Conformal PBT of Prostate Cancer—Rationale, Results, and Future Directions

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Presentation Overview

Discuss the basic radiobiology and physics of protons vs. x-rays.

Review published nonrandomized and randomized data.

Examine upcoming protocols.

Touch on impending advances in conformal proton beam treatment delivery.
The Past is Prologue…

“What has been will be again, what has been done will be done again; there is nothing new under the sun. Is there anything of which one can say, "Look! This is something new"? It was here already, long ago; it was here before our time. “Ecclesiastes 1:9-11
Ecclesiastes would have been a good Radiation Oncologist…

- Technology changes, fundamental concepts do not. **Irrespective** of delivery method, the #1 goal of radiation oncology since inception has been to hit the target harder while sparing normal tissue.

- There is **no threshold dose** below which radiation does not appear to be potentially injurious.
Nothing new under the sun?

- Brachytherapy? - early 1900’s
- Megavoltage x-rays? - 1930’s
- Particle Beams? - 1950’s
Robert R Wilson (1914-2000)

- PhD- Berkeley, 1940-worked under Ernest Lawrence.
- WWII-Manhattan Project-Calutron-Isotopic separation of U235 from U238.
- 1960’s-70’s-Founding director Fermi National Accelerator Laboratory (Fermi lab).
The insight of a physicist...

"... the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest; ... these properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose; ... since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible."

Depth-Dose tells the tale…

PHYSICAL DOSE DISTRIBUTION

% ABSORB DOSE

- Ortho 0.2 MV (1930’s)*
- Cobalt-60 1.25 MV (1950’s)*
- Linac 8 MV (1960’s)*
- Linac 25 MV (1970’s)*
- Protons 250 MV (1990’s)*

Body

Tumor volume

Hospital availability

DEPTH CM

5 10 15 20 25 30 35 40
Integral Dose….

For any given clinical situation, a proton plan will always deliver a substantially lower integral dose (dose to normal tissue) than any x-ray based external beam treatment system (IMRT, Tomo, etc.).

“So what?” Ask your patient which he would prefer…..
Prostate Cancer-80 Gy

IMRT

PROTONS

C. Rossi-LLUMC PTCOG 46
Lots of Neutrons?

- Hall, 2005-questioned neutron contamination from passively scattered proton beams = higher total-body dose than IMRT.

- Conclusion based on data from HCL did not reflect routine clinical practice.

- Measured data from LLU, Indiana, Florida demonstrate neutron levels 50-100X less than in Hall’s paper.
Radiobiology of Protons

"What has radiobiology done for radiotherapy besides making it more expensive? It gave us neutrons that didn't work and protons that did."

Radiobiology of Protons

- Experimental data obtained in the 1950’s demonstrated that the RBE of protons as compared to Megavoltage x-rays is approximately 1.1. This is not true of other subatomic particles.

- Low proton RBE = ease of use in clinical situations - if you can give the dose with x-rays, you can safely do so with protons.
A Very Brief Historical Review…

- 1977 – First prostate treatment at HCL.
- 1979 – First published report (JAMA)
- 10/08/1991 – First prostate patient treated at LLUMC
- 2000 – PROG 9509 Study completes accrual.
- 2006 – Over 8K prostate patients treated.
PBT-History

- Prostate treatment pioneered by Shipley and associates at MGH.
- Phase I/II study initiated in 1977, reported in 1979 (JAMA).
- Limited to locally advanced clinical stage T3-T4 disease.
- PBT as boost only, given via perineal field.
PBT-History


- Examined effect of dose-escalation via PBT on clinical stage T3-T4 disease.
- Randomized between 67.2 and 75.6* CGyE, delivered as conventional four-field x-rays +/- perineal PBT boost.
- Accrued 202 patients over 13 years, reported in 1995.
PBT-History

MGH Phase III results:

- Decreased local failure in all patients treated with PBT. Reached statistical significance in Gleason 8-10 tumors only.
- Increased rectal bleeding (primarily grade 1) in high-dose group.
- No difference in survival.
PBT-LLUMC FACILITY

- First center built primarily for human treatment. Designed by clinicians for clinicians.
- Hospital location permits convenient access for patients and physicians.
- Multiple treatment rooms allow for high patient throughput.
Crucial Elements of PBT

- Reproducible patient positioning.
- Patient-specific treatment aids (apertures, boluses, immobilization devices).
- Daily verification of patient position prior to treatment.
- Ability to treat meaningful numbers of patients in a manner equivalent to what is readily available with photon therapy.
Treatment Planning-Elements

- Patient Immobilization
- CT scan
- Desktop Planning System
- Device Fabrication.
- Device Verification/Calibration.
Patient Immobilization

- Supine position
- “Pod”-PVC outer shell, form-fitting inner shell.
- Average construction time 15-30 minutes, including allowing for curing of foam.
- Need lots of storage space!
Treatment Planning-Target Definition

- **GTV** = Prostate +/- Seminal Vesicles (if involved, or at high risk of involvement).
- **CTV** = GTV + 7mm - allows for microscopic extra capsular extension.
- **PTV** = CTV + 5 mm in all directions. Allows for set-up error, penumbra.
- **Dose (off protocol)** 79.2-81.0 CGE @ 1.8 CGE/day (=arm II of PROG 9509), proscribed to isocenter. Typical variation across GTV/CTV=3-5%.
Treatment Planning-Normal Tissue Definition

- Bladder-contour from dome to neck. Encourage full bladder by having patients drink 8-16 oz 30-45 min prior to tx.

- Rectum-contour anterior wall (=anterior 50% of rectal wall circumference) from recto-sigmoid junction to bottom of ischeal tuberosities. Contour entire thickness of wall.
Treatment Planning-Device Fabrication

- Apertures and boluses cut by computer-controlled milling equipment.
- All devices identified by unique bar code (don’t forget the pod!).
- Based on operational experience, majority of calibrations are performed using a calibration model.
Patient-Specific Apertures and Boluses

Aperture

Bolus
Treatment Planning - Dose Delivery

- Average 2-3 CcGyE per spill.
- Cycle time 2-3 seconds.
- Individual room and switching magnets controlled by synchrotron control room.
- Patients are set up in inactive room, so beam can be switched efficiently to maintain throughput.
- Typical schedule is ten minutes per patient total time in room.
Prostate Cancer
LLUMC Results

- 1255 patients treated between 10/91 and 12/97 with adenocarcinoma of the prostate

- Patients had no prior surgery or hormone therapy

- 74 - 75 CGE* at 1.8 - 2.0 CGE per fraction

- Follow-up: mean - 63 mos, median - 62 mos (range 1 - 132)

- Age: mean - 68 years, median - 69 years, (range 44 – 90)
Patient Assessment

- Weekly clinic visits during treatment.
- PSA 4 months post treatment, than q 6 months.
- BNED assessed as per ASTRO Consensus Conference Criteria (i.e., failure backdated to midpoint between nadir and first rising PSA).
- Morbidity scored as per RTOG scoring system.
Prostate Cancer
Stage
Prostate Cancer
Gleason Score
Prostate Cancer
Initial PSA
Prostate Cancer
Biochemical Disease-free Survival

Disease-free Survival (%)

Years post Proton Radiation

C. Rossi-LLUMC PTCOG 46
Prostate Cancer-LLUMC 10 YEAR Effect of Initial PSA on Disease-free Survival

Years post Proton Radiation

Disease-free Survival (%)

- < 4.1
- 4.1 - 10.0
- 10.1 - 20.0
- 20.1 - 50.0

p = .0001

C. Rossi-LLUMC PTCOG 46
Prostate Cancer

Effect of Gleason Score on Disease-free Survival

- Gleason 2-4: 82%
- Gleason 5-7: 73%
- Gleason 8-10: 50%

Years post Proton Radiation
Prostate Cancer

Effect of PSA Nadir on Disease-free Survival

- < .51 ng/ml (694): 87%
- .51 - 1.0 ng/ml (272): 69%
- > 1.0 ng/ml (176): 25%

p = .000

Years post Proton Radiation

C. Rossi-LLUMC PTCOG 46
Pretreatment Prognostic Factors
Multivariate Analysis

- Initial PSA: <.001
- Gleason Score: .001
- Stage: <.001
- Age (< 60 v > 60): .137
## Treatment Morbidity

### RTOG Scale

<table>
<thead>
<tr>
<th></th>
<th>Grade 2</th>
<th>Grade 3 &amp; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>3.5%</td>
<td>0</td>
</tr>
<tr>
<td>GU</td>
<td>5.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Total</td>
<td>9%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
Conclusions

Conformal PBT can achieve durable bNED rates which compare with Radical Prostatectomy.

Conformal PBT produces minimal and acceptable morbidity, with RTOG GR> Grade 3 rates < 1%, paving way for additional dose-escalation.
A Phase III Trial employing conformal photons with proton boost in early stage prostate cancer: Conventional compared with high dose radiation. Results of PROG 95-09


Massachusetts General Hospital, Harvard Medical School MA

Loma Linda University Medical Center CA

American College of Radiology and Radiation Therapy Oncology Group, Philadelphia PA
Hypothesis

That dose escalation from 70 to 79Gy will result in a detectable improvement in cancer outcome for those with early stage prostate cancer without an increase in morbidity if highly conformal techniques are used.
PROG 9509

**Trial design**

**Patients:**
- Histologically confirmed locally confined adenocarcinoma of the prostate (any grade)
- Clinical stages T1b-2b
- PSA $\leq 15$
- No involved nodes (CT scan)
- No distant metastases (CT and bone scan)
- Karnofsky performance status $\geq 70$
- No prior hormonal therapy, radiation, or chemotherapy
PROG 9509

Trial design

T1c-2b prostate cancer
PSA < 15ng/ml

randomization
ACR/RTOG

Proton boost 19.8 GyE

3-D conformal photons 50.4 Gy

Total prostate dose 70.2 GyE

Proton boost 28.8 GyE

3-D conformal photons 50.4 Gy

Total prostate dose 79.2 GyE
PROG 9509

Prostate boost with protons - MGH
Prostate boost with protons - LLUMC
PROG 9509

Endpoints

Biochemical failure
   ASTRO definition

Local failure
   Any biopsy proven LF
   Nadir >1ng/ml
   PSA rise to >1ng/ml 2 or more years after RT

Acute and late morbidity RTOG scales
PROG 9509

Study statistics

Powered with 390 patients to detect
20% improvement in 5 year bDFS
20% improvement in 5 year LC

Activated Jan 1996
Closed Dec 1999
Total 393 patients

Statistical and data support from ACR and RTOG
## PROG 9509

### Pretreatment characteristics

<table>
<thead>
<tr>
<th>Assigned dose</th>
<th>70.2GyE (n=197)</th>
<th>79.2GyE (n=195)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>60-69</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>70-79</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>median</td>
<td>67yrs</td>
<td>66yrs</td>
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</table>
## Pretreatment characteristics

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

**PROG 9509**
### PROG 9509

#### Pretreatment characteristics

<table>
<thead>
<tr>
<th>Assigned dose</th>
<th>70.2GyE (n=197)</th>
<th>79.2GyE (n=195)</th>
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<tbody>
<tr>
<td>Gleason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>7</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>8-10</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>unknown</td>
<td>1%</td>
<td>2%</td>
</tr>
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## PROG 9509

### Pretreatment characteristics

<table>
<thead>
<tr>
<th>Assigned dose</th>
<th>70.2GyE (n=197)</th>
<th>79.2GyE (n=195)</th>
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</thead>
</table>

**T-stage***

<table>
<thead>
<tr>
<th>T-stage</th>
<th>70.2GyE</th>
<th>79.2GyE</th>
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</thead>
<tbody>
<tr>
<td>1b</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>1c</td>
<td>61%</td>
<td>62%</td>
</tr>
<tr>
<td>2a</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>2b</td>
<td>17%</td>
<td>13%</td>
</tr>
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</table>

*1992 AJCC system which includes T2c
# PROG 9509

**Pretreatment characteristics**

<table>
<thead>
<tr>
<th>Assigned dose</th>
<th>70.2GyE (n=197)</th>
<th>79.2GyE (n=192)</th>
</tr>
</thead>
</table>

**Contemporary risk groups:**

<table>
<thead>
<tr>
<th></th>
<th>56% (n=197)</th>
<th>60% (n=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intermediate</td>
<td>35% (n=197)</td>
<td>32% (n=192)</td>
</tr>
<tr>
<td>high</td>
<td>9% (n=197)</td>
<td>8% (n=192)</td>
</tr>
</tbody>
</table>
## PROG 9509

### Treatment delivered

<table>
<thead>
<tr>
<th>Assigned dose</th>
<th>70.2GyE (n=197)</th>
<th>79.2GyE (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>69.8-70.2</td>
<td>92%</td>
<td>--</td>
</tr>
<tr>
<td>&gt;70.2</td>
<td>4%</td>
<td>--</td>
</tr>
<tr>
<td>&lt;69.8</td>
<td>4%</td>
<td>--</td>
</tr>
<tr>
<td>78.8-79.2</td>
<td>--</td>
<td>88%</td>
</tr>
<tr>
<td>&gt;79.2</td>
<td>--</td>
<td>3%</td>
</tr>
<tr>
<td>&lt;78.2</td>
<td>--</td>
<td>9%</td>
</tr>
</tbody>
</table>
Follow-up

Median 5.5 years (1.2 – 8.2)

Median number of PSA values 9
<table>
<thead>
<tr>
<th>Median time to nadir</th>
<th>% nadir &lt;0.5</th>
<th>% nadir &lt;1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.2GyE 28mo.</td>
<td>45%</td>
<td>73%</td>
</tr>
<tr>
<td>79.2GyE 40mo.</td>
<td>60%</td>
<td>79%</td>
</tr>
</tbody>
</table>

\[
p = <0.01 \quad p = 0.11
\]
Freedom from Biochemical Failure (ASTRO definition)

Freedom from Biochemical Failure Rate

Years Since Randomization

70.2 GyE
79.2 GyE

# at risk

197 196 171 139 118 76 31 10 10
195 194 184 163 148 99 46 20 2

P = <0.0001

* 95% confidence intervals
Freedom from Biochemical Failure (ASTRO-Modified)

Years Since Randomization

Freedom from Biochemical Failure Rate

# at risk

70.2 GyE

79.2 GyE

P = <0.0001

197 197 192 179 156 90 33 11 0

195 194 191 184 163 111 53 20 2

66% 86%
Freedom from Biochemical Failure (ASTRO)

**Low**
- 79% at 79.2 GyE
- 55% at 70.2 GyE
- n = 230
- p = 0.008

**Intermediate**
- 78% at 79.2 GyE
- 61% at 70.2 GyE
- n = 162
- p = 0.02
Freedom from Biochemical Failure
(ASTRO – without backdating)

Low
- 85% at 79.2 GyE
- 62% at 70.2 GyE
- n = 230
- p = 0.008

Intermediate
- 87% at 79.2 GyE
- 73% at 70.2 GyE
- n = 162
- p = 0.02
Overall Survival Rate

Overall Survival

- 70.2 GyE
- 79.2 GyE

Years Since Randomization
# PROG 9509

## Acute toxicity

<table>
<thead>
<tr>
<th>% toxicity grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GU</strong> 70.2GyE</td>
<td>40</td>
<td>42</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>GI</strong> 70.2GyE</td>
<td>31</td>
<td>42</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>GU</strong> 79.2GyE</td>
<td>34</td>
<td>48</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>GI</strong> 79.2GyE</td>
<td>24</td>
<td>57</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Late toxicity

### Assigned dose

<table>
<thead>
<tr>
<th></th>
<th>70.2GyE</th>
<th></th>
<th>79.2GyE</th>
</tr>
</thead>
<tbody>
<tr>
<td>% toxicity grade</td>
<td></td>
<td>% toxicity grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>1</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PROG 9509
Conclusions

Dose escalation from 70 to 79Gy can be achieved without any increase in grade 3 acute or late morbidity using highly conformal photon/proton techniques.

leads to significantly lower PSA nadir values

is associated with an improvement in 5 year biochemical DFS for low risk prostate cancer.

is accompanied by improvement in local control assessed by surrogate markers
Conclusions

It is, however.........

1. Too early to see any improvement in freedom from clinical failure, if any exists.

2. Too early to see a survival benefit, if any exists.
Status Quo-2007
Current Practice-US Centers

- LLU
- MGH
- MPRI
- UF
- MDAH
We are all treating to doses which closely approximate the “high dose” arm of the PROG 9509 protocol, e.g., 78-80 CGE.

We are all using primarily lateral beams.

We are all using some form of rectal balloon to distend the rectum and aid in prostate fixation.
Quo Vadis?
Play to our Strengths-The Past is Prologue

- Successful hypofractionation of numerous other sites- Uveal Melanoma, Lung, Liver.
- Demonstrated ability to safely perform (and advantages of) dose-escalation- Chordomas, Chondrosarcomas, Prostate.
- Concomitant Boosting-Head & Neck.
Hypofractionation

- Radiobiologic data predicts alpha/beta ratio of 1.5-3, thus implying a potential advantage to large fraction size both in terms of improving local control and reducing late morbidity.
- Published IMRT data supports the safety and efficacy of hypofractionation.
IMRT-Based Hypofractionation - Kupelian et al.

bNED Survival as per ASTRO definition.
Hypofractionation vs. PROG

(a) Graph showing Kaplan-Meier curves for proportion-free from biochemical failure by risk group and dose.

(b) Graph showing Gray's test for statistical significance between high dose and conventional dose.

No. at Risk
High Dose
116 116 114 111 105 69 29 14
Conventional Dose 111 110 99 92 90 58 23 8

Gray's test P<0.001
Hypofractionation vs. PROG-
Intermediate to High Risk

(a)

Proportion-Free From Biochemical Failure

Time From Randomization, y

No. at Risk
High Dose 76 74 69 65 58 39 17 7
Conventional Dose 86 85 80 67 61 43 17 7

Gray's test P=0.106
Proposed Trial-Hpofractionation (Phase I-II)

- Assume $a/b$ of 1.5 for prostate cancer.
- Goal is to cut treatment duration by ~50%.
- Goal is to deliver radiation dose equivalent to 79-81 CGE @ 1.8-2.0 CGE/Day.
Proposed Trial-Hpofractionation

- Daily Fractionation-2.75-3.0 CGE/ Day.
  @ 2.75 CGE Day, Total dose 63.25 CGE in 23 fx.
  @ 3.0 CGE/ Day, Total dose = 57 CGE in 19 fx.
- Treat minimum two fields daily.
Dose-Escalation

- PROG-95O9-A good place to start.
- Doses > 79 Gy= increased bNED survival-MSK data.
- Morbidity @ 79.2 CGE was low and acceptable, so further dose escalation is feasible.
Dose-escalation

- ACR 0312-85 Patients 82 CGE/41 FX.
- Acute toxicity equivalent to high dose arm of PROG 9509.
- Too early for meaningful late toxicity data.
- Next step? Since we’re probably not at the MTD yet....
Dose-Escalation-Proposed Protocol (Phase I-II)

- Low and intermediate-risk patients only = no need to treat pelvis.
- Total dose = 86 CGE.
- Use PROG 9509 margins until ~ 79 CGE, than reduce posterior margin to 3-5 mm beyond CTV.
- Fiducial Placement in all patients to facilitate exact alignment.
Conclusions

- 78-80 CGE is our current standard. We have ten-year data on this dose level and know it can be delivered with acceptable toxicity.

- Conformal PBT lends itself nicely to hypofractionation—consider experience in lung, liver, eye—and should be investigated in prostate cancer.
Conclusions

- Further dose-escalation to find the MTD of fractionated PBT should be performed.
- As technology improves localization and boosting of dominant intra-prostatic lesions will become possible, which lends to further reductions in normal tissue dose (the only “safe dose” that we’re absolutely sure of is zero dose).