Comparing Current Options in Radiation Therapy

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Cedars-Sinai Medical Center
Time Trends for Radiotherapy (and other treatments)

Cooperberg
JCO 28:1117, 2010
Dose Distribution

3D-CRT

IMRT

Prostate
<table>
<thead>
<tr>
<th>Institution</th>
<th>Rectal Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UM</strong></td>
<td>&lt;20% over 70 Gy, &lt;50% over 50 Gy</td>
</tr>
<tr>
<td><strong>Beaumont</strong></td>
<td>&lt;40% over 70, &lt;25% over 75.6</td>
</tr>
<tr>
<td><strong>Wash U</strong></td>
<td>&lt;17% over 65, &lt;35% over 40</td>
</tr>
<tr>
<td><strong>Peter Mac</strong></td>
<td>&lt;25% over 70, &lt;30% over 60, &lt;50% over 50</td>
</tr>
<tr>
<td><strong>Duke</strong></td>
<td>&lt;10% over 75, &lt;17% over 65, &lt;40% over 40</td>
</tr>
<tr>
<td><strong>Cedars</strong></td>
<td>&lt;20% over 65, &lt;50% over 45</td>
</tr>
<tr>
<td><strong>ROC</strong></td>
<td>&lt;20% over 65, &lt;45% over 40</td>
</tr>
<tr>
<td><strong>MCW</strong></td>
<td>&lt;20% over 70, &lt;45% over 50</td>
</tr>
<tr>
<td><strong>Mayo</strong></td>
<td>&lt; 5% over 75, &lt;15% over 70, &lt;25% over 65, &lt;35% over 60, &lt;50% over 50</td>
</tr>
<tr>
<td><strong>MSKCC</strong></td>
<td>&lt;53% over 47, &lt;30% over 75.6, max dose 85.5</td>
</tr>
<tr>
<td><strong>FCCC</strong></td>
<td>&lt;17% over 65, &lt;35% over 40</td>
</tr>
</tbody>
</table>
Rectal DVH Example

Cumulative Dose Volume Histogram

<table>
<thead>
<tr>
<th>Dose [cGy]</th>
<th>Lower Dose Constraint</th>
<th>High Dose Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 Gy</td>
<td>&lt; 35%</td>
<td></td>
</tr>
<tr>
<td>45 Gy</td>
<td>&lt; 40%</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td>50 Gy</td>
<td>&lt; 45%</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td>65 Gy</td>
<td>&lt; 17%</td>
<td>&lt; 15%</td>
</tr>
<tr>
<td>70 Gy</td>
<td>&lt; 20%</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>75 Gy</td>
<td>&lt; 25%</td>
<td>&lt; 20%</td>
</tr>
</tbody>
</table>
Dose volume analysis of grade 2+ late GI toxicity on RTOG 0126 after high-dose 3DCRT or IMRT

- 3DCRT 55.8 to P+pSV, then 23.4 to P only
- IMRT 79.2 to P+pSV in single plan

- Data examined: Gr 2+ late rectal toxicity and $D_{\text{eff}}$ to rectum

- 708 available patients (473 3DCRT)

- 3DCRT 25%
- IMRT 21%

- No differences once corrected for $D_{\text{eff}}$

- No impact on rectal toxicity related to doses <60 Gy
• ALWAYS “insert new slide” when adding new text.

• Adding a text box will result in bullets not formatting correctly.

• All text should be single-spaced.

• Always use Lucida Sans font.

• Upper and lower case point size of text should be 14 point.
VMAT vs. Fixed Field IMRT

- Treatment time shorter, more rapid
- Low dose is spread more widely
- VMAT = 360 correlated fixed fields
- Anecdotal cases:
  - 7 field prostate IMRT: 898 MU (128 MU/field)
  - 2 arc VMAT: 904 MU (452 MU/arc)
RART: Single arc asymmetry
RART: Single arc asymmetry
Combined single arc vs
Integrated two arc plan

Combined single arcs:
Plans obtained for half-Rx dose for each of:
  Two arcs, one CW, one CCW
Arithmetic dose sum to obtain full RX plan
Optimization for the arcs obtained sequentially

Integral plan using two arcs, same CW and CCW specifications as for the above single arc plans
Optimization for the arcs obtained concurrently
Combined single arc vs Integrated two arc plan

Combined, Max 70.4, 527MU

Integral, Max 70Gy, 580MU
Combined single arc vs Integrated two arc plan
7 field IMRT vs 2 arc RART

IMRT, Max 72, 915MU

RART, Max 70Gy, 580MU
7 field IMRT vs 2 arc RART
Implanted Fiducials
AC Wireless Magnetic Tracking

Calypso System

Dimensions:
- 8 mm
- 1.8 mm
Implanted Transponders

Ensure that the three graphs are within tolerances (Yellow denotes out-of-tolerance). Press Record to record tracking data.

- Lateral: +0.70 cm
- Longitudinal: +0.25 cm
- Vertical: -0.40 cm
AC Wireless Magnetic Tracking

- May treat through array
- Measurements at 10 Hz
- Sub-mm resolution
- Real-time tracking during treatment
- Potential for fast correction
Intra-Fraction Motion Study

- Subset of 3 patients out of 42
- Supine, knees raised
- Set to isocenter with Calypso (+/- 0.5 mm)
- Time to start of fraction (1-2 min)
- Tracked for 8 – 10 minutes at 10 Hz
Data – Patient 1

- IS
- AP
- LR

Position (mm) vs. Time (s)
Data – Patient 2

Position (mm)

Time (s)
Data – Patient 3

Position (mm)

Time (s)

IS
AP
LR
Implanted Fiducials

- Have become standard care
- Potential to reduce margins required for setup uncertainty
- Potential to decrease target misses
- Real time tracking important
- Reimbursable as part of IGRT
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.
Increase per gray, 7.4% (95% CI, 2.9–14.5)
P<0.001
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ref.</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
<th>Phase 5</th>
<th>Phase 6</th>
<th>Phase 7</th>
<th>Phase 8</th>
<th>Phase 9</th>
<th>Phase 10</th>
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<td>1.61</td>
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<tr>
<td>Breath hold time</td>
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<td>BH Gap+</td>
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</table>
Fuse DIBH CT to FB CT according to Breast location

FB heart
DIBH heart

3 cm

3 cm
<table>
<thead>
<tr>
<th>Institution</th>
<th>Dose/Fractionation, LHRH?</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM</td>
<td>1.85 to 77.7, No</td>
</tr>
<tr>
<td>FCCC</td>
<td>2 to 80, No</td>
</tr>
<tr>
<td>Wash U</td>
<td>1.8 to 75.6, No</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>2.5 to 70, No</td>
</tr>
<tr>
<td>Duke</td>
<td>2 to 76, +/- based on potency</td>
</tr>
<tr>
<td>Jefferson</td>
<td>1.8 to 79.2, No</td>
</tr>
<tr>
<td>ROC</td>
<td>1.8 to 75.6, Yes</td>
</tr>
<tr>
<td>MCW</td>
<td>1.8 to 75.6, No</td>
</tr>
<tr>
<td>Mayo</td>
<td>1.8 to 75.6, No</td>
</tr>
<tr>
<td>MSKCC</td>
<td>1.8 to 86.4, No</td>
</tr>
</tbody>
</table>
Dose-Response Relationship: Early vs. Late responding tissues

• $\alpha/\beta$ ratio:
  – Tumor & Early $\sim 10$
  – Late $\sim 1-3$
\( S = e^{-\alpha D - \beta D^2} \)
Biologically Effective Dose (BED)

BED = Total Dose \times Relative Effectiveness

\[ \frac{E}{\alpha} = n \times d \times [1 + \frac{d}{(\alpha/\beta)}] \]

- \( n \) = number of fx’s
- \( d \) = dose/fx

Late: \( \alpha/\beta \approx 3 \)
Early: \( \alpha/\beta \approx 10 \)
RTOG 0415 Schema

T1c-2a
GS <7
PSA <10

73.8 Gy/41 Fx

70 Gy/28 Fx

n=800
Endpoint is 5 Year BFFF
Non-inferiority margin 7% (Control 85%, Exp 78%)
Clinical Trial

• Michigan-led, multicenter, hypofractionation trial for low-intermediate prostate cancer.
Stereotactic body radiotherapy for primary management of early-stage, low- to intermediate-risk prostate cancer: report of the American Society for Therapeutic Radiology and Oncology Emerging Technology Committee

• The authors of this report believe further clinical trials addressing the uncertainties in the clinical implementation of this new approach to prostate cancer treatment should be conducted.

• The technique holds sufficient promise to warrant further investigation.

Buuyounouski IJROBP 76:1297, 2010
Primary Objectives

• To evaluate the safety of the proposed hypofractionation regimen and to compare it to that expected from conventional treatment.

• To assess the frequency of required interventions based on real-time prostate translations and rotations to verify that the proposed planning target volume (PTV) margins and action level are appropriate and practical.
Eligibility

• Prostate cancer, Gleason score ≤ 7
  o If Gleason 7, then <50% of biopsy cores must be positive
  o If Gleason score <7 then there is no limit on the percentage of biopsy cores involved

• PSA
  o ≤ 15 ng/ml prior to start of therapy if Gleason ≤ 6 and
  o ≤ 10 ng/ml prior to start of therapy if Gleason 7

• T1c-T2b
• No hormone use

• Exclusion Criteria:
  o Implants in the pelvic region that contain metal
  o Body habitus not conducive to tracking with Calypso Beacons
  o AUA score > 15 (alpha blockers allowed)
  o CT, MRI, or ultrasound estimate of prostate volume > 100 grams
UMHS SBRT Protocol

• Instead of 39 fractions of 2 Gy to 78 Gy over 8 weeks, 5 fractions of 7.4 Gy to 37 Gy over 2.5 weeks.
• This is predicted to have toxicity similar to the 80 Gy regimen but with efficacy in the vicinity of 94 Gy
• Using Calypso guidance will use smaller margins than previously reported
INTERMEDIATE RISK RESULTS

Weighted

% PSA Progression Free

Brachy Surgery

EBRT & Seeds

→ Years from Treatment

• Prostate Cancer Results Study Group

• Numbers within symbols refer to references

Prostate Cancer Center of Seattle

3/18/2013

BJU Int, 2012, Vol. 109(Supp 1)
RT Technology

- Tomotherapy
  - IMRT device
- Cyberknife
  - Stereotactic device
- Protons
- Carbon Ion
Current Linear Accelerators

Siemens

Varian
TrueBeam

Elekta Versa HD
40 pt phase I/II
No grade 3 toxicity
Cyberknife

Fig. 2. Grains d'or fiduciaires et contrôle radiologique.

Fig. 3. Distribution des doses obtenue avec le CyberKnife™.
Cyberknife

- Near real time target tracking (q30-90 sec)
- Take 40 min for prostate rx
- 7.25 Gy/fx to 36.25 Gy

Pawlicki Med Dosim 32:71,2007
Particle Therapy

- Protons
  - Bragg peak gives finite range
- Photons (X-rays)
  - Penetrate deeply, attenuate gradually
Proton
The Bragg Peak and Protons' Benefits

- **Bragg Peak**
  - Potential to spare more healthy tissue
  - Potential to bring higher dose to targets at depth
  - Can be added together to produce a flat top SOBP

- **Charged particles**
  - Can be deflected and focused by magnets quickly
Proton Therapy
Potential Benefits

• May allow delivery of more dose to the tumor for same dose to normal tissue
  – Possible increased tumor control

• Reduced occurrence of treatment-related tissue damage
  – Early toxicity
  – Second cancers: especially important for pediatric cases

• Less toxicity when RT and chemo are combined
Gantry and Treatment Table

Gantry at Manufacturer

Treatment Room
System Layout

I. S.C. Cyclotron

II. Energy Selection System/Beam Transfer Line

III. Gantry Rooms

Single Gantry Room Section

Eye Treatment Room

Rinecker Proton Therapy Center (Munich)
Proton Therapy Sites

• Active
  – Loma Linda
  – MPRI (Indiana U)
  – MD Anderson
  – Univ Florida
    (Jacksonville)
  – MGH
  – Oklahoma City
  – Univ Penn
  – New Jersey/Princeton
  – Hampton Univ/VA
  – Chicagoland

• Planned
  – Scripps
  – Seattle (Cancer Alliance)
  – Wash U
  – Maryland
  – Rutgers
  – New York
  – Emory
  – UT Southwestern
  – Mayo/Rochester+Phoenix
  – Johns Hopkins/Washington
  – Flint
What is the evidence in favor of proton therapy?

- Reviewed 36 published studies (only 2 phase III)
- Chordomas, ocular tumors, prostate, head and neck cancer
The phenomenon continues among men diagnosed with prostate cancer that began with the opening in 1990 of Loma Linda University Medical Center’s proton facility. Prostate patients top all other cancerous conditions treated with proton therapy between the five U.S. operating protons centers. About 8,000 men have been treated with outstanding outcomes reported in the last 17 years... A vast majority of men self-referred themselves to proton treatment centers around the country after learning about the advantages of the proton beam that minimizes serious side effects and helps to maintain a patient’s quality-of-life.
“The claim by proton therapy supporters that protons are the treatment of choice for chordoma and chondrosarcoma is no longer tenable based on the currently available evidence.”

“…there are currently no studies demonstrating improved tumor control or survival in the treatment of localized prostate cancer with protons compared with best available photon RT. In addition, there is no clear evidence that high-dose proton boost is associated with less toxicity than the toxicity expected with photons.”

“Proton and other particle therapies need to be explored as potentially more effective and less toxic RT techniques.”

Brada, et al JCO 2007
Prostate

IMRT

Trofimov, et al. IJROBP 2007

Protons
Cost Effective?

• Markov model (91.8 Gy proton vs. 81 Gy IMRT)

• $63,500/QALY for 70 yo, $55,700 for 60 yo.

• “Even when based on the unproven assumption that protons will permit a 10-Gy escalation of prostate dose compared with IMRT photons, proton beam therapy is not cost effective for most patients with prostate cancer using the commonly accepted standard of $50,000/QALY. Consideration should be given to limiting the number of proton facilities to allow comprehensive evaluation of this modality.”
Protons for medulloblastoma
Carbon Ion

- Higher LET
- Fewer fractions needed
Proton Summary

- Proton therapy has the potential to benefit a subset of cancer patients, especially children.
- Benefit for prostate cancer not established.
- More research is needed to define what patients will benefit from proton technology.
- Given the cost benefit ratio, regional centers should be considered.
- IMRT has reduced toxicity of high dose RT.
ASTRO Position Statement
Use of Proton Beam Therapy for Prostate Cancer
February 2013

At the present time, ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear.

**Approved Statement:**
While proton beam therapy is not a new technology, its use in the treatment of prostate cancer is evolving. ASTRO strongly supports allowing for coverage with evidence development for patients treated on clinical trials or within prospective registries. ASTRO believes that collecting data in these settings is essential to informing consensus on the role of proton therapy for prostate cancer, especially insofar as it is important to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy.
Why doesn’t someone do a study??

• Finally, *someone* is
• MGH/UPenn
  o Efficacy of PBT vs. IMRT
  o Compare the reduction in mean EPIC bowel scores for men with low or low-intermediate risk PCa treated with PBT versus IMRT at 24 months following radiation
  o 461 patients
  o Study to be reported in 2016
Systematic review

Is there a role for endorectal balloons in prostate radiotherapy? A systematic review

Robert Jan Smeenk\textsuperscript{a,}\textsuperscript{*}, Bin S. Teh\textsuperscript{b}, E. Brian Butler\textsuperscript{b}, Emile N.J.Th. van Lin\textsuperscript{a}, Johannes H.A.M. Kaanders\textsuperscript{a}

\textsuperscript{a} Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; \textsuperscript{b} Department of Radiation Oncology, The Methodist Hospital and The Methodist Hospital Research Institute, Houston, TX, USA

Radiotherapy and Oncology 95 (2010) 277–282
Endorectal Balloons

[Images of endorectal balloons]
Summary

• Dose sparing during 3DCRT, less evidence for benefit with IMRT

• Use with care or omit for patients with pre-existing anorectal disease

• Reproducibility?
Spacers?

- Hyaluronan gel

Wilder IJROBP 77:824,2010
Spacers?

- PEG-based hydrogels

Song ASTRO Abs 2011
<table>
<thead>
<tr>
<th>Institution</th>
<th>IGRT?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UM</strong></td>
<td>EM Transponder &gt;&gt; fiducials with CBCT &gt; CBCT alone</td>
</tr>
<tr>
<td><strong>Beaumont</strong></td>
<td>Adaptive with CBCT alone</td>
</tr>
<tr>
<td><strong>Wash U</strong></td>
<td>EM Transponder, MV with fiducials,</td>
</tr>
<tr>
<td><strong>Peter Mac</strong></td>
<td>kV and fiducials</td>
</tr>
<tr>
<td><strong>Duke</strong></td>
<td>EM Transponder, CBCT and fiducials,</td>
</tr>
<tr>
<td><strong>Cedars</strong></td>
<td>EM Transponder (preferred), CBCT</td>
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<td><strong>MCW</strong></td>
<td>CBCT without fiducials</td>
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<td><strong>Mayo</strong></td>
<td>kV and fiducials</td>
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<td><strong>MSKCC</strong></td>
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<td><strong>FCCC</strong></td>
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<td>CTV-PTV Margin (mm)</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>MCW</td>
<td>3 post, 5 elsewhere</td>
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<tr>
<td>Mayo</td>
<td>4-5 post, 5-7 laterally, 5 elsewhere</td>
</tr>
<tr>
<td>MSKCC</td>
<td>6 everywhere</td>
</tr>
<tr>
<td>FCCC</td>
<td>3-5 mm post, 6-8 elsewhere</td>
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</tbody>
</table>
Current Practice

- Intermediate risk patient:
  - Insert Calypso Beacons, if the patient is a candidate
  - CT simulation 7+ days after insertion (MR before Beacons if necessary)
  - Contour, verify Beacon location with dosimetry
  - PTV margin generally 5 mm
  - Plan, usually RapidArc with two arcs
  - Deliver RT with 3 mm action threshold