SBRT for Prostate Cancer

Patrick Kupelian, M.D.
Professor and Vice Chair
University of California Los Angeles
Department of Radiation Oncology
pkupelian@mednet.ucla.edu

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Localized Prostate Cancer: Competing Treatment Modalities

Surveillance (No Dose option)

Radiotherapy:  
- Brachytherapy: LDR / HDR
- High dose EBRT ( IMRT)
- Hypofractionation (including SBRT)

Surgery:  
- Radical Retropubic
- Laparoscopic / Robotic

Cryosurgery
HIFU
Radiotherapy Terms...

SABR (Stereotactic Ablative Body Radiotherapy) = SBRT (Stereotactic Body Radiotherapy) = Hypofractionated Radiotherapy
EXPERIENCE WITH HYPOFRACTIONATED RT

LOW DOSE (OLD):
Equivalent to doses less than 70 Gy in conventional fractionation

ADEQUATE DOSE (MODERN):
Equivalent to doses more than 70 Gy in conventional fractionation
OLD (LOW-DOSE) EXPERIENCES: 2D, no IMRT, no IGRT

**St. Thomas Hospital (London):**
Lloyd-Davies, Urology. 36: 107, 1990
55 Gy in 12 fractions
36 Gy in 6 fractions: **6 Gy per fraction**

**Canadian randomized trial:**
Lukka, JCO. 23: 6132-6138, 2005
66 Gy in 33 fractions versus 52.5 Gy/20 fractions (**2.6 Gy per fraction**)
- Hypofractionated arm worse? 5yr bRFS: 53% vs. 56%; *p < 0.05*
- No difference in toxicity

**Australian randomized trial:**
64 Gy/32 fractions versus 55 Gy/20 fractions (**2.75 Gy per fraction**)
- Hypo arm better bRFS.
- Median FU 90 mos needed to show difference.
- GI toxicity slightly worse with hypo.

Yeoh, IJROBP, 66: 1072-83, 2006
Yeoh, IJROBP 81, 1271-8, 2011
## MODERN HYPOFRACTIONATION EXPERIENCES: IMRT / IGRT

<table>
<thead>
<tr>
<th>Single arm</th>
<th>Fraction Size(Gy)</th>
<th>Total Dose (Gy)</th>
<th>BED (α/β=2)</th>
<th>Med FU (mos)</th>
<th>Last report</th>
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<tbody>
<tr>
<td>Cleveland Clinic</td>
<td>2.5</td>
<td>70.0</td>
<td>158</td>
<td>103</td>
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<td>McGill</td>
<td>3.0</td>
<td>66.0</td>
<td>165</td>
<td>90</td>
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<tr>
<td></td>
<td>2.94</td>
<td>64.7</td>
<td>160</td>
<td>59</td>
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<td>U Wisconsin</td>
<td>3.63</td>
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<td>4.30</td>
<td>51.6</td>
<td>163</td>
<td>55</td>
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(Many more…)

<table>
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<th>Randomized</th>
<th>Hypofrac Arm</th>
<th>BED</th>
<th>Conv Arm</th>
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<tbody>
<tr>
<td>MDACC</td>
<td>72.0 at 2.4 Gy</td>
<td>158</td>
<td>75.6 at 1.8 Gy</td>
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<tr>
<td>FCCC</td>
<td>70.2 at 2.7 Gy</td>
<td>165</td>
<td>76.0 at 2.0 Gy</td>
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<tr>
<td>PMH / PROFIT</td>
<td>60.0 at 3.0 Gy</td>
<td>150</td>
<td>78.0 at 2.0 Gy</td>
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<td>RTOG 0415</td>
<td>70.0 at 2.5 Gy</td>
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<td>73.8 at 1.8 Gy</td>
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<td>CHHiP(UK)</td>
<td>60.0 at 3.0 Gy</td>
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<td>74.0 at 2.0 Gy</td>
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<td>Italian Study</td>
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<td>80.0 at 2.0 Gy</td>
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<tr>
<td>Dutch Study</td>
<td>64.6 at 3.4 Gy</td>
<td>174</td>
<td>78.0 at 2.0 Gy</td>
</tr>
</tbody>
</table>
POSTOP RT
Hypofractionation

San Raffaele: Cozzarini. Radiother Oncol 88: 26, 2008
2.9 Gy x 20 = 58 Gy

2.6 Gy x 26 = 65 Gy

3.0 Gy x 18 = 54 Gy
PROSTATE SBRT
("Extreme hypofractionation")

Faster, Better, Cheaper
PROSTATE SBRT: 5 fractions or less
Faster, Better, Cheaper

**Faster (more convenient):** 5 vs 45 treatments

**Cheaper:** In US: SBRT $20,571 vs Fractionated IMRT $36,837

**Better?:** Multiple studies, showing excellent control
TECHNIQUE
Planning and Delivering SBRT
IG – EBRT technique

Planning
PTV: 95% of PTV volume to get 95-110% of Rx dose.

**SBRT: (8 Gy x 5)**

OAR Dose Constraints:

**Rectum**
- V50 (20 Gy) ≤ 50%
- V80 (32 Gy) ≤ 20%
- V90 (36 Gy) ≤ 10%
- V100 (40 Gy) ≤ 5%

**Bladder**
- V50 (20 Gy) ≤ 40%
- V100 (40 Gy) ≤ 1.1%

**Femurs**
- V40 (16 Gy) ≤ 5%

**Small Bowel**
- V50 (20 Gy) < 1%

Delivery
## SBRT Doses

<table>
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<tr>
<th>Dose ranges:</th>
<th>BED</th>
<th>Reference</th>
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<td>$6.70 \times 5 = 33.5,\text{Gy}$</td>
<td>146</td>
<td>Madsen IJROBP 2007</td>
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<tr>
<td>$7.25 \times 5 = 36.25,\text{Gy}$</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>$7.5 \times 5 = 37.5,\text{Gy}$</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>$9.0 \times 4 = 36.0,\text{Gy}$</td>
<td>198</td>
<td>Fuller IJROBP 2008</td>
</tr>
<tr>
<td>$8.0 \times 5 = 40.0,\text{Gy}$</td>
<td>200</td>
<td>King RO 2013</td>
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<tr>
<td>$9.0 \times 5 = 45.0,\text{Gy}$</td>
<td>248</td>
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<tr>
<td>$9.5 \times 5 = 47.5,\text{Gy}$</td>
<td>273</td>
<td>Boike JCO 2011 / Kim ASTRO 2013</td>
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<tr>
<td>$10.0 \times 5 = 50.0,\text{Gy}$</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>$24 \times 1 = 24,\text{Gy}$</td>
<td>312</td>
<td>Greco, Lisbon</td>
</tr>
</tbody>
</table>

References:
- King IJROBP 2009
- Friedland TCRT 2009
- Katz BMC Urol 2010
- Wiegner IJROBP 2010
- Bolzicco TCRT 2010
- Aluwini J Endourol 2010
- Freeman RO 2010
- Townsend AJCO 2011
- Kang Tumori 2011
- Jabbari IJROBP 2011
- Mantz IJROBP 2011
- Greco, Lisbon
Delivery Platform

**Linac based vs Robotic delivery:**
- Most experience with robotic delivery
- Coplanar vs non-coplanar delivery
- Platforms seem comparable

Figure 3. Comparison of mean dose–volume histograms for the CyberKnife (CK, the solid line) and RapidArc (RA, the dot line) techniques used for Group 1. The gray zone indicated the statistically significant differences between the CK and RA plans ($P < 0.05$). (a) Clinical target volume. (b) Planning target volume. (c) Rectum. (d) Urinary bladder.

Contouring / Target Volumes
MRI preferred, not required

**Prostate:** Whole gland

**Seminal vesicles:**
Low risk: No SV coverage necessary
Intermediate/High risk: Unclear.
Options:
- Cover to full dose the proximal 2 cm (provided OAR dose limits are respected)
- Cover to proximal SVs to lower dose level (e.g. 35 Gy in 5)

If SVs are grossly abnormal: Cover to full dose
Treatment Planning

- Prostate prescribed $8 \text{ Gy} \times 5 = 40 \text{ Gy}$: $\text{EQD}_{2,\alpha/\beta=1.5} = 109 \text{ Gy}$
- Prostate + *proximal 2 cm seminal vesicles* + 3-5mm: $7.25 \text{ Gy} \times 5 = 36.25 \text{ Gy}$
- MRI fusion to assist target definition

Meier et al., ASTRO 2012
Image Guidance / Tracking / Set up

**Intrafraction Tracking:**
Need some form of intrafraction tracking, particularly if times are extended.
- Calypso
- Repeat X-rays

**CBCT:**
- Document / assess rotations
- Document / assess deformations
- Document bladder / rectal filling

**Endorectal Balloons**

**Rectal Spacers**
UT Southwestern Protocol (R. Timmerman)

Stereotactic, Image guidance

Prescription line: >60%

2-3 mm post margin

Fiducials
Intrafraction imaging

Endorectal balloon
BALLOON PROBLEM?: INTRODUCING DEFORMATION

Without balloon

Increased length of rectum irradiated?
Superior and inferior parts of the rectum get closer to high dose areas.

Anal canal:
Increased doses?

With balloon

Beware of SV coverage;
Increase rectal doses superiorly?
PROSTATE SBRT

RESULTS

Mostly for low and low/intermediate risk
SBRT for Prostate Cancer

Multiple reports, single arm studies:
Adequate control
Acceptable toxicity (-1)

- Madsen IJROBP 2007
- Fuller IJROBP 2008
- King IJROBP 2009
- King IJROBP 2011
- Friedland TCRT 2009
- Katz BMC Urol 2010
- Wiegner IJROBP 2010
- Bolzicco TCRT 2010
- Aluwini J Endourol 2010
- Freeman RO 2010
- Townsend AJCO 2011
- Kang Tumori 2011
- Jabbari IJROBP 2011
- Mantz IJROBP 2011
- Boike JCO 2011
  / Kim ASTRO 2013
Efficacy of SBRT
Efficacy of SBRT

Multi-institutional pooled data; 8 institutions

1100 patients, ~ 3 yr median FU (6-72 mos)

335 cases with a >4 years follow-up (median 53 mos)

35-40 Gy in 4-5 fractions, ADT in14%

Risk groups:
Low: 639 59%
Intermediate: 326 30%
High: 124 11%

Subset with longer follow-up:

335 cases with >4 years follow-up (median: 53 months)

5-year bRFS rates:
Low risk: 97%
Intermediate-risk: 89%

Hypofractionated SBRT versus conventionally fractionated EBRT for prostate cancer: comparison of PSA slope and nadir

Mehkail Anwar*, Vivian Weinberg, Albert J. Chang, I-Chow Hsu, Mack Roach III and Alexander Gottschalk

Table 3 Results (all patients)

<table>
<thead>
<tr>
<th>Through year</th>
<th>SBRT</th>
<th>CF-EBRT</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>PSA Measurements</strong></td>
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<td>Mean (range)</td>
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<td></td>
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<tr>
<td>1</td>
<td>3.9 (2 – 6)</td>
<td>4.1 (3 – 11)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.8 (4 – 9)</td>
<td>5.6 (3 – 15)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7.6 (5 – 11)</td>
<td>7.3 (3 – 21)</td>
<td></td>
</tr>
<tr>
<td><strong>Nadir PSA (ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (range)</td>
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<td></td>
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<tr>
<td>1</td>
<td>0.70 (0 – 2.5)</td>
<td>1.00 (0 – 8.5)</td>
<td>p = 0.005*</td>
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<tr>
<td>2</td>
<td>0.40 (0 – 1.4)</td>
<td>0.72 (0 – 2.7)</td>
<td>p = 0.002*</td>
</tr>
<tr>
<td>3</td>
<td>0.24 (0.1 – 1.4)</td>
<td>0.60 (0 – 2.2)</td>
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<tr>
<td><strong>Time to Nadir PSA (mos.)</strong></td>
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<td></td>
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<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12.0 (2.7 – 15.0)</td>
<td>11.5 (1.2 – 15.0)</td>
<td>p = 0.004^</td>
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<tr>
<td>2</td>
<td>21.0 (2.7 – 26.9)</td>
<td>18.0 (1.2 – 26.9)</td>
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<tr>
<td>3</td>
<td>32.3 (2.7 – 41.6)</td>
<td>28.6 (1.0 – 41.1)</td>
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<tr>
<td><strong>Rate of PSA change: ng/mL/month</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Median slope (range)</td>
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</tr>
<tr>
<td>1</td>
<td>-0.09 (-0.88, 0.04)</td>
<td>-0.09 (-0.60, 0.06)</td>
<td>p = 0.04*</td>
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<tr>
<td>2</td>
<td>-0.06 (-0.38, 0.01)</td>
<td>-0.04 (-0.65, 0.05)</td>
<td>p = 0.006*</td>
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<tr>
<td>3</td>
<td>-0.05 (-0.19, 0.00)</td>
<td>-0.02 (-0.38, 0.04)</td>
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</table>
SBRT FOR LOCALIZED PROSTATE CA

PHYSICIAN-REPORTED TOXICITY
Late Urinary Toxicity: Gr 2+

SBRT vs 3D-conf, IMRT, Protons

% of Patients

0% 10% 20% 30% 40% 50%

Stanford 36.25 Gy 3.5% (5.3%) Winthrop 35-36.25 0.5% (5.8%) Meier (multi-inst) 0.8% (11%) Dutch 78Gy 3D-conf 13% (26%) MDA 78Gy 3D-conf 3.3% (7.3%) MSK 86.4Gy IMRT 2.5% (13%) MGH 79.2Gy Proton 1.5% (27%)

Adapted from Meier et al., ASTRO 2012
Late Bowel Toxicity: Gr 2+

SBRT vs 3D-conf, IMRT, Protons

- Stanford 36.25 Gy: 2%
- Winthrop 35-36.25: 2%
- Meier (multi-inst): 1.6%
- Dutch 78 Gy 3D-conf: 27%
- MDA 78 Gy 3D-conf: 6.6%
- MSK 86.4 Gy IMRT: 0.4%
- MGH 79.2 Gy Proton: 24%

Adapted from Meier et al., ASTRO 2012
SBRT FOR LOCALIZED PROSTATE CA

PATIENT-REPORTED TOXICITY
Multi-institutional prospective study
PATIENT REPORTED OUTCOMES

Mean AUA Score after SBRT

Similar to an implant

Meier et al., ASTRO 2012
Quality of Life after SBRT: Consortium Data

Health-Related Quality of Life After Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Results From a Multi-institutional Consortium of Prospective Trials

Christopher R. King, PhD, MD,* Sean Collins, MD,† Donald Fuller, MD,‡ Pin-Chieh Wang, PhD,*, Patrick Kupelian, MD,*, Michael Steinberg, MD,*, and Alan Katz, MD, JD§

*Department of Radiation Oncology, University of California, Los Angeles, California; †Department of Radiation Oncology, Georgetown University, Washington, District of Columbia; ‡Genesis Healthcare Partners, San Diego, California; and §Flushing Radiation Oncology, Flushing, New York

EPIC QOL data: Patient numbers

<table>
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<tr>
<td>Baseline</td>
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<tr>
<td>12 month</td>
<td>658</td>
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<td>36 month</td>
<td>388</td>
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<td>48 month</td>
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<tr>
<td>60 month</td>
<td>194</td>
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<tr>
<td>72 month</td>
<td>63</td>
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</table>

King et al., IJROBP 2013
QOL (EPIC) data from 864 SBRT patients

Patient numbers with EPIC QOL data:

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<tr>
<th>Time</th>
<th>N</th>
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<td>Baseline</td>
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<td>1-3 month</td>
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<tr>
<td>6 month</td>
<td>500</td>
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<tr>
<td>9 month</td>
<td>388</td>
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<tr>
<td>12 month</td>
<td>658</td>
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<td>24 month</td>
<td>489</td>
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</tr>
<tr>
<td>72 month</td>
<td>63</td>
</tr>
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King et al. IJROBP 87:939-45, 2013
ASTRO 2012: SBRT for Intermediate-risk Organ-confined Prostate Cancer: Interim Toxicity & Quality of Life Outcomes from a Multi-Institutional Study

ASTRO 2013: Patient-Reported QOL Outcomes in Intermediate-Risk Prostate CA Patients Treated With SBRT

ESTRO 2014: Quality of life outcomes from a multicenter study of SBRT for low- and intermediate-risk prostate CA

Robert Meier MD, Swedish Cancer Institute, Seattle WA
I. Kaplan2, A. Beckman3, G. Henning4, S. Woodhouse5, S. Williamson6, N. Mohideen7, D. Herold8, C. Cotrutz1, M. Sanda2

2Beth Israel Deaconess Medical Center, Boston, MA
3Central Baptist Hospital, Lexington, KY; 4St. Joseph Mercy Hospital System, Ypsilanti, MI;
5Community Cancer Center, Normal, IL; 6Capital Health System, Trenton, NJ; 7Northwest Community Hospital, Arlington Heights, IL
8Jupiter Medical Center, Jupiter, FL
EPIC Urinary Incontinence Score

External Beam RT →

LDR Brachytherapy →

Sanda M. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. N Engl J Med 2008;358:1250

Meier et al., ESTRO 2014
EPIC Urinary Irritation or Obstruction Score

External Beam RT →

LDR Brachytherapy →

Sanda M. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. N Engl J Med 2008;358:1250

Meier et al., ESTRO 2014
EPIC Bowel Score

External Beam RT →

LDR Brachytherapy →

Sanda M. *Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors.* N Engl J Med 2008;358:1250

Meier et al., ESTRO 2014
EPIC Sexual Score

External Beam RT → LDR Brachytherapy →

Sanda M. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. N Engl J Med 2008;358:1250

Meier et al., ESTRO 2014
SBRT DOSE

How high can we go?
UT SOUTHWESTERN SBRT PROSTATE PROTOCOL

Phase I/II trial. Multi-institutional. Started 2006

Phase I 45 patients

5 fractions: 9 Gy, 9.5 Gy, 10 Gy

Phase II 50 patients

T1-T2b
PSA ≤10
GS 6 and PSA <20
GS7 and PSA <15
Gland <60 cc
No TURP or other treatment
Low IPSS score (<15)

Boike et al, JCO, 2011
Median follow-up is 25.5 months

Dose groups:
- 9.0 Gy x 5 = 45 Gy
- 9.5 Gy x 5 = 47.5 Gy
- 10.0 Gy x 5 = 50 Gy

10% developed High Grade Rectal Toxicity (Grade 4)

Predictors of Gr4 rectal toxicity:
- Diabetes (trend p=0.07)
- > 35% of rectal wall at 39 Gy (p=0.03)
- Volume of rectal wall receiving 50 Gy (p=0.01)

Gr4 toxicity occurred in all with > 3.5 cm$^3$ of rectal wall ≥ 50 Gy (p < .0001).
All patients with no rectal toxicity had < 3.5 cm$^3$ rectal wall at 50 Gy.

DO NOT treat with 50 Gy at 10 Gy per fraction
# RANDOMIZED SBRT TRIALS

<table>
<thead>
<tr>
<th>Hypofrac Arm</th>
<th>Arm 2</th>
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<tbody>
<tr>
<td>Widmark: 42.7 at 6.1 Gy vs 78 at 2Gy</td>
<td>7 fractions vs 39 fractions</td>
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<tr>
<td>RTOG 0938: 36.25 at 7.25 Gy vs 51.6 at 4.3 Gy</td>
<td>5 fractions vs 12 fractions</td>
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<tr>
<td>PACE trial:</td>
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</tbody>
</table>
PACE TRIAL

Randomized trial. UK. N=1036.
PSA < 20 ng/ml
Gleason score \( \leq 3 + 4 = 7 \)
Clinical stage T1c -T2c, N0-X, M0-X

Surgical candidate?

Yes

Surgery: RALP, LP
vs
SBRT

No

SBRT
vs
Conventional fractionated IMRT

First patients enrolled at Royal Marsden
SBRT for High Risk Disease?

UCLA High-Risk SBRT Trial

High-Risk Prostate cancer

Aim 1: PSA RFS
Aim 2: toxicity (CTCAE)
Aim 3: QOL (EPIC)

-Eligibility: High risk:
  - Pre-biopsy PSA ≥ 20
  - Biopsy Gleason score 8-10
  - Clinical stage T3

Predict 85% 5-year bNED (c/w 75% IMRT)

Expected accrual 220 pts in 2 years
UCLA High-Risk SBRT Trial

SBRT: Not delivery platform specific.
CT/MRI planning

8 Gy x 5 (40 Gy*) to prostate PTV
5 Gy x 5 (25 Gy) to pelvic LN (optional)
SV: Full dose or 5 Gy x 5 (respecting ROI constraints)

*Minimum dose, 30-50% heterogeneous ‘Hot Shell’
Prostate Cancer:

Many clinical studies supporting the efficacy and safety of SBRT in the treatment of prostate cancer have been published. At least one study has shown excellent five year biochemical control rates with very low rates of serious toxicity. Additionally, numerous studies have demonstrated the safety of SBRT for prostate cancer after a follow-up interval long enough (two to three years) to provide an opportunity to observe the incidence of late GU or GI toxicity. While it is necessary to observe patients treated for prostate cancer for extended intervals to gauge the rate of long term (beyond 10 years) biochemical control and overall survival, the interim results reported appear at least as good as other forms of radiotherapy administered to patients with equivalent risk levels followed for the same duration post-treatment.

It is ASTRO’s opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease.
SBRT for Prostate Cancer

Patrick Kupelian, M.D.
Professor and Vice Chair
University of California Los Angeles
Department of Radiation Oncology
pkupelian@mednet.ucla.edu

June 2014
Quality of Life after SBRT: Consortium Data

Clinical Investigation

Health-Related Quality of Life After Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Results From a Multi-institutional Consortium of Prospective Trials

Christopher R. King, PhD, MD, * Sean Collins, MD, † Donald Fuller, MD, † Pin-Chieh Wang, PhD, ‡ Patrick Kupelian, MD, * Michael Steinberg, MD, * and Alan Katz, MD, JD

* Department of Radiation Oncology, University of California, Los Angeles, California; † Department of Radiation Oncology, Georgetown University, Washington, District of Columbia; ‡ Genesis Healthcare Partners, San Diego, California; and * Flushing Radiation Oncology, Flushing, New York

Received Jun 25, 2013, and revised Feb 17, 2013. Accepted for publication Aug 19, 2013

Summary
Self-reported quality of life was prospectively measured among 864 patients from Phase II trials of stereotactic body radiation therapy for localized prostate cancer. Transient decline in urinary/bowel domains occurred within 3 months and remained so beyond 5 years. The same pattern was observed with good versus poor baseline function and was independent of early toxicities. Sexual quality of life declined predominantly observed within 9 months, a pattern...
QOL (EPIC) data from 864 SBRT patients

Best 75% vs Worse 25%
- Lower 25th percentile  - Top 75th percentile

Best 95% vs Worse 5%
- Lower 5th percentile  - Top 95th percentile

King et al., IJROBP 2013
Stereotactic Body Radiotherapy for Intermediate-risk Organ-confined Prostate Cancer: Interim Toxicity and Quality of Life Outcomes from a Multi-Institutional Study

Robert Meier, MD
Swedish Cancer Institute, Seattle WA

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6Capital Health System, Trenton, NJ
7Northwest Community Hospital, Arlington Heights, IL
8Jupiter Medical Center, Jupiter, FL

Meier et al., ASTRO 2012
SBRT QUESTIONS

• TESTING DIFFERENT SCHEDULES

• HETEROGENEOUS DELIVERY

• DOSE PAINTING
  • BOOSTING OF INTRAPROSTATIC LESIONS
  • NORMAL TISSUE AVOIDANCE
    • URETHRA
    • RECTUM SUBSECTIONS / ANUS
    • ERECTILE TISSUES
    • SPHINCTERS
PSA Failure: CyberKnife SBRT
Intermediate-risk Group

Meier et al., ESTRO 2014
HIGH DOSE HYPOFRACTIONATION
THE CLEVELAND CLINIC EXPERIENCE

70 GY / 28 FRACTIONS
STARTING 1998

Image Guidance: Daily trans abdominal ultrasound

Technique: IMRT

Target/Volume: Prostate +/- SV

Margins: Lat 8 mm Ant 5 mm
Sup/Inf 5 mm Post 4 mm

Kupelian et al., IJROBP, 63(5):1463-68, 2005
Kupelian et al., IJROBP, 68(5):1424-30, 2007
Cleveland Clinic experience: 2.5 Gy x 28

TOXICITY UPDATE


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RT (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs), (range)</td>
<td>68, (48–84)</td>
</tr>
<tr>
<td>Median follow-up time (yrs), (range)</td>
<td>8.9, (0.13–11.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modality most common toxicities</th>
<th>GU toxicities no. (%)</th>
<th>GI toxicities no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>5 (2.9%)</td>
<td>8 (4.7%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>7 (4.0%)</td>
<td>4 (2.3%)</td>
</tr>
<tr>
<td>Retention</td>
<td>6 (3.5%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td></td>
<td>Rectal bleeding</td>
<td>Radiation Proctitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased freq.</td>
</tr>
</tbody>
</table>

How much longer follow is needed?
McGill Experience: 3 Gy x 22 (66 Gy)

Rene et al. IJROBP. 77: 805, 2010
Patel et al. IJROBP. 86: 534, 2013

N = 129, Median follow-up: 7.5 years

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gastrointestinal toxicity</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2/3</td>
</tr>
<tr>
<td>Temporary</td>
<td>50 (39)</td>
<td>44 (34)</td>
<td>35 (27)</td>
</tr>
<tr>
<td>Persistent</td>
<td>119 (92)</td>
<td>8 (6)</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Genitourinary toxicity</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Temporary</td>
<td>24 (18.5)</td>
<td>63 (49)</td>
<td>36 (28)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Persistent</td>
<td>106 (82)</td>
<td>21 (16)</td>
<td>6 (4.5)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

How much longer follow up is needed?
Potency after SBRT
Potency preservation following stereotactic body radiation therapy for prostate cancer

Olusola Obayomi-Davies¹, Leonard N Chen¹, Aditi Bhagat¹, Henry C Wright², Sunghae Uhm¹, Joy S Kim¹, Thomas M Yung¹, Siyuan Lei¹, Gerald P Batipps², John Pahira², Kevin G McGeagh², Brian T Collins¹, Keith Kowalczyk², Gaurav Bandi², Deepak Kumar³, Simeng Suy¹, Anatoly Dritschilo¹, John H Lynch² and Sean P Collins¹*

N=216
35–36.25 Gy
5 fractions

Average Sexual Domain Scores
Figure 2 Average individual EPIC sexual function scores at baseline and following SBRT for prostate cancer. (a) ability to have an erection—Question 8A of the EPIC-26; (b) ability to reach orgasm—Question 8B of the EPIC-26; (c) reliability of erections—Question 10 of the EPIC-26; (d) ability to function sexually—Question 11 of the EPIC-26. Thresholds for clinically significant changes in scores (± standard deviation above and below the baseline) are marked with dashed lines. EPIC scores range from 0-100 with higher values representing a more favorable health-related QoL.

Obayomi-Davies et al. Radiation Oncology 2013, 8:256
Sexual Bother

Figure 3 EPIC sexual bother at baseline and following SBRT for prostate cancer. Question 12 of the EPIC-26. Average sexual bother scores. Thresholds for clinically significant changes in scores (± standard deviation above and below the baseline) are marked with dashed lines. EPIC scores range from 0–100 with higher values representing a more favorable health-related QOL.

Figure 4 Pre- and post-treatment testosterone levels and EPIC hormonal scores. (a) Box-and-Whisker plot of total testosterone levels. The p values were from χ²-analysis with baseline testosterone levels. (b) Average EPIC hormonal scores. Thresholds for clinically significant changes in scores (± standard deviation above and below the baseline) are marked with dashed lines. EPIC scores range from 0–100 with higher values representing a more favorable health-related QOL.
HYPOFRACTIONATION PROTOCOLS: Phase III trials
Fox Chase Trial

76.0 at 2.0 Gy vs 70.2 at 2.7 Gy
n=151 n=152
Median follow-up 68 months
HYPOFRACTIONATION PROTOCOLS: Phase III trials
Fox Chase Trial

Biochemical Failure

Overall Survival
Prostate Ca Death

Pollack, JCO. 31: 3860-8, 2013
HYPOFRACTIONATION PROTOCOLS: Phase III trials
Fox Chase Trial

Pollack, JCO. 31: 3860-8, 2013
HYPOFRACTIONATION PROTOCOLS: Phase III trials
Fox Chase Trial

Pollack, JCO. 31: 3860-8, 2013

Hypofrac
IPSS >12

GU
Grade >2

P < .001
P = .668

Pollack, JCO. 31: 3860-8, 2013
HYPOFRACTIONATION TRIALS

CHHiP randomized trial

2002 and 2011 – UK
T1B–T3A N0 M0, PSA <30 ng/mL, estimated LN risk <30%

3 Phases: Total recruitment 3216 patients
Subset: No IGRT, standard margins
          IGRT, standard margins
          IGRT, tighter margins

Dose: 74 Gy vs 60 Gy vs 57 Gy
Fraction: 2 Gy 3 Gy 3 Gy

Acute toxicity analysis
N= 153 153 151

HYPOFRACTIONATION TRIALS

CHHiP randomized trial: Acute Toxicity


Prevalence
Acute Bowel Toxicity (RTOG scores)

Prevalence
Acute Bladder Toxicity (RTOG scores)

4 mos

4 mos
HYPOFRACTIONATION TRIALS

HYPRO randomized trial

Dutch Hypofractionation Trial - Aluwini et al. ESTRO 2013
N=820 Intermediate / high risk
Med FU: 43 months

<table>
<thead>
<tr>
<th>Dose</th>
<th>Standard</th>
<th>Hypofrac</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>78 Gy</td>
<td>64.6 Gy</td>
</tr>
<tr>
<td>2 Gy x 39</td>
<td>vs</td>
<td>3.4 Gy x 19</td>
</tr>
<tr>
<td>5 fx/wk</td>
<td></td>
<td>3 fx/wk</td>
</tr>
</tbody>
</table>

Late GU toxicity:
- Gr2: 34% vs 30%
- Gr3: 9% vs 15%

Late GU toxicity:
- Gr2: 19% vs 15%
- Gr3: 2% vs 2%

Late toxicity predictors: Acute toxicity, age, ADT use
THE CLEVELAND CLINIC EXPERIENCE: FIRST 770 PATIENTS

Biochemical Relapse Free Survival By Risk Group

Median follow-up: 45 months

ASTRO definition

Phoenix definition

Kupelian et al., IJROBP, 68(5):1424-30, 2007
Cleveland Clinic experience update: 2.5 Gy x 28

**DISEASE CONTROL**

70 Gy at 2.5 (N= 822, Med FU: 103 mo)

Comparison with 78 Gy at 2.0 (N=522, med FU: 71 mo)

<table>
<thead>
<tr>
<th></th>
<th>Hypo</th>
<th>Conv</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-yr bRFS rate</td>
<td>70%</td>
<td>65%</td>
</tr>
<tr>
<td>10-yr DM rate</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>10-yr PCSM rate</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>10-yr OS rate</td>
<td>72%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Weller et al. ASTRO 2013. Abstract 1013
High Dose IMRT Results - MSKCC

Long-term Survival and Toxicity in Patients Treated With High-Dose Intensity Modulated Radiation Therapy for Localized Prostate Cancer

Daniel E. Spratt, MD, Xin Pei, PhD, Josh Yamada, MD, Marisa A. Kollmeier, MD, Brett Cox, MD, and Michael J. Zelefsky, MD


Methods and Materials: Between August 1997 and December 2008, 1002 patients were treated to a dose of 86.4 Gy using a 5-7 field IMRT technique. Patients were stratified by prognostic risk group based on National Comprehensive Cancer Network risk classification criteria. A total of
Effectiveness of IMRT (even “high” dose modern IMRT) still being questioned

EBRT (IMRT) vs Brachytherapy
Comparison of Tumor Control and Toxicity Outcomes of High-dose Intensity-modulated Radiotherapy and Brachytherapy for Patients With Favorable Risk Prostate Cancer

Michael J. Zelefsky, Yosiya Yamada, Xin Pei, Margie Hunt, Gilad Cohen, Zhigang Zhang, and Marco Zaider


SBRT vs Brachytherapy: Efficacy?
MSKCC: Favorable risk patients
Effectiveness of IMRT (even “high” dose modern IMRT) still being questioned

EBRT (IMRT) vs Prostatectomy

Metastasis-free survival: IMRT vs Surgery

Zelefsky et al., JCO, 28, 1508-1513, 2010
EBRT: Effectiveness questions…

Metastasis-free survival: RP v RT
ALL PATIENTS

Need for technical improvement?
No image guidance during RT delivery

Zelefsky et al., JCO, 28, 1508-1513, 2010
EBRT: Improving Outcomes
IMAGE GUIDANCE

MSKCC: STARTED IGRT IN 2007
Less biochemical failures
Less toxicity (GU)

Zelefsky, IJROBP, 84, 125-129, 2012
RADIOTHERAPY FOR LOCALIZED PROSTATE CA

TECHNIQUE OF RADIATION DELIVERY

IMRT
RADIOTHERAPY FOR
LOCALIZED PROSTATE CA

HYPOFRACTIONATION
(including SBRT)
CONCLUSIONS –
IMRT for Low risk Prostate Ca

RT dose is important to control prostate cancer, even low risk diseases

RT technique is important to decrease toxicity:
Need IMRT

Current RT doses (conventionally fractionated) might not be enough to control disease in the long term compared to brachytherapy.
Brachytherapy: Quality

VA's prostate treatment woes began at Penn Prior to the VA program, leading brachytherapists said the Penn doctors performing the radioactive seed implants lacked the proper skills and safeguards.
Figure 1:

Numbers of prostate seed implants reported as MEs to regulatory agencies (1999 – 2012). The peak at year 2008 is largely due to the investigation to PVAMC where 97 out of 116 prostate seed implants were classified as ME.
Prostate seed implant ME categories based on reporting methods: Type I – incorrect source strength/planning errors; Type II – seed/needle misplacement or excessive dose to normal tissue/organ; and Type III – discrepancy in dose to target.
PROSTATE SBRT CRITIQUES: No long term follow-up…

“New and unproven”

• Efficacy? What’s an acceptable follow-up period? 5, 10, 15 years?

• Toxicity: Is 5 years follow-up sufficient?
Brachytherapy was once “new” and “unproven”...

**First case: ~1985**

Transperineal ultrasound-guided implantation of the prostate: morbidity and complications.
Blasko JC, Ragde H, Grimm PD.

Should brachytherapy be considered a therapeutic option in localized prostate cancer?
Blasko JC, Ragde H, Luse RW, Sylvester JE, Cavanagh W, Grimm PD.

Prostate brachytherapy: importance of technique
Blasko JC, Ragde H, Grimm PD, Cavanagh W.
NCCN risk groups:

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>T1c-2a, GS ≤ 6 and PSA &lt; 10</td>
</tr>
<tr>
<td>Intermediate</td>
<td>T2b-c, or GS 7, or 10-20</td>
</tr>
<tr>
<td>High</td>
<td>T3a, GS 8-10, or &gt; 20</td>
</tr>
<tr>
<td>Very High</td>
<td>T3b-4 or N1</td>
</tr>
</tbody>
</table>
Intensity Modulation is a radiation delivery technique: IMRT

Image Guidance is the use of imaging in the treatment room: IGRT

Hypofractionation, including SBRT, is a radiation therapy schedule; use of higher than conventional doses per fraction.
IMRT and IGRT aim at improving radiotherapy delivery:

- Enable dose escalation
- Reduce normal tissue dose: Reduce toxicity

Hypofractionation aims at getting a higher cancer cell kill through an assumed increased radio-sensitivity of prostate cancer cells to large fraction sizes.
### 2009 AJCC Staging System

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1a-2a, GS 6, PSA &lt;10 T1-2a</td>
<td>Low risk</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b or GS 7 or PSA 10-20</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>IIB</td>
<td>T2c or GS 8-10 or PSA ≥ 20</td>
<td>High risk</td>
</tr>
<tr>
<td>III</td>
<td>T3a: ECE / T3b:SV</td>
<td>Locally-advanced</td>
</tr>
<tr>
<td>IV</td>
<td>T4, metastases</td>
<td>Mets T4, N1, M1</td>
</tr>
</tbody>
</table>
Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group

Peter Grimm¹, Ignace Billiet², David Bostwick³, Adam P. Dicker⁴, Steven Frank⁵, Jos Immerzeel⁶, Mira Keyes⁷, Patrick Kupelian⁸, W. Robert Lee⁹, Stefan Machtens¹⁰, Jyoti Mayadev¹¹, Brian J. Moran¹², Gregory Merrick¹³, Jeremy Millar¹⁴, Mack Roach¹⁵, Richard Stock¹⁶, Katsuto Shinohara¹⁵, Mark Scholz¹⁷, Ed Weber¹⁸, Anthony Zietman¹⁹, Michael Zelefsky²⁰, Jason Wong²¹, Stacy Wentworth²², Robyn Vera²³ and Stephen Langley²⁴

Low Risk

Importance of Dose
PSA failure by Treatment modality

Localized Prostate Cancer – Radiotherapy Today

Improved Cure Rates: Dose escalation
Doses in the 75-85 Gy range
10yr bRFS - Low risk: >95%
- Int risk: >80%

Decreased toxicity
Grade 3 toxicities < 5%

Convenience / Cost
Hypofractionation / SBRT / Brachytherapy
RADIOTHERAPY FOR LOCALIZED PROSTATE CA

RT DOSE
HIGHER THAN STANDARD RADIATION DOSES (≥72 GY) WITH OR WITHOUT ANDROGEN DEPRIVATION IN THE TREATMENT OF LOCALIZED PROSTATE CANCER

PATRICK A. KUPELIAN, M.D.,* DASARAHALLY S. MOHAN, M.D.,* JANICE LYONS, M.D.,* ERIC A. KLEIN, M.D.,† AND CHANDANA A. REDDY, M.S.*

Departments of *Radiation Oncology and †Urology, Cleveland Clinic Foundation, Cleveland, OH

Fig. 4. bRFS by radiation dose grouped in three dose levels; <72 Gy, 72.0 to 75.0 Gy, and 78.0 Gy. Symbols represent censored events.
RT DOSE: Randomized Trials

MDACC Trial:

MGH/LLUMC (Proton Trial):

Dutch Multi-institutional Trial:

UK (MRC) Trial:
## RT DOSE: Randomized Trials

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDACC Trial (Pollack):</strong></td>
<td>70 vs 78 Gy</td>
<td>50 vs 73%</td>
<td>bNED</td>
<td>at 10 years</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>MGH/LLUMC (Proton Trial):</strong></td>
<td>70 vs 79.2 Gy</td>
<td>72 vs 93%</td>
<td>bNED</td>
<td>at 10 years</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Low risk</td>
<td>58 vs 70%</td>
<td>p=0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dutch Multi-institutional Trial:</strong></td>
<td>68 vs 78 Gy</td>
<td>45 vs 56%</td>
<td>bNED</td>
<td>at 7 years</td>
<td>0.03</td>
</tr>
<tr>
<td>(some ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UK (MRC) Trial:</strong></td>
<td>64 vs 74 Gy</td>
<td>71 vs 60%</td>
<td>bNED</td>
<td>at 5 years</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(some ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BENEFIT FROM DOSE ESCALATION

Questions

Who benefits?

Magnitude of benefit?
BENEFIT FROM DOSE ESCALATION

Literature Review;
Series reported up to 2008
External beam RT, at least 2 dose groups
No brachytherapy
No hypofractionation
>200 patients

Data adapted from Diez et al. IJROBP 2010
### BENEFIT - LOW RISK

#### Diez et al. IJROBP 2010

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Gamma IV, Fixed, 95% CI</th>
<th>Gamma IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-randomized studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zelensky 1998</td>
<td>3.6%</td>
<td>0.60 [-2.34, 3.54]</td>
<td></td>
</tr>
<tr>
<td>Hanks 2000</td>
<td>3.6%</td>
<td>4.50 [1.56, 7.44]</td>
<td></td>
</tr>
<tr>
<td>Lyons 2000</td>
<td>1.4%</td>
<td>5.40 [0.70, 10.10]</td>
<td></td>
</tr>
<tr>
<td>Pollack 2000</td>
<td>2.5%</td>
<td>3.10 [-0.43, 6.63]</td>
<td></td>
</tr>
<tr>
<td>Kupelian 2005</td>
<td>9.1%</td>
<td>0.26 [-1.58, 2.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20.1%</td>
<td>1.78 [0.54, 3.02]</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zietman 2005</td>
<td>29.7%</td>
<td>1.70 [0.68, 2.72]</td>
<td></td>
</tr>
<tr>
<td>Peeters 2006</td>
<td>23.9%</td>
<td>-0.85 [-1.99, 0.29]</td>
<td></td>
</tr>
<tr>
<td>Dearmaley 2007</td>
<td>22.3%</td>
<td>0.11 [-1.07, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Kuban 2008</td>
<td>4.1%</td>
<td>3.00 [0.26, 5.74]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>79.9%</td>
<td>0.56 [-0.06, 1.18]</td>
<td></td>
</tr>
</tbody>
</table>

Test for subgroup differences: $\chi^2 = 2.97$, df = 1 ($P = 0.08$), $I^2 = 66.3\%$
### BENEFIT - INTERMEDIATE-HIGH RISK

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Gamma IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-randomized studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zelefsky 1998</td>
<td>4.2%</td>
<td>2.50 [1.09, 3.91]</td>
</tr>
<tr>
<td>Lyons 2000</td>
<td>3.2%</td>
<td>3.10 [1.47, 4.73]</td>
</tr>
<tr>
<td>Pollack 2000</td>
<td>2.5%</td>
<td>3.10 [1.28, 4.92]</td>
</tr>
<tr>
<td>Hanks 2000</td>
<td>10.8%</td>
<td>1.30 [0.42, 2.18]</td>
</tr>
<tr>
<td>Kupelian 2005</td>
<td>12.4%</td>
<td>0.95 [0.13, 1.77]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33.1%</td>
<td>1.63 [1.13, 2.14]</td>
</tr>
</tbody>
</table>

| **Randomized studies**    |        |                         |
| Zietman 2005              | 4.3%   | 1.60 [0.21, 2.99]       |
| Peeters 2006              | 27.8%  | 0.65 [0.10, 1.20]       |
| Dearnaley 2007            | 32.3%  | 0.90 [0.39, 1.41]       |
| Kuban 2008                | 2.5%   | 3.40 [1.56, 5.24]       |
| Subtotal (95% CI)         | 66.9%  | 0.93 [0.58, 1.29]       |

Test for subgroup differences: \( \chi^2 = 4.94, \text{df} = 1 (P = 0.03), \text{I}^2 = 79.8\% \)
EFFECT OF INCREASING RADIATION DOSES ON LOCAL AND DISTANT FAILURES IN PATIENTS WITH LOCALIZED PROSTATE CANCER

Patrick A. Kupelian, M.D.,* Jay Ciezki, M.D.,† Chandana A. Reddy, M.S.,† Eric A. Klein, M.D.,‡ and Arul Mahadevan, M.D.†

*Department of Radiation Oncology, M.D. Anderson Cancer Center Orlando, Orlando, FL; †Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH; and ‡Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, Cleveland, OH

919 Stage T1-T3N0M0 - RT alone - treated between 1986 and 2000

<table>
<thead>
<tr>
<th>RT dose</th>
<th>N</th>
<th>Median Dose</th>
<th>Median FU (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>919</td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>&lt;72 Gy</td>
<td>552</td>
<td>68 Gy</td>
<td>112</td>
</tr>
<tr>
<td>&gt;72 &lt;82 Gy</td>
<td>215</td>
<td>78 Gy</td>
<td>94</td>
</tr>
<tr>
<td>&gt;82 Gy</td>
<td>152</td>
<td>83 Gy</td>
<td>65</td>
</tr>
</tbody>
</table>
IMPACT OF INCREASED DOSE

919 Stage T1-T3N0M0 - RT alone - treated between 1986 and 2000

Kupelian et al. IJROBP. 71, 6–22, 2008
LONG-TERM FAILURE PATTERNS AND SURVIVAL IN A RANDOMIZED DOSE-ESCALATION TRIAL FOR PROSTATE CANCER. WHO DIES OF DISEASE?

Deborah A. Kuban, M.D.,* Lawrence B. Levy,* M. Rex Cheung, M.D. Ph.D.,*
Andrew K. Lee, M.D., M.P.H.,* Seungtaek Choi, M.D.,* Steven Frank, M.D.,* and Alan Pollack, M.D., Ph.D.†

Need Better Local Therapy: Doses >80 Gy?
Prostate Biopsy: Local Failure Endpoint
Zelefsky et al., MSKCC

3 mos AD: 29%  Median RT dose: 76 Gy (range: 65-81 Gy)

<table>
<thead>
<tr>
<th>RT Dose</th>
<th>Positive biopsies</th>
<th>Positive biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>64.8 Gy</td>
<td>52%</td>
<td>No ADT 34%</td>
</tr>
<tr>
<td>70.2 Gy</td>
<td>34%</td>
<td>ADT 11%</td>
</tr>
<tr>
<td>75.6 Gy</td>
<td>24%</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>81 Gy</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

NO IMAGE GUIDANCE:
GEOGRAPHIC MISS versus INSUFFICIENT DOSE?
Clinical Investigation: Genitourinary Cancer

Preliminary Toxicity Analysis of 3-Dimensional Conformal Radiation Therapy Versus Intensity Modulated Radiation Therapy on the High-Dose Arm of the Radiation Therapy Oncology Group 0126 Prostate Cancer Trial

Jeff M. Michalski, MD, * Yan Yan, MD, MS, † Deborah Watkins-Bruner, PhD, ‡ Walter R. Bosch, DSc, * Kathryn Winter, MS, † James M. Galvin, DSc, § Jean-Paul Bahary, MD, ‖ Gerard C. Morton, MB, ¶ Matthew B. Parliament, MD, # and Howard M. Sandler, MD**


IMRT vs 3DRT
Subset analysis:
High dose Arm of RTOG 0126
IMRT vs 3DRT: RTOG 0126 - Acute Toxicity

Acute GI/GU Toxicity

Grade 2+

15.1%
P = 0.042

Grade 2+ GU/GI

9.7%
P = 0.25

Grade 2+ GI

P = 0.14

Grade 3+

P = 0.45

P = 0.95

P = 0.75

IMRT vs 3DRT: RTOG 0126 - Late GI Toxicity

Late Grade 2+ GI Toxicity

IMRT vs 3DRT: RTOG 0126 - Late GI Toxicity

Late Grade 3+ GI Toxicity

Long-term Survival and Toxicity in Patients Treated With High-Dose Intensity Modulated Radiation Therapy for Localized Prostate Cancer

Daniel E. Spratt, MD, Xin Pei, PhD, Josh Yamada, MD, Marisa A. Kollmeier, MD, Brett Cox, MD, and Michael J. Zelefsky, MD


Methods and Materials: Between August 1997 and December 2008, 1002 patients were treated to a dose of 86.4 Gy using a 5-7 field IMRT technique. Patients were stratified by prognostic risk group based on National Comprehensive Cancer Network risk classification criteria. A total of
Long-term Survival and Toxicity in Patients Treated With High-Dose Intensity Modulated Radiation Therapy for Localized Prostate Cancer

Daniel E. Spratt, MD, Xin Pei, PhD, Josh Yamada, MD, Marisa A. Kollmeier, MD, Brett Cox, MD, and Michael J. Zelefsky, MD

(c)

![Graph showing prostate cancer specific mortality rate over years for different risk categories.]

Probabilty

0.0  0.2  0.4  0.6

Grade 2+ GU Toxicity

Grade 2+ GI Toxicity

Years

0  2  4  6  8  10

Fig. 2. Late grade $\geq 2$ GI and GU toxicity actuarial outcomes.
EBRT: Improving Outcomes
IMAGE GUIDANCE

MSKCC: STARTED IGRT IN 2007
Less biochemical failures
Less toxicity (GU)

Zelefsky, IJROBP, 84, 125-129, 2012
EBRT (IMRT) vs Brachytherapy

Brachytherapy more effective?
Comparison of Tumor Control and Toxicity Outcomes of High-dose Intensity-modulated Radiotherapy and Brachytherapy for Patients With Favorable Risk Prostate Cancer

Michael J. Zelefsky, Yoshliya Yamada, Xin Pei, Margie Hunt, Gilad Cohen, Zhigang Zhang, and Marco Zaider

Figure 1. PSA relapse-free survival for favorable risk patients. PSA relapse-free survival rate for brachytherapy versus IMRT at 7 years was 95% and 89%, respectively ($P = .004$).
Brachytherapy more effective?

Comparison of Tumor Control and Toxicity Outcomes of High-dose Intensity-modulated Radiotherapy and Brachytherapy for Patients With Favorable Risk Prostate Cancer

Michael J. Zelefsky, Yoshiya Yamada, Xin Pei, Margle Hunt, Gilad Cohen, Zhigang Zhang, and Marco Zalder


Table 2. Univariate and multivariate analyses for predictors of PSA relapse

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
<th>Multivariate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment mode (brachytherapy vs EBRT)</td>
<td>0.43</td>
<td>.005</td>
<td></td>
<td></td>
<td>0.416</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Pretreatment PSA</td>
<td>1.18</td>
<td>.027</td>
<td></td>
<td></td>
<td>1.18</td>
<td>.025</td>
<td></td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>0.966</td>
<td>.09</td>
<td></td>
<td></td>
<td>0.955</td>
<td>.025</td>
<td></td>
</tr>
<tr>
<td>Age (&gt;65 vs ≤65 y)</td>
<td>0.767</td>
<td>.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy (yes vs no)</td>
<td>0.783</td>
<td>.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; other abbreviations as in Table 1.
EBRT (IMRT) vs Brachytherapy

IMRT less toxic?
A COMPARISON OF ACUTE AND CHRONIC TOXICITY FOR MEN WITH LOW-RISK PROSTATE CANCER TREATED WITH INTENSITY-MODULATED RADIATION THERAPY OR $^{125}$I PERMANENT IMPLANT

THOMAS N. EADE, MB.CH.B., F.R.A.N.Z.C.R.,* ERIC M. HORWITZ, M.D.,* KAREN RUTH, M.S.,† MARK K. BUYYOUNOSKI, M.D., M.S.,* DAVID J. D’AMBROSIO, M.D.,* STEVEN J. FEIGENBERG, M.D.,* DAVID Y. T. CHEN, M.D.,‡ AND ALAN POLLACK, M.D., PH.D.*


Grade 2+ GI

Grade 2+ GU
IMRT less toxic?

Comparison of Tumor Control and Toxicity Outcomes of High-dose Intensity-modulated Radiotherapy and Brachytherapy for Patients With Favorable Risk Prostate Cancer

Michael J. Zelefsky, Yoshiya Yamada, Xin Pel, Margle Hunt, Gilad Cohen, Zhigang Zhang, and Marco Zalder


Table 3. Late toxicity outcomes

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Brachytherapy (n = 448)</th>
<th>EBRT (n = 281)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal late toxicity (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>23 (5.1)</td>
<td>4 (1.4)</td>
<td>.018</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5 (1.1)</td>
<td>0 (0.0)</td>
<td>.19</td>
</tr>
<tr>
<td>Genitourinary late toxicity (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>70 (15.6)</td>
<td>12 (4.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>10 (2.2)</td>
<td>4 (1.4)</td>
<td>.62</td>
</tr>
</tbody>
</table>

EBRT, external beam radiotherapy.

P values determined from binomial tests considering overall number of events in each group.
FCCC Hypofractionation Trial – Late Toxicity

GU Late Toxicity:
  Few Grade 3 GU events
  Majority of Gr 2 GU events were “incontinence/urgency”
  Pre-RT urinary status: Important predictor of GU toxicity

Pollack, JCO. 31: 3860-8, 2013

Physician-Reported versus Patient-Reported Outcomes:
Similar patient-reported QOL measures at 2 years between HIMRT and CIMRT.
Turaka et al. ASTRO 2010, Abstract 142
Hypofractionated RT For Localized Prostate Cancer

- Efficacy
- Dose Equivalence (biologic dose-escalation?)
- Toxicity (late)
- Patient convenience
- Shorter courses (vs fractionated RT)
- Non-invasive (vs RP or Brachytherapy)
- Economics: Cost versus Revenue
CONVENTIONAL FRACTIONATION  
versus  
HYPOFRACTIONATION  
versus  
STEREOTACTIC BODY RADIOSURGERY (SBRT)

<table>
<thead>
<tr>
<th>SBRT</th>
<th>Hypofractionation</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of fractions</td>
<td>~35</td>
<td>45</td>
</tr>
<tr>
<td>Fraction Size</td>
<td>&gt;7 Gy</td>
<td>1.8-2.0 Gy</td>
</tr>
<tr>
<td>Total Dose</td>
<td>~35-50 Gy</td>
<td>~50-75 Gy</td>
</tr>
<tr>
<td>Biological Rationale</td>
<td>Ablative??</td>
<td>Normal tissue sparing</td>
</tr>
</tbody>
</table>
CONCLUSIONS

Prostate SBRT is a faster, cheaper and better way of treating prostate cancers. It is the obvious evolution of EBRT for localized prostate cancer.

SBRT is considered an acceptable option for low and intermediate risk patients.

Late rectal toxicity is minimal with hypofractionated RT (including SBRT).

Urinary toxicity is pronounced early after RT and is self limited.