Current and Future Trends in Proton Treatment of Prostate Cancer

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Outline

- Physical, biological, & technical aspects of proton beams
- Results of proton treatment – can we improve?
- Anatomy of prostate cancer
- Need for new imaging strategies for targeting
- Controlling the motion of the prostate
- Image-guided proton therapy
The Physics of Protons

- Highest energy deposition per unit length at end of range (Bragg peak)
- No exit dose
- Dose advantage over any photon beam
- Depth of peak (proton range) adjustable with energy or bolus material
- Modulation generates spread-out Bragg peak
- Next step in the evolution of radiotherapy
“What has radiobiology done for radiotherapy besides making it more expensive?

“It gave us neutrons, which did not work, and protons, that did.”

Eric Hall, Ph.D., ASTRO Gold Medal Address, 1994
- Radiobiologic effects of protons and x-rays are nearly identical
  - 1 CGE protons = 1.1 Gy of Cobalt-60 or MV photons

- Therefore,
  - An identical dose of protons and photons will produce an identical tumor response
  - This is not the case with neutrons or heavy charged particles

- Superior physical properties of protons
  = reduced integral dose
Proton Beam Delivery

- Isocentric beam delivery with proton gantry
- Patient immobilized
- Robotic 6-degrees of freedom positioner (future)
- Digital X-ray verification
- 1-2 minutes per Gy
- 1-2 fields per day
- Physical, biological, & technical aspects of proton beams
- Results of proton treatment – can we improve?
- Anatomy of prostate cancer
- Need for new imaging strategies for targeting
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- Image-guided proton therapy
# Prostate Cancer-LLUMC Results

## Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients</th>
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<tbody>
<tr>
<td>1A/1B</td>
<td>35</td>
</tr>
<tr>
<td>1C</td>
<td>314</td>
</tr>
<tr>
<td>2A</td>
<td>291</td>
</tr>
<tr>
<td>2B</td>
<td>248</td>
</tr>
<tr>
<td>2C</td>
<td>283</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
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# Prostate Cancer-LLUMC Results

## Initial PSA

<table>
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<th>Initial PSA</th>
<th>Patients</th>
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<tbody>
<tr>
<td>$\leq 4$</td>
<td>106</td>
</tr>
<tr>
<td>4.1 – 10.0</td>
<td>606</td>
</tr>
<tr>
<td>10.1 – 20.0</td>
<td>339</td>
</tr>
<tr>
<td>&gt; 20.0</td>
<td>133</td>
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</table>
Prostate Cancer-LLUMC
Effect of Initial PSA on Disease-free Survival

Disease-free Survival

Years post Proton Radiation

< 4.1: 90%
4.1 - 10.0: 81%
10.1 - 20.0: 62%
20.1 - 50.0: 43%

p = .0001
PROG 95-09

Randomization
ACR/RTOG

T1b-2b prostate cancer
PSA <15ng/ml

Proton boost
19.8 GyE

Proton boost
28.8 GyE

3-D conformal photons
50.4 Gy

3-D conformal photons
50.4 Gy

Total prostate dose
70.2 GyE

Total prostate dose
79.2 GyE
## Pretreatment characteristics

<table>
<thead>
<tr>
<th>T-stage</th>
<th>Assigned dose</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>70.2GyE</td>
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<tr>
<td></td>
<td>(n = 197)</td>
</tr>
<tr>
<td>1b</td>
<td>1%</td>
</tr>
<tr>
<td>1c</td>
<td>61%</td>
</tr>
<tr>
<td>2a</td>
<td>22%</td>
</tr>
<tr>
<td>2b</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>(n = 195)</td>
</tr>
<tr>
<td></td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>13%</td>
</tr>
</tbody>
</table>
# PROG 9509

## Pretreatment characteristics

<table>
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<tr>
<th>Assigned dose</th>
<th>70.2GyE (n = 195)</th>
<th>79.2GyE (n = 197)</th>
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<tbody>
<tr>
<td>PSA</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 4</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>4- &lt; 10</td>
<td>74%</td>
<td>74%</td>
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<tr>
<td>10-15</td>
<td>14%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Freedom from Biochemical Failure (ASTRO)

Low risk*

Intermediate to high risk

Years since randomization

n = 230

n = 162

p = 0.008

p = 0.02

* PSA < 10, Stage T1b-T2a, Gleason score <7

Zietman et al. JAMA 294, 10 1233-1239; 2005
**Morbidity**

- **Acute GU or GI (rectal) morbidity**
  - RTOG grade 3 vs grade 2:
    - Low dose: 1% vs 42%
    - High dose: 2% vs 49% (n.s.)

- **Late GU or GI morbidity of RTOG grade 3 vs. grade 2**
  - Low dose: 1% vs 17%
  - High dose: 2% vs 8% (p < 0.05)

Zietman et. al JAMA 294, 10 1233-1239; 2005
How can we improve these results?

- **Image-guided proton beam therapy**
  - Separate macroscopic tumor volume (GTV) from volume of subclinical disease (CTV)
  - Generate *inhomogeneous dose distribution* by targeting these GTV separately to much higher dose (80-90 CGE) than CTV (70-75 CGE)
Physical, biological, & technical aspects of proton beams

Results of proton treatment – can we improve?

Anatomy of prostate cancer

Need for new imaging strategies for targeting

Controlling the motion of the prostate

Image-guided proton therapy
Prostate Cancer: A Multifocal Disease

- Number of tumor foci in whole-mount radical prostatectomy specimens
  - ~75% contain 1-4 macroscopic foci (distance > 4 mm)
  - Most foci are in the peripheral zone (~75%)


Prostate Cancer: A Locally Invasive Disease

- Frequency and radial distance of microscopic extensions in radical prostatectomy specimens (N = 712)
  - Microscopic extension in 42% of specimens
  - Extension beyond capsule in 26%
  - Median radial extension 2 mm (0-12 mm)
  - 97% had less than 5 mm extension


Prostate cancer with macroscopic extracapsular extension seen in MRI
Physical, biological, & technical aspects of proton beams

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Image-guided proton therapy
Targeting with New Imaging Modalities

- Available and upcoming imaging modalities
  - MRI (+ endorectal coil)
    - 1.5 -> 3.0 T
    - MRS (improved resolution)
    - DWI, DTI
    - DCE
  - PET/SPECT (+ CT or MRI)
    - New metabolic tracers (\(^{11}\)C choline, \(^{11}\)C acetate, \(^{18}\)F-choline, \(^{18}\)F-fluoroacetate)
    - Cancer specific tracers (molecular imaging), e.g., antibodies against PSMA or peptide receptors, Na-I symporter (NIS), etc.
Physical, biological, & technical aspects of proton beams

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Controlling the motion of the prostate

Image-guided proton therapy
Prostate Motion

- respiration
- bladder filling
- Rectal filling
Prostate Motion

- **Motion Parameters**
  - **intra-treatment motion** (motion during treatment)
    - respiratory
    - bowel-movement
    - bladder filling
  - **inter-treatment motion** (motion between treatments)
    - Rectal filling
    - Bladder filling
    - Setup error
Intra-Treatment Motion
(20 patients with implanted gold seeds, 83 treatment sessions)

Vertical range: ± 4.8 mm

Lateral range: ± 3.3 mm

Longitudinal range: ± 4.6 mm
Inter-Treatment Motion

- **Vertical range:** $\pm 6.1 \text{ mm}$
- **Lateral range:** $\pm 3.0 \text{ mm}$
- **Longitudinal range:** $\pm 5.8 \text{ mm}$
Controlling Prostate Motion

- General measures
  - Water-filled rectal balloon
  - Full bladder
  - Patient instruction (shallow breathing)

- Patient-dependent measures
  - Deep-inspiration breath-hold (DIBH)
  - Beam interlock control by patient

- Respiratory gating with surface markers
Respiratory Gating

- Already in clinical use
- Visual tracking of markers on the abdomen
- 4D-imaging (CT, MRI, PET)
- 4D-treatment
Image-Guided Proton Therapy of Prostate Cancer

**Principles**

- Implant seeds into prostate for image guidance
- Image patient with respiration-gated CT or proton CT
- Develop treatment plan for prostate + margins (CTV) and tumor subvolumes (GTV)
- Verify correct position in treatment room with X-ray or proton radiography or CT
- Treat GTV(s) with respiratory-gated proton beam
From X-ray to Proton CT

Conventional X-ray CT Scanner

Planned Proton CT Radiography/Scanner in the LLUMC Gantry
Advantages of a Proton CT

- Uses same radiation for treatment and imaging
- No separate X-ray source for imaging in treatment room
- 3D image set acquired with one Gantry revolution
- Better density resolution than with X-ray CT or X-ray imaging at low dose
- More accurate dose treatment planning
The Future: Gold-Nanoparticle Enhanced Proton CT Imaging

- **Principles**
  - Attach solid gold nanoparticles (1-100 nm) to monoclonal antibodies
  - Antibodies & nanoparticles attach specifically to cancer cells
  - Gold-loaded tumors have higher density than surrounding normal tissue
Conclusions

- The future of conformal proton beam therapy for prostate cancer has just begun
- Imaging with protons is around the corner (collaboration between INFN, LLUMC, UC Santa Cruz)
- Contributions from multiple subspecialties required (physics, nuclear medicine, MRI)
Thank you!