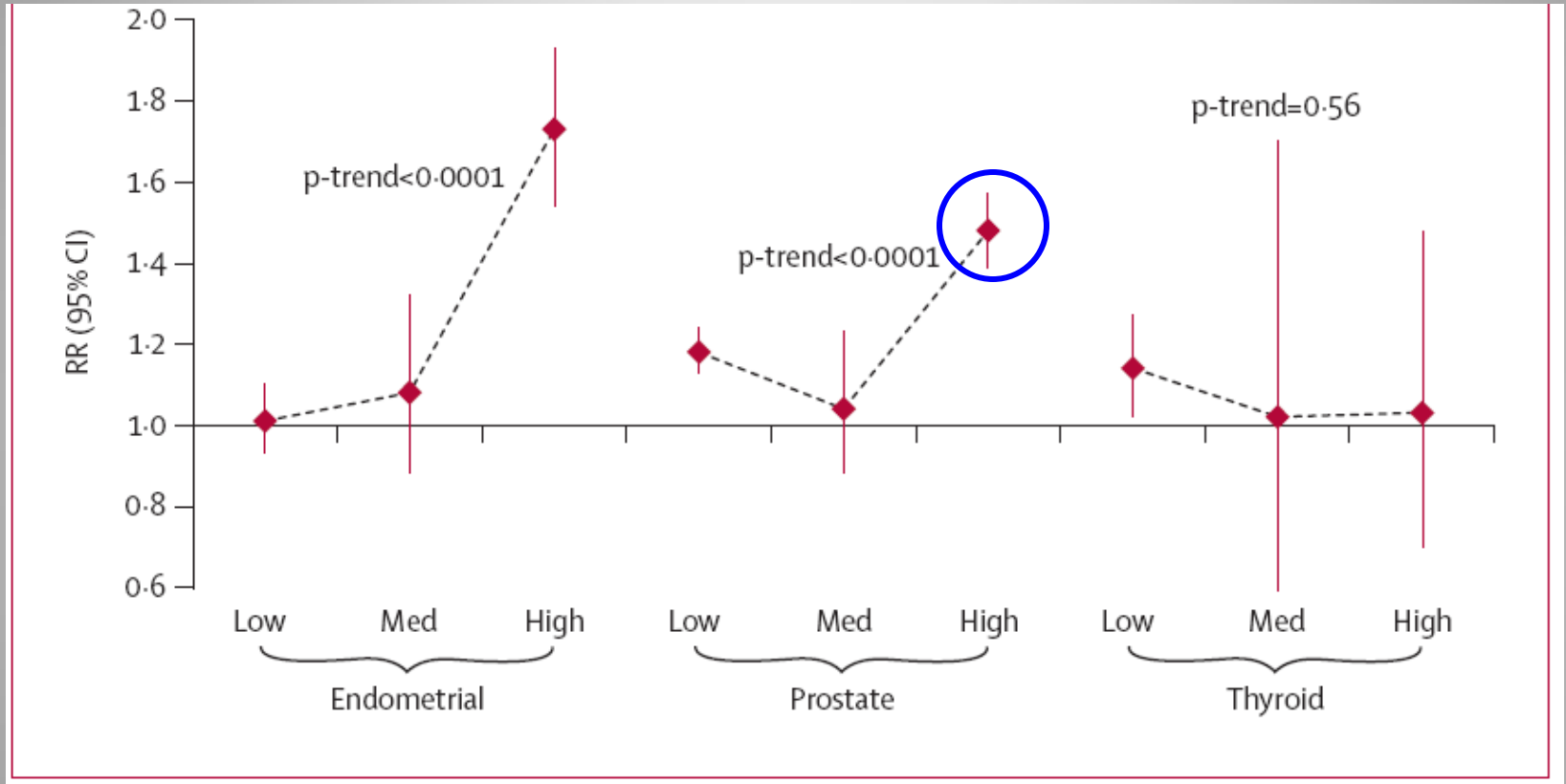


Figure 2: Relative risk (95% CI) of second solid cancers at low (<1 Gy), medium (1–5 Gy), and high (>5 Gy) dose sites for radiotherapy versus no radiotherapy by site of first cancer

de Gonzalez et al. Lancet Oncol, Mar 2011

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 2, pp. 616–622, 2009

0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.01.001

PHYSICS CONTRIBUTION

RISK OF SECONDARY MILIGNANT NEOPLASMS FROM PROTON THERAPY AND INTENSITY-MODULATED X-RAY THERAPY FOR EARLY-STAGE PROSTATE CANCER

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<u>Results:</u> Proton therapy reduced the risk of SMN by 26 to 39% compared to IMRT.

Protons reduced 2nd Cancers

MGH report spanning 26 years (1974-2001)

Compared 503 patients treated with protons vs. 1591 x-ray patients from NCI-SEER registry

Mostly CNS, HN, epithelial tumors, sarcomas, prostate (no ocular)

Adjusted for gender and age @ treatment

2nd Ca rates were 6.4 vs. 13.1% for protons vs. XRT, respectively

[Chung et al. ASTRO 2008]