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

• Use adequate treatment margins

• Proactively position the patient and target
  – Minimize inter- and intra-fraction variation
  – Address systematic variations and minimize random ones

• Opposed lateral beams are relatively forgiving

• Do not treat more of seminal vesicles than needed
What we know about XRT

• Higher doses = improve disease control

• High doses may increase side effects

• Advanced techniques needed to deliver high doses optimally
Randomized studies showing benefit to higher dose

- MDACC randomized study of 70 vs. 78 Gy
  - Clinical benefit for 78 Gy in FFF
  - Especially for PSA >10
  - Increase in rectal toxicity
  - No difference in GU toxicity

- Dutch multicenter trial 68 vs 78 Gy (isocenter)
  - 664 men (Low 18%, Int 27%, High 55%)
  - 3D-CRT various techniques, 22% HT (11% short-, 11% long-term)
  - 5-y FFF 64 vs 54%
  - Benefit primarily in intermediate and high risk
  - No difference in clinical failure, OS
  - No significant difference in toxicity
     - (3D-CRT, rectal DVH constraints)

- 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
  - Increase in rectal toxicity (GU toxicity similar)
  - Patient-reported quality of life similar
More Grade $\geq 2$ rectal complications in 78 Gy arm

[IJROBP 53, 2002]
Is IMRT better than 3D-CRT?

- Subset of patients in Dutch trial received IMRT compared to 3D-CRT at same institution to 78Gy

- No statistical difference between two groups for PSA control (nadir+2), grade ≥2 GU/GI toxicity

IJROBP 73:685, 2009
Absolute incidence for grade ≥2 toxicity was 20% for IMRT

IJROBP 73:685, 2009
Maybe they just needed **IGRT**

- Fiducials help decrease PTV
- Improve disease control
- Decrease side effects

- Daily imaging cost and dose is small price to pay for better outcomes…or is it?
How IGRT can “help”

- 70-78 Gy
- 25 treated w/ fiducials

- 5-y FFBF: 58% w/ fiducials vs. 91% w/out (p=0.02)!
  - MVA: worse for fiducials p=0.047

Engels. IJROBP 2009
Use adequate treatment margins!
PROG 95-09
PROTON-photon randomized trial

T1-2b, PSA<15
N=393

70.2 GyE
- Protons
  19.8 GyE
- 4F X-rays
  50.4 Gy

79.2 GyE
- Protons
  28.8 GyE
- 4F X-rays
  50.4 Gy

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.

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

92% PSA-FFS
PROG 9509-UPDATE
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

• Trend towards improved survival in high dose arm.
PROG update w/ median FU 9 years
J Clin Oncol Mar 2010

ASTRO
Phoenix
(nadir + 2)
PROG update w/ median FU 9 years
J Clin Oncol Mar 2010
Comments

• PROG study has 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)
## Grade 2+ side effects from RCT’s

<table>
<thead>
<tr>
<th>Study</th>
<th>Grade $\geq$2 GI</th>
<th>Grade $\geq$3 GI</th>
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<tr>
<td>MDACC X-rays</td>
<td>13 vs. 26%</td>
<td>1 vs. 7%</td>
<td>5 vs. 4%</td>
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<td>70 vs. 78Gy</td>
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<td>Dutch X-rays</td>
<td>27 vs. 37%</td>
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<td>68 vs. 78Gy</td>
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<td>PROG Protons 70.2 vs. 79.2Gy</td>
<td>9 vs. 18%</td>
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<td>UFPTI Protons</td>
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<td>78-82GyE</td>
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ACR 0312: A **prospective** study of radiation dose escalation to 82GyE in early prostate cancer

85 men MGH and LLUMC 2004–6

- T1–2a prostate cancer
- PSA <15ng/ml
- 82 GyE at 2GyE/fraction
- Opposed lateral beams
ACR 0312: A *prospective* study of radiation dose escalation to 82GyE in early prostate cancer

“Late” rectal side effects w/ median FU 32 mos.

Grade 2+ 12%*
Grade 3+ 1%

*This is less than the previous study despite using higher daily dose (2 vs. 1.8 GyE) and total dose (82 vs. 79.2GyE).

Note: This study used all protons (no x-rays).
Proton therapy for Prostate Ca
MDACC technique

• Supine
• ER Balloon
• Bony and fiducial alignment
• 2-fields every day (opposed lats)
• CTV = Prostate + proximal SV
• 2 CGE x 39 = 76-78 CGE to “PTV”
• Mean dose to CTV ~80-81 CGE
Range depends on radiologic path length
Dancing prostate & hips using vacuum bag

25 treatment CTs
Acquired during a course of 42 fxs treatment

Dong (MDA), 2002
• Immobilization and reproducible setup is important for protons just like IMRT

• Reproduce radiologic path length

• “Pro-active” target localization
Knee and foot cradles are index-able

Cut out wedge for er-balloon
Reduce PTV

- Decrease **inter**-fractional **variation** (not just motion)
- Pro-actively minimizes anatomic distortion
  - Control the prostate-rectal interface!!

- Typical IGRT does not guarantee SV coverage or account for changes in contour deformation
- Decrease **intra**-fractional variation
- PTV’s ≤3mm likely not be feasible w/ IGRT alone
Gas causes changes in pitch/rotation (as well as translation) and deforms prostate-rectal interface
Fiducials vs. MRI

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

Yellow >9mm and Red >10mm displacement

[Nichol et al. IJROBP 67, 2007]
Prostate alignment does **not** guarantee SV alignment

[Frank et al. IJROBP 71, 2008]
Is intra-fractional variation a concern?

• Maybe

• Longer treatment times increase chances of prostate changes due to gas, patient movement, muscle tension/relaxation
Gas may migrate superiorly!

Note change in rectum, bladder, and prostate (translation, rotation)

Do you think fiducials alone can handle this?

IJROBP 2007
Prostate motion w/ Calypso
Langen et al. IJROBP 71, 2008

Drift motion

Transient motion
Intra-fractional motion

• Displacements >3mm occurred in 25% of the time within 10 minutes

• ER balloon can decrease large variations

• Increase through-put by minimizing number of corrections during treatment
Better RT through geometry

• ERB displaces the posterior/ superior rectum away from the treatment field
  – Allows more room for error
    (e.g. implication of 2-3mm posterior shift w/ balloon is less than w/out)

• ERB also displaces low-lying bowel (less reliance on bladder filling)
Endoscopies after RT

Van Lin et al. IJROBP 67, 2007
Telangiectasias w/out and w/ ERB

Van Lin et al. IJROBP 67, 2007
Not all balloons are created equal
Gas-release double-ported ERB

Anterior groove helps in alignment

Stopper positioned on depth marker

Two way stopcock valve
Sagittal and Coronal

Fiducial marker

Rectal balloon

Prostate
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
Gold fiducial
All 3 large fiducials to 3000 HU

No fiducials (over-ridden to tissue density)
Fiducial markers
To fiducial or not to fiducial

• **PROS**
  - Target guidance
  - Still need margin >4mm posteriorly

• **CONS**
  - Endorectal balloon + **bony alignment** adequate
  - Large motion may change radiologic path length
  - More work for dosimetry!
  - **Triple jeopardy**
    - CT artifact has additional uncertainty
    - Dose shadowing
    - Volume averaging results in artificially large fiducial on CT
    - Effects compensator design & dose heterogeneity
Ca$^{++}$ vs. Carbon-coated ZrO$_2$
Carbon-coated ZrO₂ on kV
If you plan on using fiducials

• Use smallest and least dense material visible on your lateral KV OBI
  – Carbon fiducials
  – Consider fewer markers
    • 1-2 fiducials give reasonable accuracy (Kudchadker. IJROBP 2009)
  – Orient fiducials perpendicular to beam path

• Consider pros and cons

• Do you really need it?
If NOT using fiducials

• Consider ER balloon
• Need good external immobilization for beam path
• Address systematic errors from simulation to treatment
• Re-imaging patient 2-3x in first week or before patient starts
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** 15-30 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 conformity
  – 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 76-78 CGE (2 CGE/fxn) to 100% CTV+margin
  – Usually prescribe to 98-96% isodose line
  – Mean CTV dose ~79-80CGE

• CTV = Prostate + Proximal SV
• 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

- $\text{LM} = \text{setup uncertainty} + \text{penumbra}$
- Setup uncertainty = 0.5cm
- 225-250 MeV beam penumbra (95-50%) = 1.0-1.2cm
- $\text{LM} = 1.5-1.7$ cm
- Posteriorly sometimes less
Two opposed lateral beams
Rectal DVH V70=10%
Patient alignment at PTC-H

- Daily orthogonal kV images to align bony anatomy with reference DRR’s using 2-D matching

[Image: Diagram of X-ray tubes and image receptors]
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
Translational shifts < 6mm and rotational shifts < 5° 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 (in press)
Fig. 1. Dose–volume curves for 5-mm prostate shifts with (triangles, suns, circles, squares) and without (hearts) beam realignment shown. Curves for all prostate positions overlap each other.
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?

0°

3°

5°

0°

+3°

-3°
Worst case scenario is underdosing by 0.06 GyE (<0.08%) [Sejpal et al. IJROBP]

<table>
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<th>Variation</th>
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</table>

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

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%
PTC-H initial clinical experience

• May 4, 2006 first patient treated at PTCH
• ~900 prostate cancer patients have completed Rx
  – cT1-3, Gleason 6-9, PSA <30 ng/ml
  – ER balloon tolerated well

• ~600 men have min 3-month FU evaluation
  – <2% recurrence
  – Gr 2-3 GI <6%
Future directions

• Fractional dose-escalation
  – 72 CGE (2.4 CGE)
  – 66 CGE (3.0 CGE)

• Spot scanning → MFO IMPT

• Combined modality therapy

• Alternative beam angles

• Combination protons + hormone therapy: randomized trial
What is spot scanning?
“Conventional” proton therapy

Prostate
The Pencil Beam Scanning Mode of Proton Beam Delivery

Spot-scanning SFUO (80 CGE)

Right lat field only

Bilateral fields

Purple is 80 CGE
Spot-scanning SFUO
80 CGE
Rectal V70 <10% (green)
Protons
Take home points

- Higher radiation doses yield higher PSA control rates
- Use adequate treatment margins
- Proactively position the patient and target
  - Minimize inter- and intra-fraction variation
  - Address systematic variations and minimize random ones
- Opposed lateral beams are relatively forgiving
- Do not treat more of seminal vesicles than needed
Thank you