# Hypofractionation and SBRT for Prostate Cancer

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# Disclosures

Accuray, Advisory Board

# Agenda

- Rationale for Hypofx for Prostate Ca
- Hypofx Prospective and RCTs
- SBRT
  - Virtual HDR?  How does it compare?
  - Retrospective Series: Biochemical Control
  - QOL Series, Cost Effectiveness Models
- ASTRO/NCCN and RCTs

# Dose Escalation, 4 RCT + 5 Retrospective

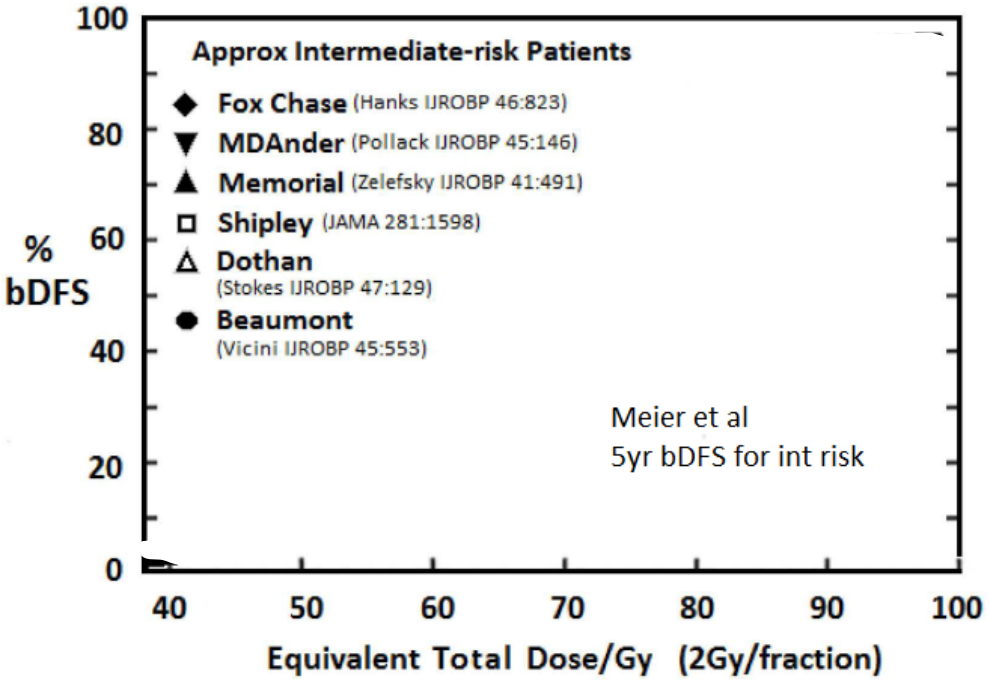
- Improved bDFS→ *cancer control*
- Toxicity limited with
  - better treatment delivery (3DCRT→ IMRT) and targeting (IMRT→ IGRT)

Table 1. Summary of the data extracted from 9 included studies

| Study | Randomized | No. of patients | Dose (Gy) Low (median) | Int. (median) | High (median) | Follow-up Median (y) | Failure rate reported (y) | Method of analysis* | bNED (%) Risk group | Low dose | Int. dose | High dose | bNED definition† |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zelefsky 1998 | — | 530 | 70.2 | | 75.6 | 3 | 5 | KM | Low | 84 | | 95 | ASTRO |
| | | | | | | | | KM | Int. | 55 | | 79 | |
| | | | | | | | | KM | High | 19 | | 53 | |
| Hanks 2000‡ | — | 618 | 70 (<10 f) | | 73 (<10 f) | 4.4 | 5 | KM | <10 f | 77 | | 89 | ASTRO |
| | | | | | | | | | <10 unf | 70 | | 92 | |
| | | | | | | | | | 10–19.9 f | 72 | | 86 | |
| | | | 73 (rest) | | 78 (rest) | | | | 10–19.9 | 51 | | 82 | |
| | | | | | | | | | ≥20 f | 23 | | 63 | |
| | | | | | | | | | ≥20 unf | 29 | | 26 | |
| Pollack 2000 | — | 1127 | 66 | 70 | 78 | 4.3 | 4 | KM | Low | 73 | 85 | 84 | ASTRO |
| | | | | | | | | | Int.-high | 31 | 51 | 68 | |
| Lyons 2000 | — | 738 | 68.4 | | 74 | 3.4 | 5 | HR | Low | 81 | | 98 | ASTRO |
| | | | | | | | | KM | Int.-high | 41 | | 75 | |
| Zietman 2005 | + | 393 | 70.2 | | 79.2 | 5 | 5 | KM | Low | 60 | | 81 | ASTRO |
| | | | | | | | | | Int.-high | 63 | | 80 | |
| Kupelian 2005 | — | 1325 | 68.4 | | 75.6 | 5.8 | 5 | KM point | Low | 75 | | 79 | ASTRO |
| | | | | | | | | KM | Int. | 63 | | 72 | |
| | | | | | | | | KM point | High | 38 | | 46 | |
| Peeters 2006 | + | 664 | 68 | | 78 | 4.2 | 5 | HR | Low | 88 | | 84 | ASTRO |
| | | | | | | | | | Int. | 64 | | 79 | |
| | | | | | | | | | High | 48 | | 66 | |
| Dearnaley 2007 | + | 843 | 64 | | 74 | 5 | 5 | HR | Low | 79 | | 85 | PSA >2 |
| | | | | | | | | | Int. | 70 | | 79 | And PSA |
| | | | | | | | | | High | 43 | | 57 | >nadir + 50% |
| Kuban 2008 | + | 301 | 70 | | 78 | 8.7 | 8 | KM | Low | 63 | | 88 | Phoenix |
| | | | | | | | | | Int. | 76 | | 86 | |
| | | | | | | | | | High | 26 | | 63 | |

Diez et al, IJROBP 2010

# Conceptualized model




$$S = e^{-(\alpha D - \beta D^2)}$$

$$BED = nd(1 + \frac{d}{\alpha / \beta})$$

- Cell Survival
  - Linear Quadratic model
  - Sigmoidal curve

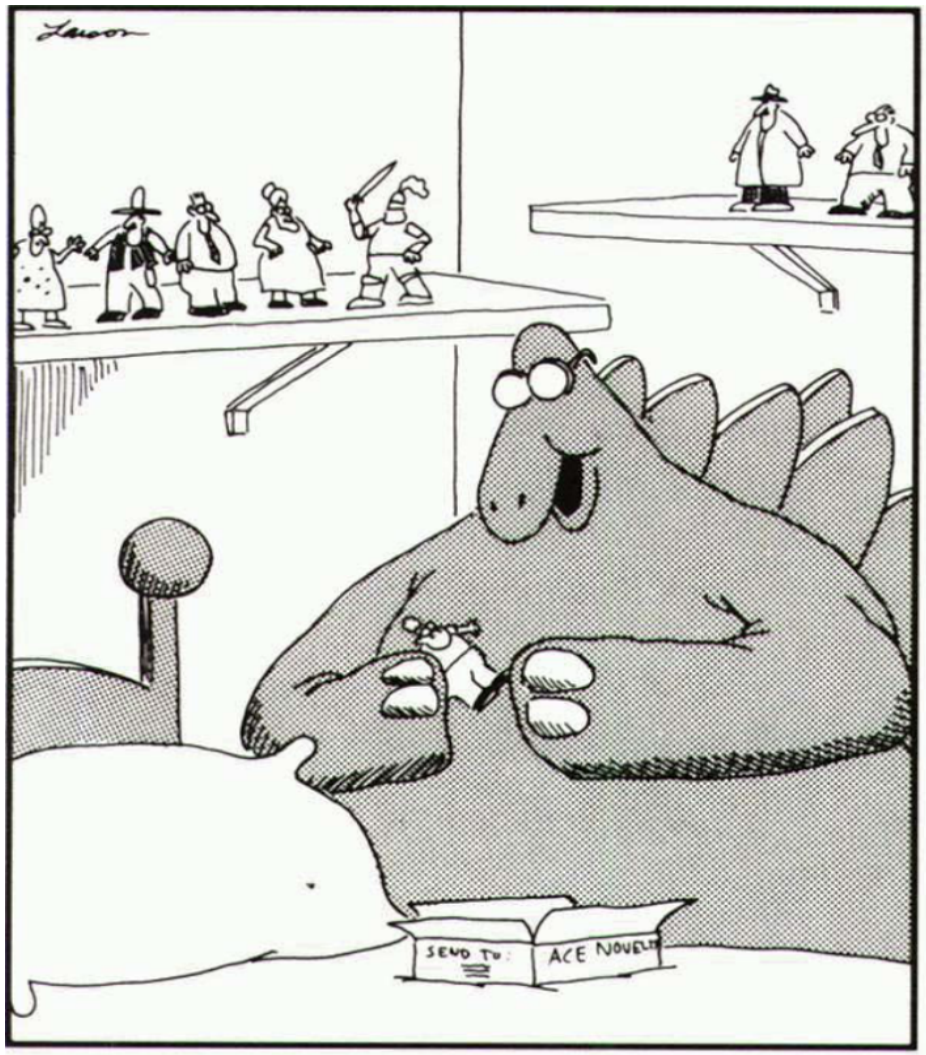
- Historically, increase dose by increasing the *number of fractions*
  - *With low dose per fraction → widen therapeutic index*
  - use 1.8-2.0Gy/fx
    - Because of α and β

# Radiobiologic Rationale

$$S = e^{-(\alpha D - \beta D^2)}$$

$$BED = nd(1 + \frac{d}{\alpha/\beta})$$

α β η θ ν ξ τ υ α β η θ ν ξ τ υ




ε ζ λ μ ρ σ φ ω ε ζ λ μ ρ σ φ ω

"Oh, boy! The 'Nerd'! ... Now my collection's complete!"

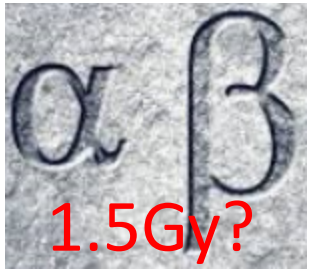
# Radiobiologic Rationale

$$S = e^{-(\alpha D - \beta D^2)}$$

$$BED = nd(1 + \frac{d}{\alpha/\beta})$$

- Dose response of tumors/tissue to radiation→ α/β
  - High α/β (10) = little sensitivity to dose/fx
    - ie: most tumors, early responding normal tissues (mucosa, skin)
  - Low α/β (<5Gy) = greater sensitivity to dose/fraction
    - ie: late responding tissues
- Fractionation: use of many fractions of low dose radiation
  - Since most tumors not sensitive to fraction size whereas normal tissues are
    - Tumor control while minimizing long term toxicity
- Prostate cancer cells diff from most epithelial tumors
  - Lower α/β (~1.5)= higher degree of sensitivity to dose/fraction
  - Advantage of prostate cancer's unique radiobiology
    - Deliver fewer fractions with a larger dose
      - Increase BED to tumor and not normal tissues
      - Enhance Therapeutic ratio

| Delivery | Prostate Cancer (α/β = 1.5Gy) | Equiv Dose in 1.8Gy/fx | Late Responding Tissue (α/β = 3Gy) | Equiv Dose in 1.8Gy/fx |
|---|---|---|---|---|
| IMRT: 81Gy, 1.8Gy/fx x 45 → 5-10mm expansion | 178.2Gy | 81Gy | 129.6Gy | 81Gy |
| SBRT: 35Gy, 7.0Gy/fx x 5 → 3-5mm expansion | 198.3Gy | 90.2Gy | 116.7Gy | 72.9Gy |




**Summary of α/β values**

| Ref | α/β (Gy) | 95% Confidence interval |
|---|---|---|
| Brenner and Hall [8] | 1.5 | [0.8,2.2] |
| Arcangeli 2010 | −0.45 | [−1.31, 0.41]* |
| Leborgne 2011[10] | 1.86 | [0.7, 5.1] |
| Lukka 2005[11] | 2.02 | [−1.03, 5.07]* |
| Valdagni 2005 | 7.44 | [−13.97, 28.86]* |
| Yeoh 2011[12] | 0.13 | [−1.06, 1.31]* |
| Vogelius 2013 [13] | −0.07 | [−0.73 – 0.59] |
| Williams 2007 [14] | 2.6 | [0.9, 4.8] |
| Fowler 2001 [15] | 1.49 | [1.25, 1.76] |
| Brenner 2002 [16] | 1.2 | [0.03, 4.1] |

(*Taken from Vogelius et al. [13]).

Clinical results from various treatment modalities support the hypothesis of a low α/β ratio. Shown are the biologically equivalent doses at 1.8 Gy per fraction for α/β ratios of 10, 3 and 1.5 Gy.

| Study | Treatment | BED α/β = 10 Gy | BED α/β = 3 Gy | BED α/β = 1.5 Gy | Biochemical Control Rate |
|---|---|---|---|---|---|
| Kupelian *et al.* (14) | IMRT, 70 Gy in 28 fractions | 72 Gy | 81 Gy | 84 Gy | 95% for low-risk; 85% for intermediate-risk patients at 7-years |
| Cahlon *et al.* (21) | IMRT, 86.4 Gy in 48 fractions | 86.4 Gy | 86.4 Gy | 86.4 Gy | 98%, 85% and 70% for low-, intermediate-, and high-risk patients at 5-years |
| Martinez *et al.* (22) | HDR, 38 Gy in 4 fractions or 42 Gy in 6 fractions | 63 Gy | 97 Gy | 125 Gy | 91% at 5-years |
| Demanes *et al.* (23) | HDR + EBRT, range of doses | 58-85 Gy | 70-95 Gy | 87-120 Gy | 87% and 69% for intermediate- & high-risk patients at 10-years |
| King *et al.* (8) | SBRT, 36.25 Gy in 5 fractions | 52 Gy | 78 Gy | 96 Gy | 100% at 33 months |
| Katz *et al.* (10) | SBRT, 35 Gy in 5 fractions | 50 Gy | 72 Gy | 92 Gy | 100% at 30 months |
| Katz *et al.* (38) | EBRT, 45 Gy in 25 fractions, plus SBRT 18-21 Gy in 3 fractions | 69-76 Gy | 77-89 Gy | 88-98 Gy | 92.5% for intermediate-risk<br>79% for high-risk |

# Hypofx and SBRT

- Hypofractionated Radiation
  - Early stage breast cancer
  - Melanoma
- SBRT
  - Early stage NSCLC
  - CNS
    - Brain mets→ SRS/SBRT→ Standard option
    - Meningioma
    - Adenomas
  - Pancreatic cancer
  - Colorectal oligometastatic hepatic mets

# Benefits/Risks of Hypofx

- Benefits
  - Better access to care
  - Shorter course→ improved compliance
  - More cost-effective
  - Higher BED→ widen therapeutic index
  - Phase 3 Data is Matur$_{(e)}$ing
- Downside
  - Increased reliance on planning and tx technology to deliver high doses accurately and safely
    - Machine variability
  - long-term toxicity continues to evolve

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- Hypofx Prospective and RCTs
- SBRT
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  - Retrospective Series: Biochemical Control
  - QOL Series, Cost Effectiveness Models
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# Prospective trials of hypo-fx

| Study | Median FU, | Risk GS | Technique | Regimen | BED | n | Outcome | Toxicity |
|---|---|---|---|---|---|---|---|---|
| Lukka et al. [15] | 68 | | | | | | | Gr ≥3 2% (NS) |
| Yeoh et al. [17] | 90 | | | | | | | Gr ≥3 1%<br>Late GU; HR: 1.58 (95% CI, 1.01–2.47) favoring hypofractionation |
| Dearnaley et al. [18] | 51 | | | | | | | Gr ≥2 GU 0% (NS)<br>Gr ≥2 GI 1% (NS)<br><br>Gr ≥2 GU 2%<br>Gr ≥2 GI 4%<br>Gr ≥2 GU 2%<br>Gr ≥2 GI 4% |
| Kuban et al. [14]; Hoffman et al. [19] | 60 | | | | | | | 5 yr Gr ≥2 GU 16% (NS)<br>5 yr Gr ≥2 GI 10% (NS)<br><br>5 yr Gr ≥2 GU 17%<br>5 yr Gr ≥2 GI 5% |
| Arcangeli et al. [12,13] | 70 | | | | | | | 3 yr Gr ≥2 GU 16% (NS)<br>3 yr Gr ≥2 GI 17% (NS) |
| | | | | | | | | 5 yr Gr ≥2 GI 9% |

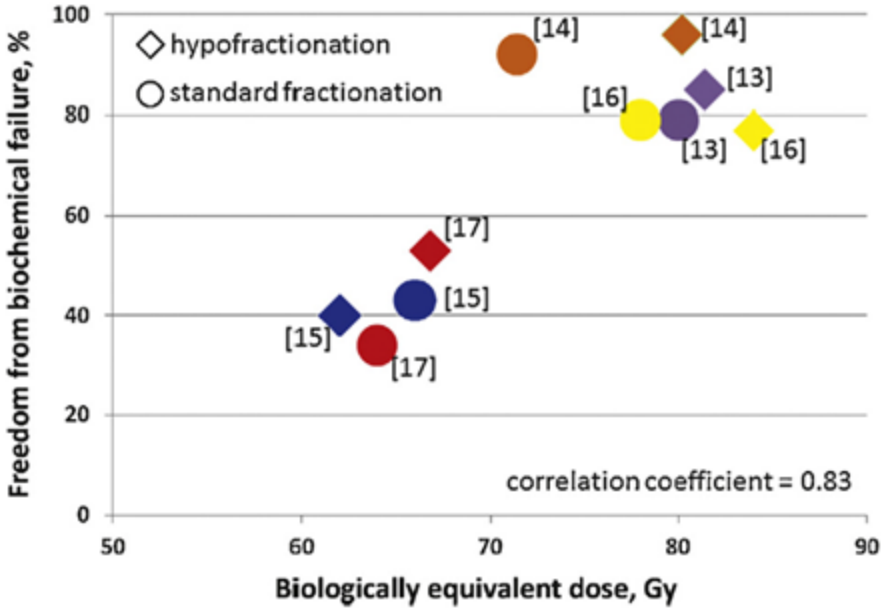



**Fig. 2 – Relationship between biologically equivalent dose (calculated to be equivalent in 2-Gy fractions using an α/β of 1.5 Gy) and biochemical outcome for both arms of the six randomized phase 3 studies of moderate hypofractionation and standard fractionation.**

- moderate hypofx→ predominantly low and int risk dz
- similar biochem control and late grade 2 + toxicities

Koontz et al, EAU, 2015 Review

# RCT's for Hypo-fx

ASTRO: 2015→ Present

| Study | 'Longer' Arm | 'Shorter' Arm | Efficacy at 5 years | Late Toxicity |
|---|---|---|---|---|
| **CHHiP** | 37fx/2.0Gy | 20fx/3.0Gy | Similar | Similar |
| **PROFIT** | 39fx/2.0Gy | 20fx/3.0Gy | Similar | Similar |
| **NRG 0415** | 41fx/1.8Gy | 28fx/2.5Gy | Similar | Small↑ GU/GI |
| **HYPRO** | 39fx/2.0 Gy | 19fx/3.4Gy | Similar | ↑GU |

2015 ASTRO
Plenary session

2016 ASTRO update

**RTOG 0415**

**A PHASE III RANDOMIZED STUDY OF HYPOFRACTIONATED 3D-CRT/IMRT VERSUS CONVENTIONALLY FRACTIONATED 3D-CRT/IMRT IN PATIENTS WITH FAVORABLE-RISK PROSTATE CANCER**

**SCHEMA**

**STRATIFY**

**Gleason Score**
1. Gleason 2-4
2. Gleason 5-6

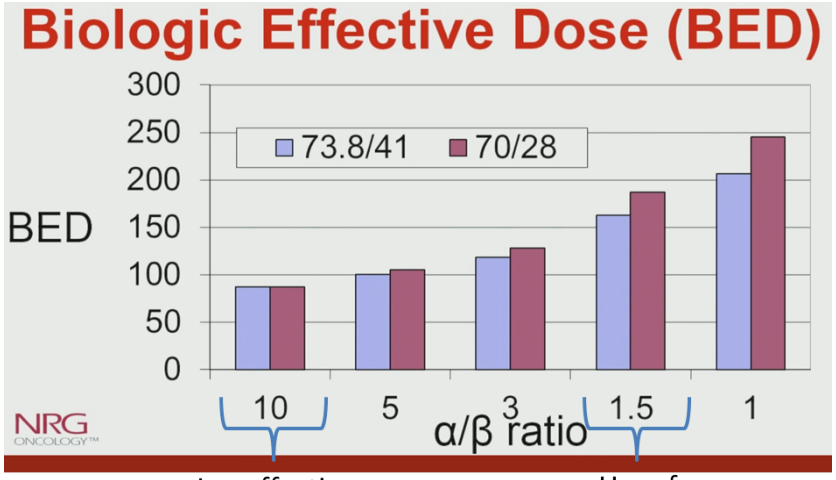
**PSA**
1. < 4 ng/mL
2. 4- < 10 ng/mL

**Radiation Modality**
1. 3D-CRT
2. IMRT

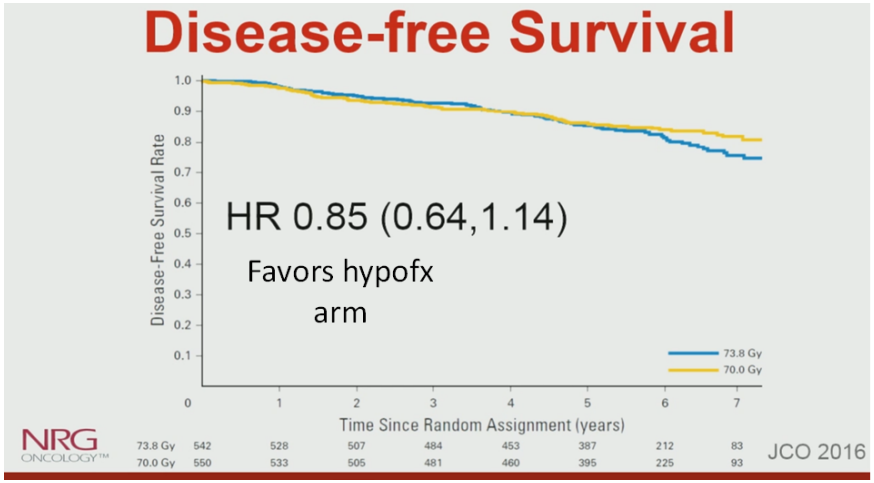
**RANDOMIZE**

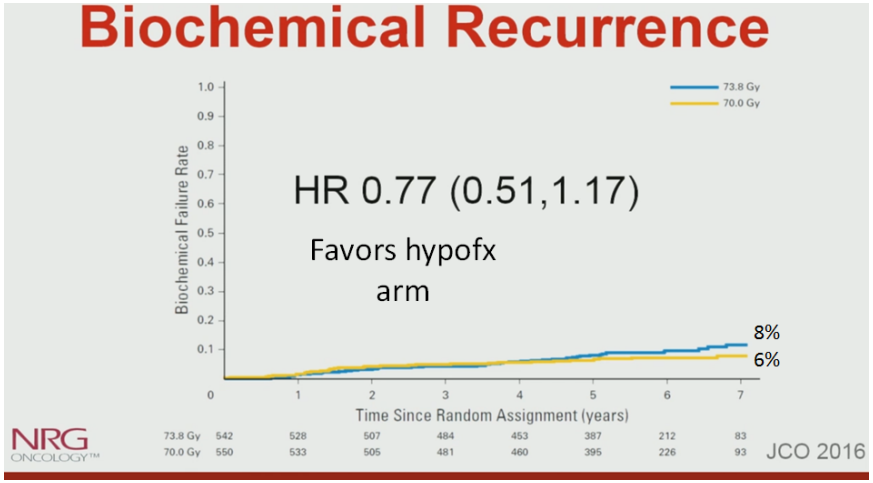
**Arm 1** ***(Minimum PTV prescription)***
3D-CRT or IMRT: 73.8 Gy in 41 fractions

**Arm 2** ***(Minimum PTV prescription)***
3D-CRT or IMRT: 70 Gy in 28 fractions

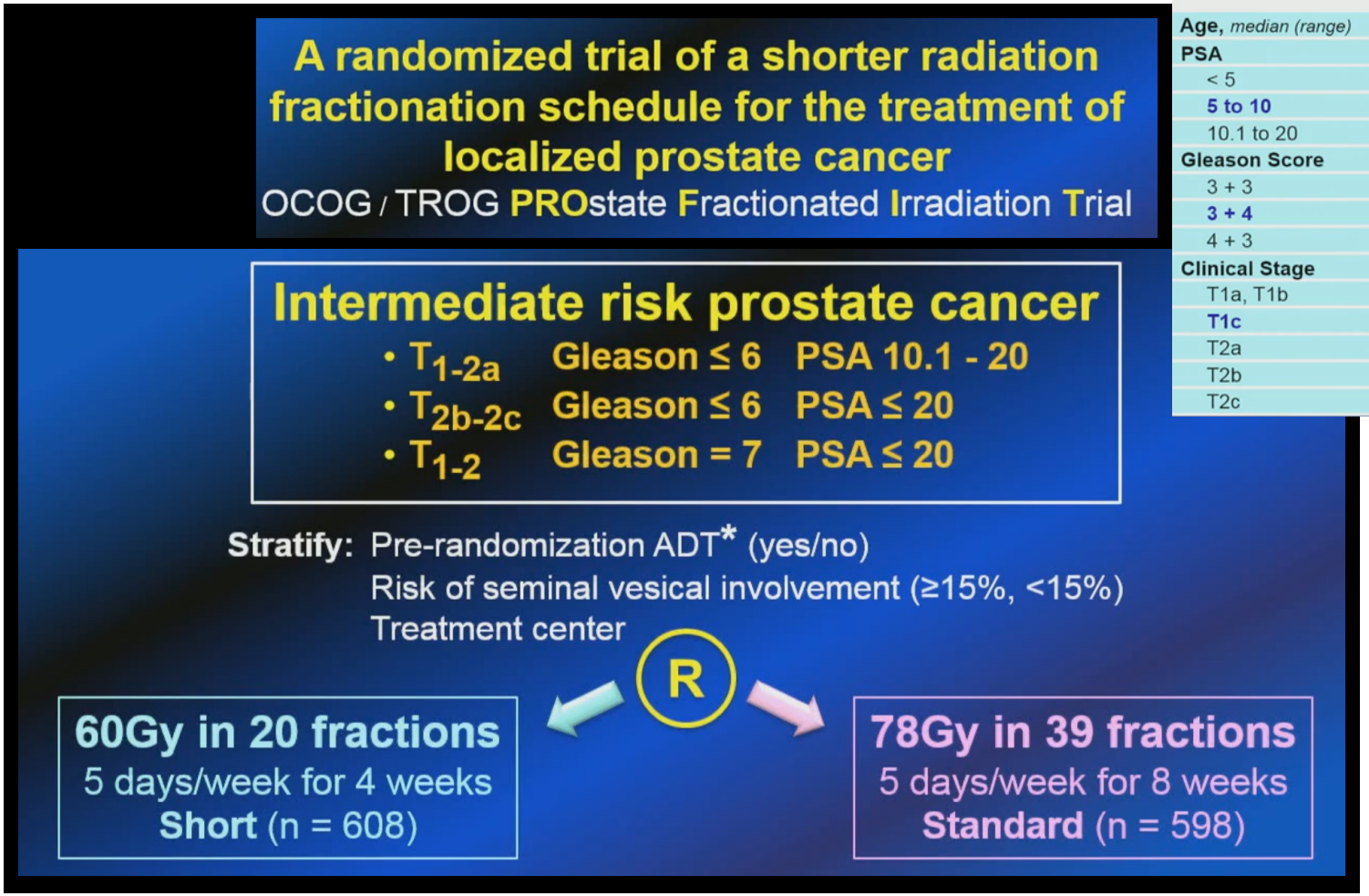


# Median FU 5.8yrs



# PROFIT Trial, PMH




| Characteristic | Short n=608 | Standard n=598 |
|---|---|---|
| Age, *median (range)* | 72 (48-87) | 71 (50-88) |
| PSA | | |
| < 5 | 17% | 19% |
| 5 to 10 | 50% | 51% |
| 10.1 to 20 | 33% | 30% |
| Gleason Score | | |
| 3 + 3 | 9% | 9% |
| 3 + 4 | 63% | 64% |
| 4 + 3 | 28% | 27% |
| Clinical Stage | | |
| T1a, T1b | <1% | <1% |
| T1c | 54% | 52% |
| T2a | 27% | 27% |
| T2b | 12% | 15% |
| T2c | 7% | 6% |

Median FU 6yrs

# PROFIT Trial, PMH

## Results: BCF

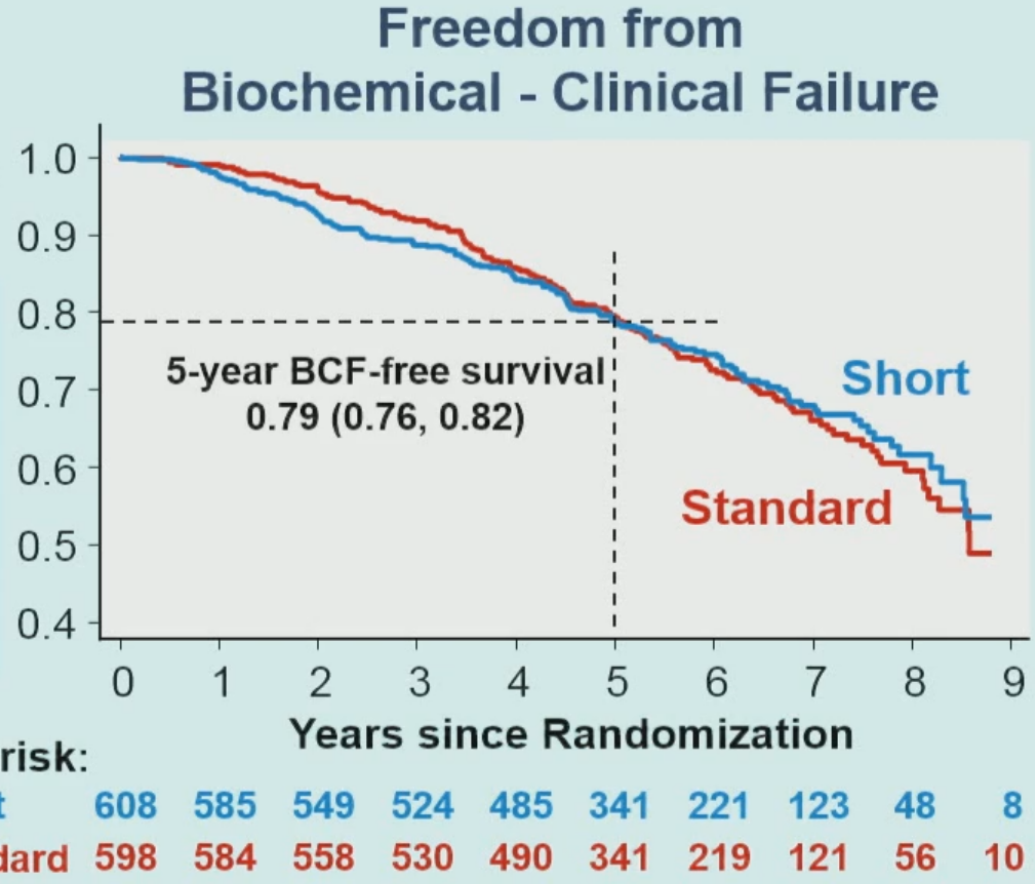
$HR_{Short|Standard} = 0.99$

90% CI, **0.83** to **1.19** < 1.32

$p_{non\text{-}inf} = 0.0044$

Adjusted for strata

HR 0.99; confirms non inferiority of shorter arm

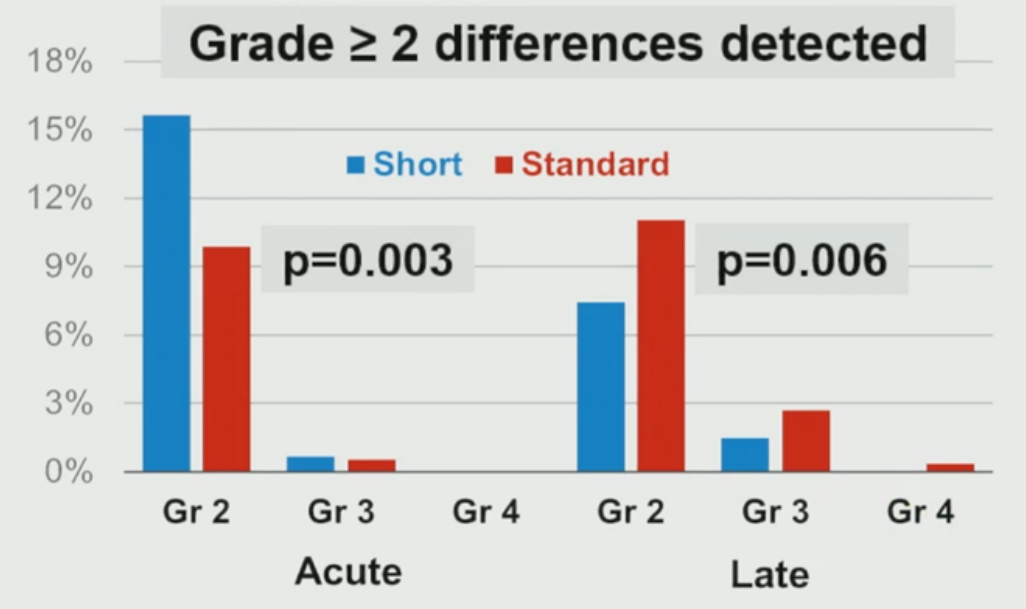



ASTRO 2016

# PROFIT Trial, PMH

| Type | Short n=608 | Standard n=598 | P-value |
|---|---|---|---|
| GU | 13 (2.1%) | 18 (3.0%) | 0.33 |
| GI | 9 (1.5%) | 17 (2.8%) | 0.10 |
| GU or GI | 22 (3.6%) | 32 (5.4%) | 0.14 |

- No diff in Late GR3+ Toxicity
- trend favors shorter arm




- Overall GI Toxicity
  - higher Acute Gr2
  - less Late Gr2

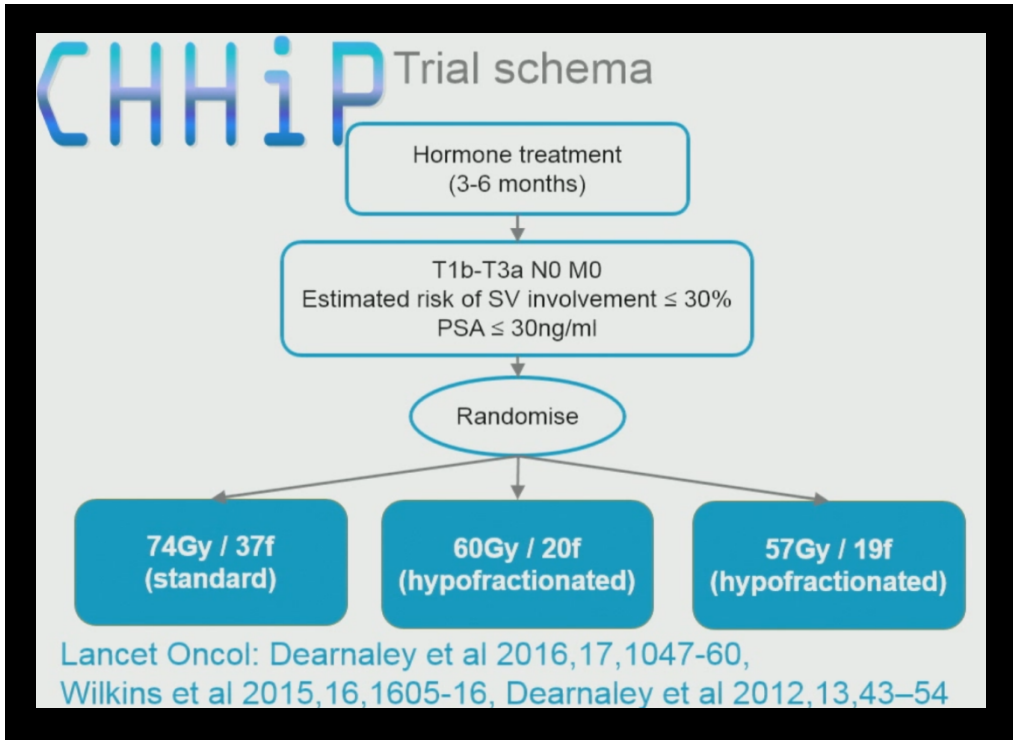
# PROFIT Trial, PMH

## Conclusions

- Based on patient convenience and cost, the shorter RT regimen should be considered as a new standard for intermediate risk prostate cancer.

ASTRO 2016

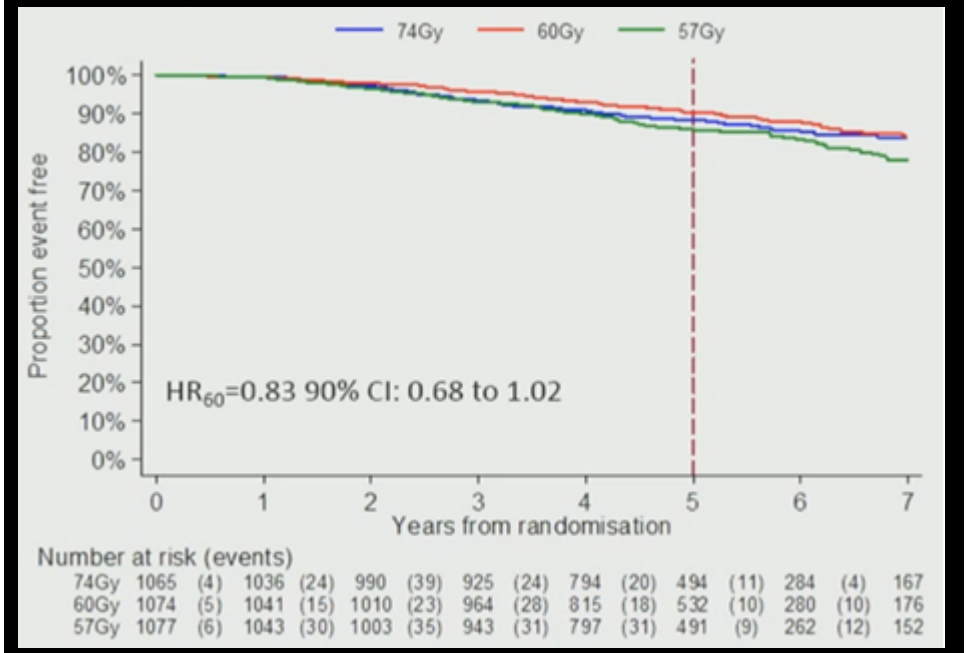
# CHHIP Trial, UK



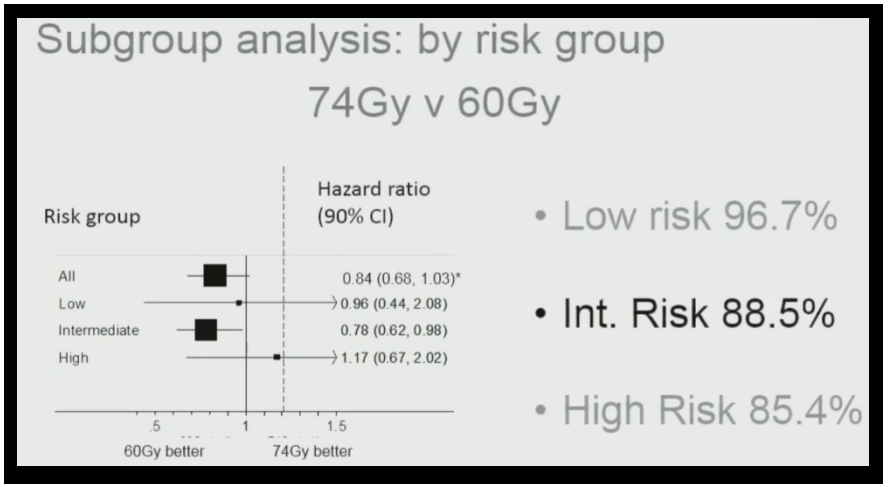

UK RCT 3diff dose levels

- mostly Int risk dz, but allowed high risk dz

# CHHIP Trial, UK

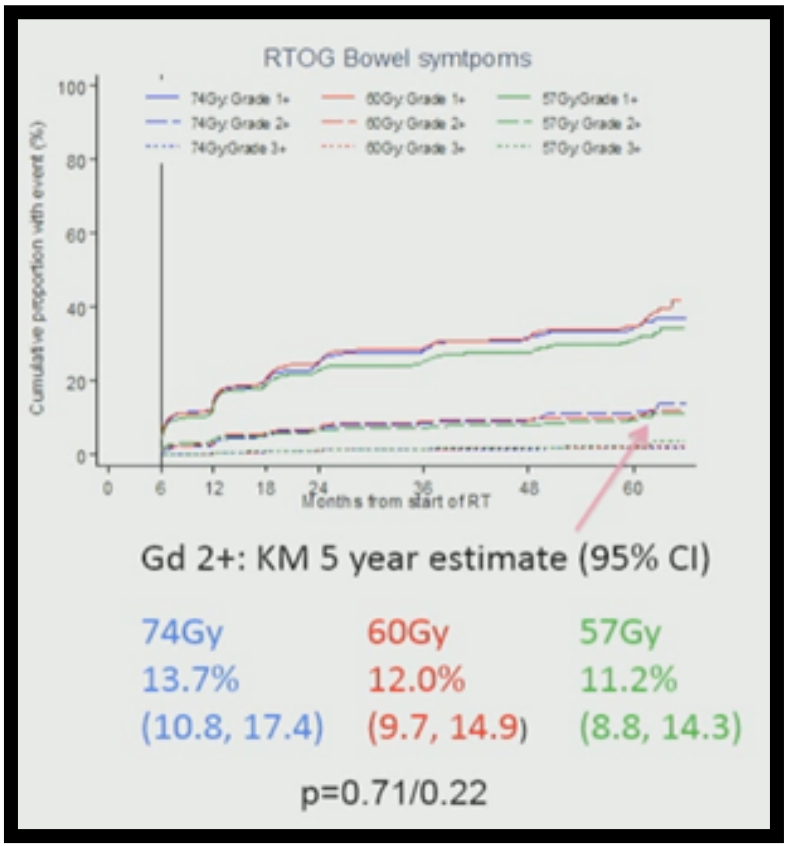



| Biochemical failure or prostate cancer recurrence | 74Gy/37f (n=1065) | 60Gy/20f (n=1074) | 57Gy/19f (n=1077) |
|---|---|---|---|
| Number of events | 138 | 119 | 164 |
| KM 5 year proportion event-free estimate (95% CI) | 88.3 (86.0, 90.2) | 90.5 (88.4, 92.2) | 85.8 (83.3, 87.9) |
| **Hazard ratio (90% CI)** | | **0.83 (0.68, 1.02)** | **1.19 (0.99, 1.44)** |
| **Pr(HR<1.208)** | | **p=0.003** | **p=0.91** |
| Log rank p-value | | p=0.14 | p=0.13 |
| | | p=0.003 | |
| **Absolute difference at 5 years (90% CI)** | | **1.86 (-0.26, 3.62)** | **-2.10 (-4.74, 0.16)** |
| Absolute difference at 5 years (90% CI) | | -3.84 (-6.52, -1.58) | |

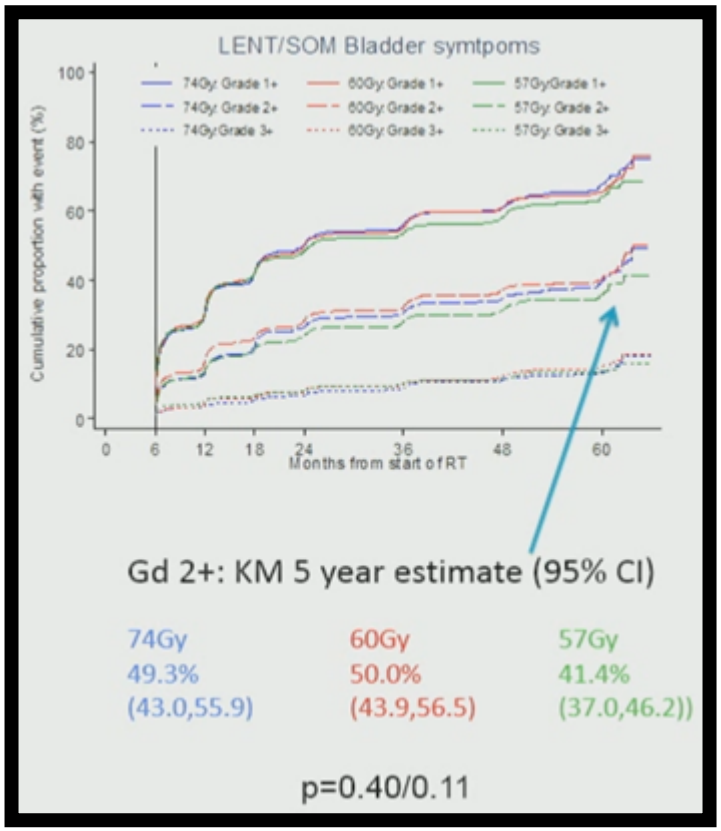



# CHHIP Trial, UK

## Late Gr2+ Rectal




## Late Gr2+ Bladder

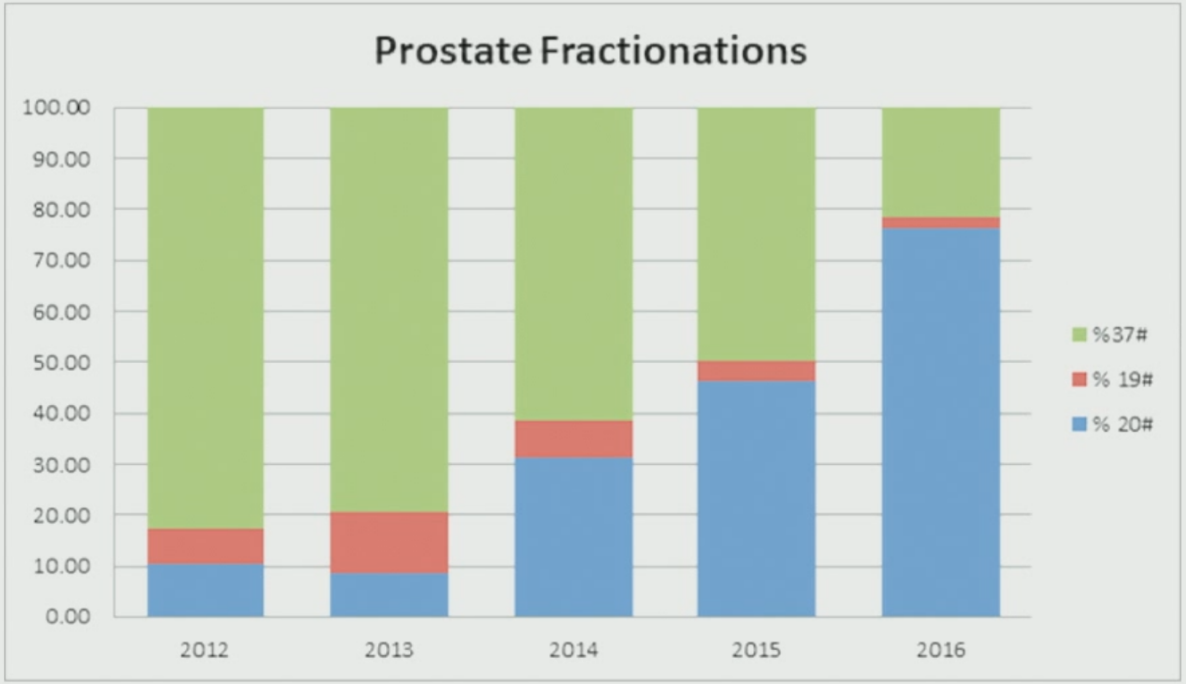


# CHHIP Trial, UK

## Conclusions

- With a median follow up of 62 months, 60Gy in 20 fractions is non-inferior to 74Gy in 37 fractions, with no statistically significant differences in late toxicity
- ***Modest hypofractionation using 60Gy/20f using high quality RT techniques can be recommended as a new standard of care***

## Change in Fractionation Schedule for Prostate Cancer at Royal Marsden Hospital 2012-2016



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- NYU-Winthrop Hospital

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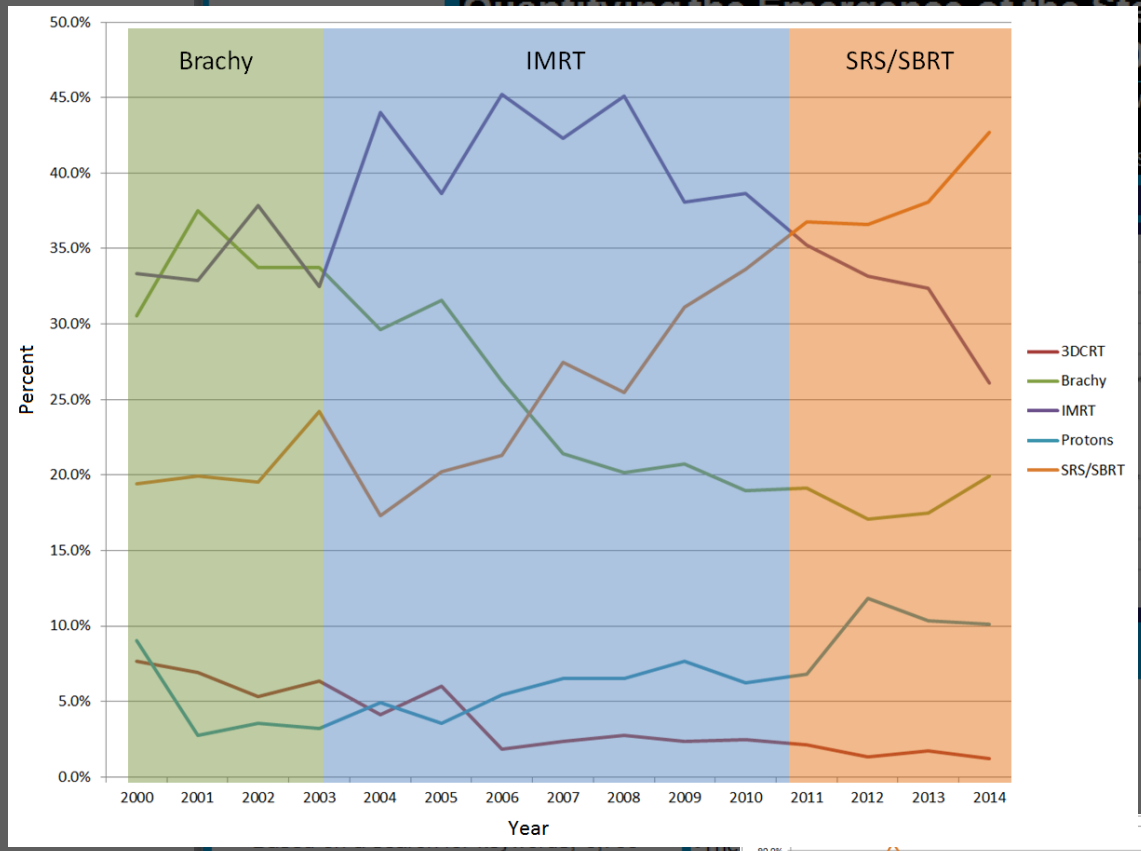
COMMENTS AND CONTROVERSIES

# Brachytherapy: Where Has It Gone?

Daniel G. Petereit, *Rapid City Regional Cancer Center, Rapid City, SD*
Steven J. Frank, *University of Texas MD Anderson Cancer Center, Houston, TX*
Akila N. Viswanathan, *Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
Beth Erickson, *Medical College of Wisconsin, Milwaukee, WI*
Patricia Eifel, *University of Texas MD Anderson Cancer Center, Houston, TX*
Paul L. Nguyen, *Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
David E. Wazer, *Tufts Medical Center, Tufts University School of Medicine, Boston, MA, and Rhode Island Hospital, The Alpert Medical School of Brown University, Providence, RI*

# SBRT As Historical Trend




# Quantifying the Emergence of the Stereotactic Era: A Fifteen Presentations, 2000-2014

ven Clancey, Ph.D., Allison R. Powers, M.Sc.,

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abstracts were also assigned a treatment technique.

- The median number of authors per abstract was 7 ± 2.7 (range 1, 22).
- The median number of accepted abstracts per year was 1339 (range 522, 2253).
- Fisher's Exact Test and Multinomial Logistic Regression were utilized to characterize trends during this period.

## Results:

- The number of accepted abstracts increased during the course of inquiry, with 6,794 from 2000-2007 and 13,082 from 2008-2014.
- There was an increase in presentations related to Gastrointestinal (8.4% vs. 10.7%, p<.0001) and Lung malignancy (9.2% vs. 12.6%, p<.0001) and a decrease in presentations related to Prostate cancer

Figure 2: Abstracts by Treatment Technique

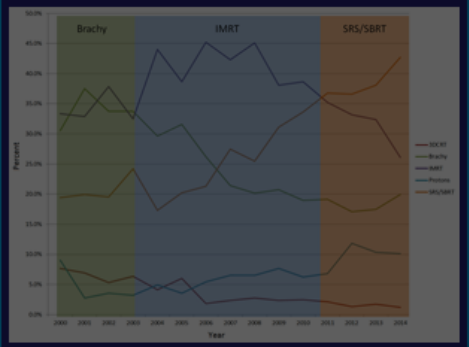
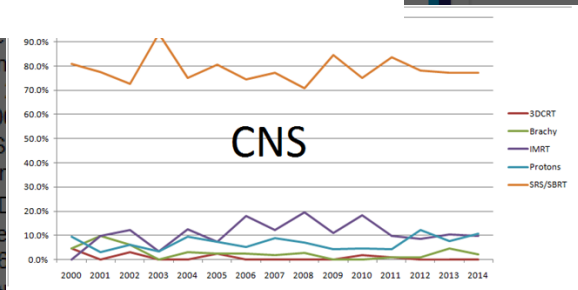
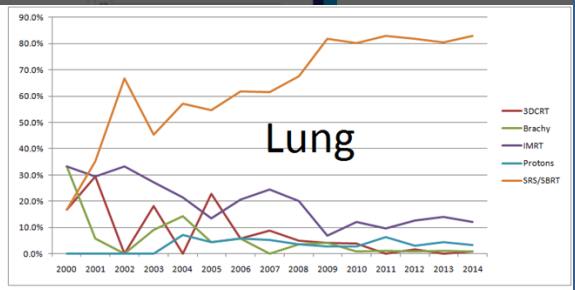
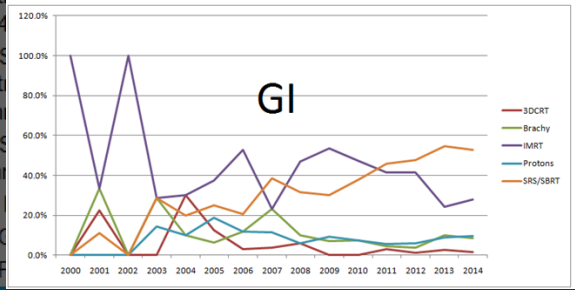
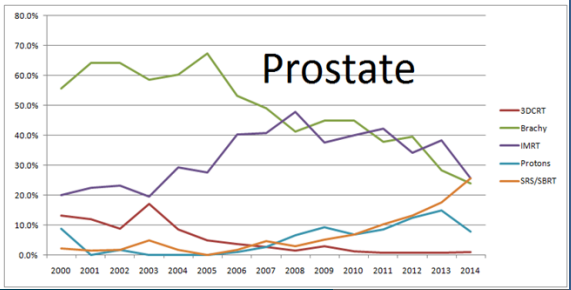


Figure 3: Treatment Technique by Disease

# SBRT

Brachy | Fractionated RT | Hypo-fx RT | SBRT

LDR
HDR

~Virtual
Modern doses IMRT
HDR?

**Diffusion of Technology**

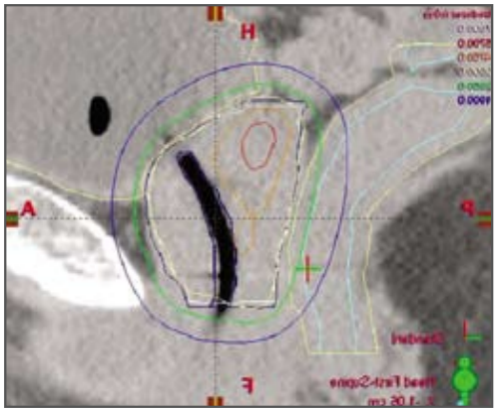
Kinship

**AMERICAN BRACHYTHERAPY SOCIETY**
**PROSTATE HIGH-DOSE RATE TASK GROUP**
**I-Chow Hsu, MD, Yoshiya Yamada MD, Eric Vigneault MD, Jean Pouliot, PhD**
**August, 2008**

**Prescription Doses:**

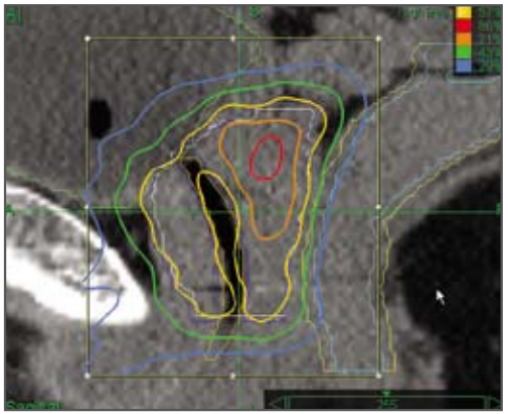
Monotherapy

10.5 Gy x 3
8.5-9.5 Gy x 4
6.0-7.5 Gy x 6



**Arm 1**

36.25 Gy in 5 fractions of 7.25 Gy over two and a half weeks (in 15-17 days)*



# SBRT as “virtual” HDR?

- Rapid Dose Fall off
- Capable of Delivering Heterogeneous Tx Plans
- Cost Effective relative to IMRT
- Compared to LDR—and like HDR—more forgiving of
  - larger prostate size (>60cc)
  - Higher baseline IPSS
  - History of TURP
- Easier to Teach to Residents?

Sean Collins, MD 2016 ASTRO

# HDR and Hypofx

**TABLE 1.** Clinical Outcomes of HDR and EBRT Moderate Hypofractionation

| Reference | Method | No. of Patients | Risk Group | Total Dose, Gy | No. of Fractions | Median Follow-up, y | bPFS, % | Late ≥G3 GU Toxicity | Late ≥G3 GI Toxicity |
|---|---|---|---|---|---|---|---|---|---|
| Hauswald et al.,[3] 2016 | HDR | 448 | Low–intermediate | 42–43.5 | 6 | 6.5 | 97.8 | 4.9% | 0% |
| Martinez et al.,[8] 2010 | HDR | 248 | Low–intermediate | 38 | 4 | 4.8 | 91 | 9% | 0.5% |
| Corner et al.,[9] 2008 | HDR | 110 | Low–high | 31.5–36 | 3–4 | 2.5 | 100 | 2% | 0% |
| Lee et al., 2016 | Hypofx | 554 | Low | 70 | 28 | 5.9 | 81.8 (DFS) | 6.4% | 4.6% |
| Kupelian et al.,[5] 2007 | Hypofx | 770 | Low–high | 70 | 28 | 3.7 | 82 (95, 85, 68) | 5% | 1% |
| Livsey et al.,[6] 2003 | Hypofx | 705 | Low–high | 50 | 16 | 4.0 | 82, 56, 39* | 9% | 5% |

*Lischalk et al.* *The Cancer Journal* • Volume 22, Number 4, July/August 2016

"SBRT" doses are not new!

"The dose is the dose" Jon Haas, M.D.

Clinical Investigation

# High-Dose-Rate Brachytherapy as Monotherapy for Intermediate- and High-Risk Prostate Cancer: Clinical Results for a Median 8-Year Follow-Up

International Journal of Radiation Oncology biology • physics

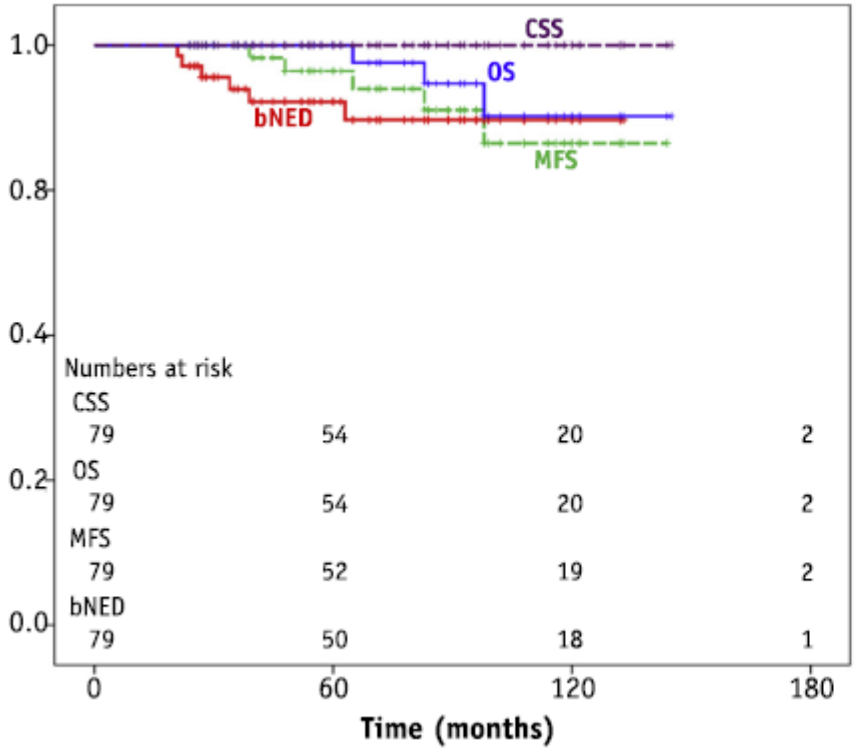
Yasuo Yoshioka, MD,* Osamu Suzuki, MD,* Fumiaki Isohashi, MD,* Yuji Seo, MD,* Hirofumi Okubo, MD,* Hiroko Yamaguchi, MD,* Michio Oda, MS,* Yuki Otani, PhD,* Iori Sumida, PhD,* Motohide Uemura, MD,† Kazutoshi Fujita, MD,† Akira Nagahara, MD,† Takeshi Ujike, MD,† Atsunari Kawashima, MD,† Ken Yoshida, MD,‡ Hideya Yamazaki, MD,§ Norio Nonomura, MD,† and Kazuhiko Ogawa, MD*

*Departments of *Radiation Oncology and †Urology, Osaka University Graduate School of Medicine, Osaka, Japan; ‡Department of Radiation Oncology, Osaka Medical College, Osaka, Japan; and §Department of Radiology, Kyoto Prefectural University of Medicine, Kyoto, Japan*

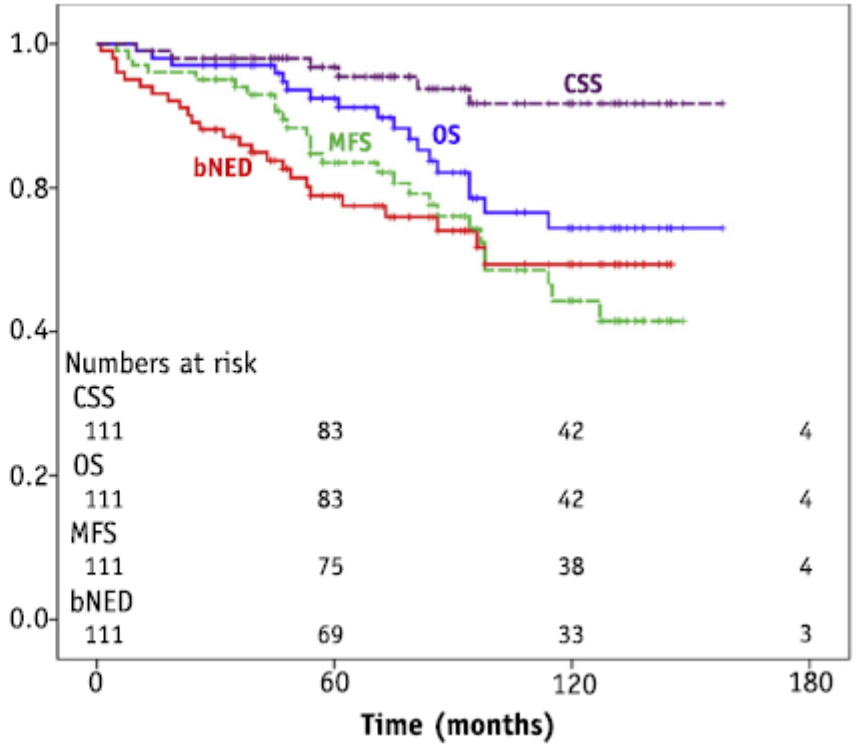
Received Mar 18, 2015, and in revised form May 11, 2015. Accepted for publication May 26, 2015.

79 Int Risk Dz (35 w ADT)
111 High Risk Dz ( 104 w ADT)
6Gy x 8, 6Gy x 6, 6.5Gy x 7

Int Risk Dz




High Risk Dz



Clinical Investigation

# High-Dose-Rate Monotherapy for Localized Prostate Cancer: 10-Year Results

Henrik Hauswald, MD, Mitchell R. Kamrava, MD, Julia M. Fallon, BA, Pin-Chieh Wang, PhD, Sang-June Park, PhD, Thanh Van, BS, Lalaine Borja, PA-C, Michael L. Steinberg, MD, and D. Jeffrey Demanes, MD

*California Endocurietherapy at UCLA, Department of Radiation Oncology, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California*

Received Mar 12, 2015, and in revised form Jul 22, 2015. Accepted for publication Jul 29, 2015.

International Journal of Radiation Oncology biology • physics

288 Low Risk
160 Int Risk, 9% ADT
7.25Gy x 6, 6.5yr F/u

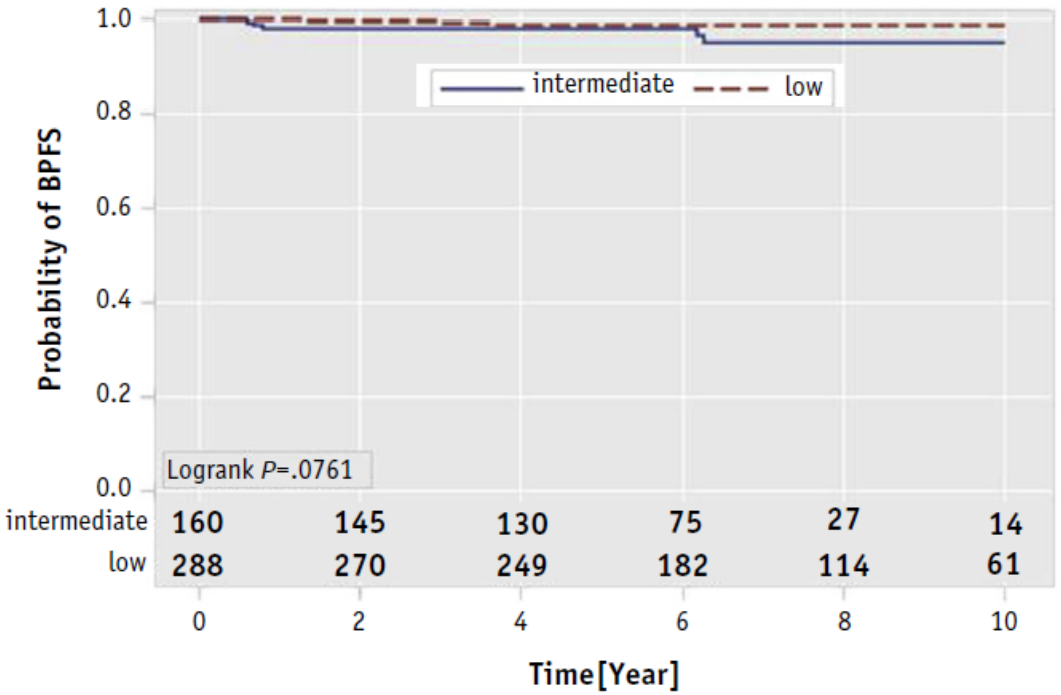
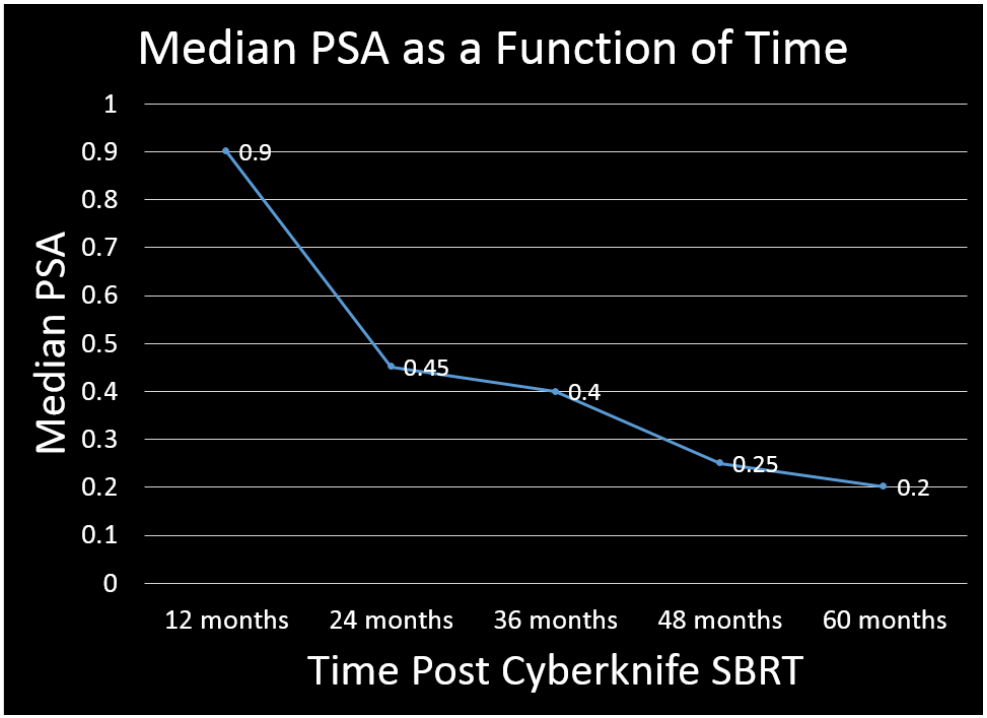



**Table 3** Late grade 3 or 4 CTCAEs

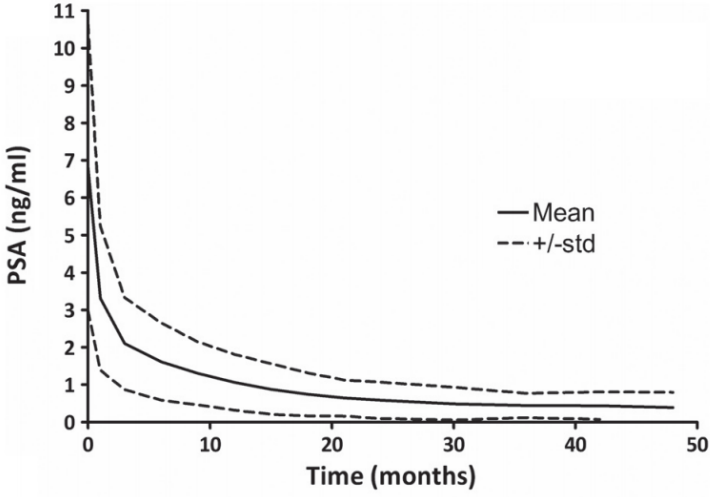
| Adverse event | Patients (n) |
|---|---|
| Total patients | 22 (4.9) |
| Rectal grade 3 or 4 | 0 (0) |
| Urinary grade 3 | |
| Urgency | 1 (0.2) |
| Pelvic pain | 1 (0.2) |
| Incontinence | 3 (0.6) |
| Outflow impairment | |
| BPH | 4*,† (1.2) |
| Bladder neck contracture | 5* (1.2) |
| Bulbomembranous stricture | 4* (0.8) |
| Unspecified | 3* (0.6) |
| Urinary grade 4 | |
| Fistula after multiple TUR procedures | 1* (0.2) |

# SBRT PSA nadirs

## Comparable to HDR, lower than EBRT




Haas J, Blacksburg S, et al, RSNA 2015




Kole T , et al, Acta Oncol, 2015

RESEARCH Open Access

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

Anwar *et al. Radiation Oncology* 2014, 9:42
http://www.ro-journal.com/content/9/1/42

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

Matched pts w low-int risk dz @UCSF, CF-EBRT vs. SBRT

- Pts w SBRT experienced
  - lower PSA nadir
  - greater rate of decline in PSA 2/3yrs after tx
  - → c/w higher BED

**Table 3 Results (all patients)**

| | | SBRT | CF-EBRT | p-value |
|---|---|---|---|---|
| | Through year | | | |
| PSA Measurements # | | | | |
| Mean (range) | 1 | 3.9 (2 – 6) | 4.1 (3 – 11) | |
| | 2 | 5.8 (4 – 9) | 5.6 (3 – 15) | |
| | 3 | 7.6 (5 – 11) | 7.3 (3 – 21) | |
| Nadir PSA (ng/mL) | | | | |
| Median (range) | 1 | 0.70 (0 – 2.5) | 1.00 (0 – 8.5) | |
| | 2 | 0.40 (0 – 1.4) | 0.72 (0 – 2.7) | p = 0.0005* |
| | 3 | 0.24 (0.1 – 1.4) | 0.60 (0 – 2.2) | p = 0.002* |
| Time to Nadir PSA (mos.) | | | | |
| Median (range) | 1 | 12.0 (2.7 – 15.0) | 11.5 (1.2 – 15.0) | |
| | 2 | 21.0 (2.7 – 26.9) | 18.0 (1.2 – 26.9) | |
| | 3 | 32.3 (2.7 – 41.6) | 28.6 (1.0 – 41.1) | p = 0.004^ |
| Rate of PSA change: ng/mL/month | | | | |
| Median slope (range) | 1 | −0.09 (−0.88, 0.04) | −0.09 (−0.60, 0.06) | |
| | 2 | −0.06 (−0.38, 0.01) | −0.04 (−0.65, 0.05) | p = 0.04* |
| | 3 | −0.05 (−0.19, 0.00) | −0.02 (−0.38, 0.04) | p = 0.006* |

# SBRT PSA nadirs

## Comparable to HDR, lower than EBRT

Original Report

**SBRT and HDR brachytherapy produce lower PSA nadirs and different PSA decay patterns than conventionally fractionated IMRT in patients with low- or intermediate-risk prostate cancer**

practical radiation oncology
pro
www.practicalradonc.org

Amar U. Kishan MD [a,*], Pin-Chieh Wang PhD [a], Shrinivasa K. Upadhyaya PhD [b], Henrik Hauswald MD [c], D. Jeffrey Demanes MD [a], Nicholas G. Nickols MD, PhD [a,d], Mitchell Kamrava MD [a], Ahmad Sadeghi MD [e], Patrick A. Kupelian MD [a], Michael L. Steinberg MD [a], Nicolas D. Prionas MD, PhD [d], Mark K. Buyyounouski MD, MS [d], Christopher R. King MD, PhD [a]

[a]*Department of Radiation Oncology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California*
[b]*Department of Biological and Agricultural Engineering, University of California, Davis, Davis, California*
[c]*Department of Radiation Oncology and Radiation Therapy, Heidelberg University Hospital, Heidelberg, Germany*
[d]*Department of Radiation Oncology, Stanford University, Stanford, California*
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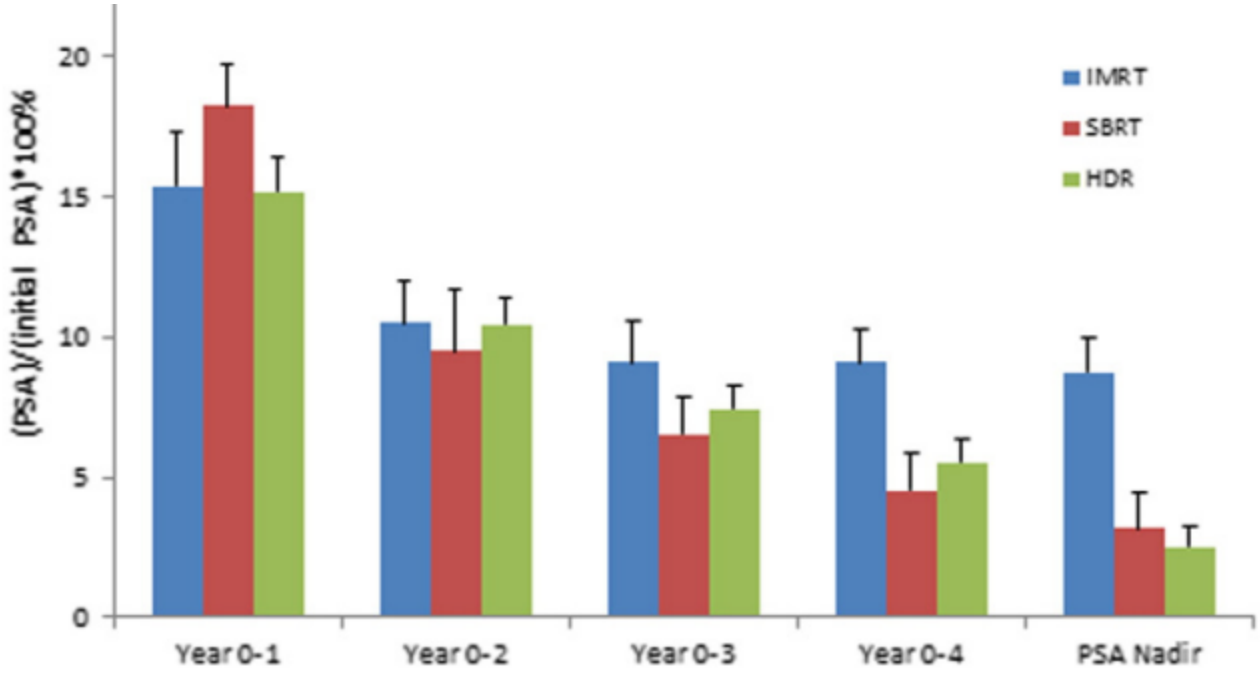
Received 1 August 2015; revised 30 October 2015; accepted 5 November 2015 Practical Radiation Oncology (2016) 6, 268-275

UCLA UCSF



# SBRT PSA nadirs

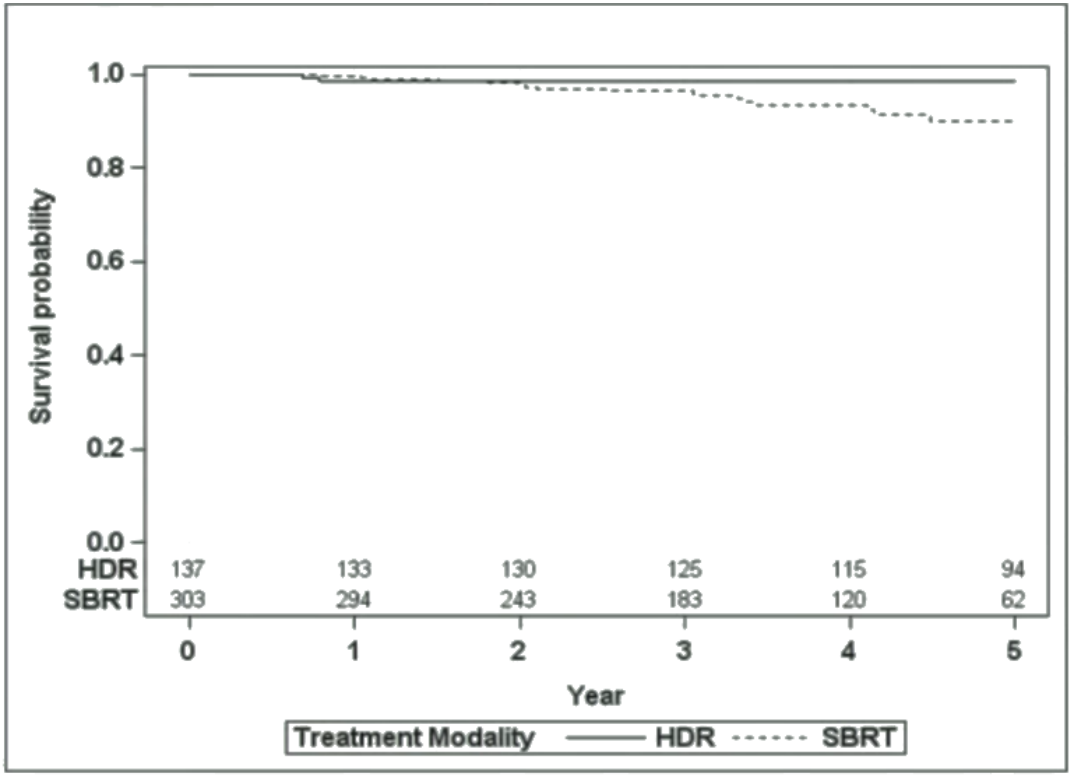
## Comparable to HDR, lower than EBRT

ORIGINAL ARTICLE

A Pooled Analysis of Biochemical Failure in Intermediate-risk Prostate Cancer Following Definitive Stereotactic Body Radiotherapy (SBRT) or High-Dose-Rate Brachytherapy (HDR-B) Monotherapy

*John V. Hegde, MD,* Sean P. Collins, MD,† Donald B. Fuller, MD,‡ Christopher R. King, PhD, MD,* D. Jeffrey Demanes, MD,* Pin-Chieh Wang, PhD,* Patrick A. Kupelian, MD,* Michael L. Steinberg, MD,* and Mitchell Kamrava, MD**

(*Am J Clin Oncol* 2016;00:000–000)




Multi-Institutional Cohort

- 5yr bDFS, p=NS
  - HDR 98.5%
  - SBRT 95.4%

SBRT cohort w higher unfav risk

# Agenda

- Rationale for Hypofx for Prostate Ca
- Hypofx Prospective and RCTs
- SBRT
  - Virtual HDR?  How does it compare?
  - Retrospective Series: Biochemical Control
  - QOL Series, Cost Effectiveness Models
- ASTRO/NCCN and RCTs

# SBRT

TABLE 2. Institutional Experience With SBRT for Localized Prostate Cancer

| Refer | No. of | | Total | No. of | | Median | Late ≥G3 | Late ≥G3 |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | xicity |
| Bolzi 20 | | | | | | | | % |
| Chen 20 | | | | | | | | % |
| Freen and 20 | | | | | | | | % |
| Fried 20 | | | | | | | | % |
| Hann 20 | | | | | | | | % |
| Jabba 20 | | | | | | | | % |
| Kang 20 | | | | | | | | % |
| Katz | | | | | | | | % |
| Kang,[36] 2014 | | intermediate | | | | 89.6‡ | | |
| King et al.,[20] 2009 | 41 | Low | 36.25 | 5 | Prostate alone | 2.75 | 100 | 5% | 0% |
| King et al.,[35] 2012 | 67 | Low | 36.25 | 5 | Prostate alone | 2.7 | 94.0 | 3% | 0% |
| Mantz et al.,[38] 2010 | 54 | Low | 40 | 5 | Prostate alone | 2.2 | 100 | 0% | 0% |
| McBride et al.,[39] 2012 | 45 | Low | 36.25–37.5 | 5 | Prostate alone | 3.7 | 97.7 | 2% | 4% |
| Oliai et al.,[40] 2012 | 70 | Low–high | 35–37.5 | 5 | Prostate +/− SV* | 3.1 | 100, 95, 77.1† | 3% | 0% |



Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 877–882, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.11.054

**CLINICAL INVESTIGATION** **Genitourinary Cancer**

## LONG-TERM OUTCOMES FROM A PROSPECTIVE TRIAL OF STEREOTACTIC BODY RADIOTHERAPY FOR LOW-RISK PROSTATE CANCER

CHRISTOPHER R. KING, PH.D., M.D.,* JAMES D. BROOKS, M.D.,† HARCHARAN GILL, M.D.,† AND JOSEPH C. PRESTI, JR., M.D.†

*Departments of Radiation Oncology and Urology, University of California Los Angeles School of Medicine, Los Angeles, CA; and †Department of Urology, Stanford University School of Medicine, Stanford, CA

Pooled 1100 patients

Contents lists available at ScienceDirect

Radiotherapy and Oncology

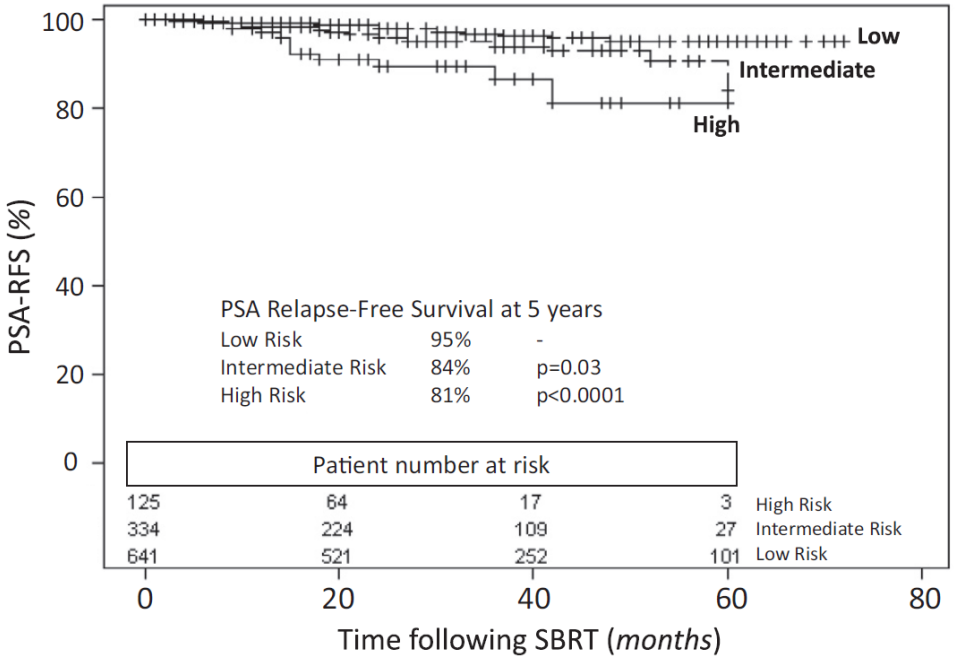
journal homepage: www.thegreenjournal.com

Phase II trial

# Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆,☆☆

Christopher R. King [a,*], Debra Freeman [b], Irving Kaplan [c], Donald Fuller [d], Giampaolo Bolzicco [e], Sean Collins [f], Robert Meier [g], Jason Wang [a], Patrick Kupelian [a], Michael Steinberg [a], Alan Katz [h]

[a] Department of Radiation Oncology, UCLA, Los Angeles, CA; [b] Naples Radiation Oncology, Naples, Florida; [c] Department of Radiation Oncology, Beth Israel Deaconness, Boston, MA; [d] Radiosurgery Medical Group, San Diego, CA, United States; [e] Division of Radiation Oncology, San Bortolo Hospital, Vicenza, Italy; [f] Department of Radiation Oncology, Georgetown University, Washington DC; [g] Department of Radiation Oncology, Swedish Medical Center, Seattle, WA; and [h] Flushing Radiation Oncology, Flushing, NY, United States



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# Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆,☆☆

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Comparisons of 5-year PSA relapse-free survival rates by risk group and substratified by use of ADT or total dose.

| | Low risk | | Intermediate risk | | High risk | |
|---|---|---|---|---|---|---|
| | 5-yr bRFS | *p*-Value | 5-yr bRFS | *p*-Value | 5-yr bRFS | *p*-Value |
| ADT use | 96.8% | * | 97.2% | * | 82.5% | * |
| No ADT | 95.1% | 0.46 | 79.7% | 0.17 | 80.2% | 0.50 |
| Dose 35 Gy | 95.8% | * | 72.3% | * | NE | * |
| Dose 36.25 Gy | 95.0% | 0.77 | 87.2% | 0.73 | 74.1% | 0.99 |
| Dose 38–40 Gy | 94.4% | 0.41 | 96.7% | 0.58 | NE | 1.0 |

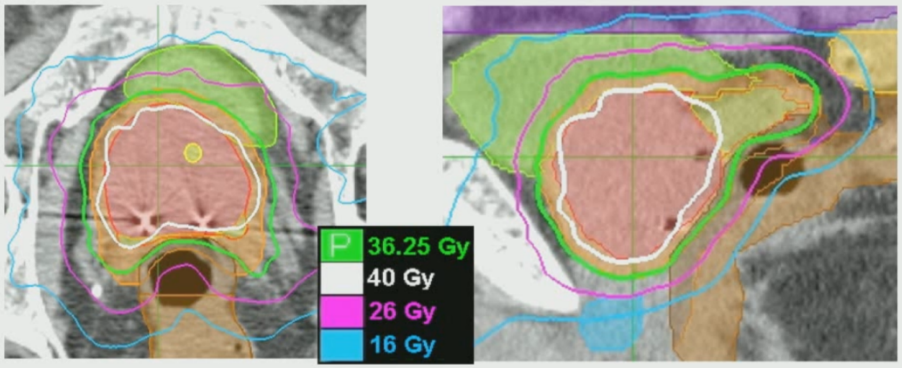
# Five-Year Outcomes from a Multi-Center Trial of Stereotactic Body Radiotherapy for Low- and Intermediate-Risk Prostate Cancer

R. Meier[1], A. Beckman[2], G. Henning[3], N. Mohideen[4], S. A. Woodhouse[5], C. Cotrutz[1], and I. D. Kaplan[6]

*[1]Swedish Cancer Institute, Seattle, WA, [2]Central Baptist Hospital, Lexington, KY, [3]Huron River Radiation Oncology, Brighton, MI, [4]Northwest Community Hospital, Arlington Heights, IL, [5]Community Cancer Center, Normal, IL, [6]Beth Israel Deaconess Medical Center, Boston, MA*

## Treatment Planning

- MRI fusion to assist target localization
- Prostate prescribed 8Gy x 5 = 40Gy: $EQD_{2,\alpha/\beta=2}$ = 100Gy
- 2nd Rx of 7.25Gy x 5 to: Low-risk: Prostate + 3-5mm
  Interm-risk pts: Prostate + 2cm seminal vesicles + 3-5mm



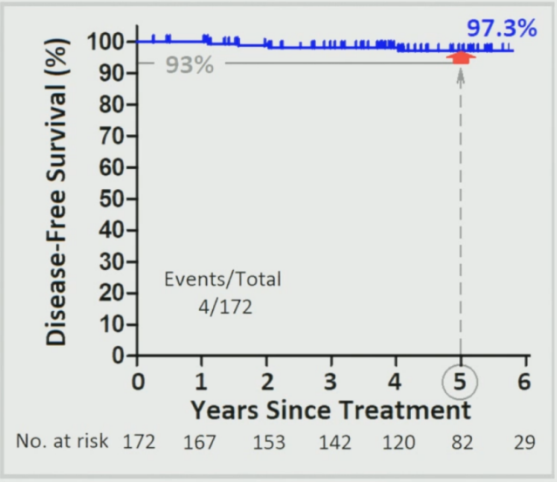
## Low-risk Patients

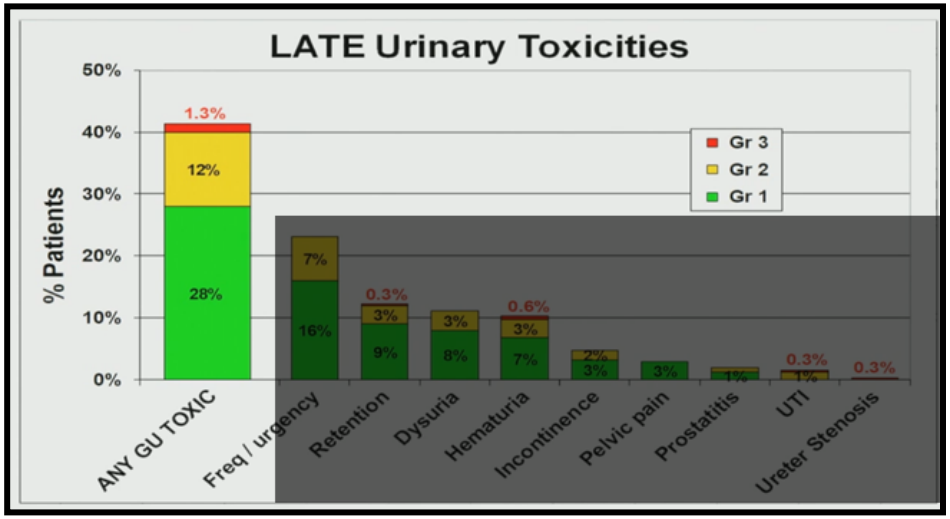
**5-yr Nadir+2 Disease-Free Survival**

93% expected from EBRT historical controls

**97.3%** SBRT rate proved superior to historic comparison

**P=0.014**



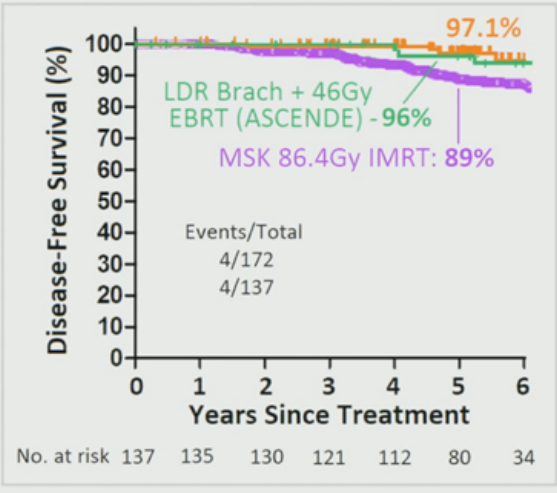



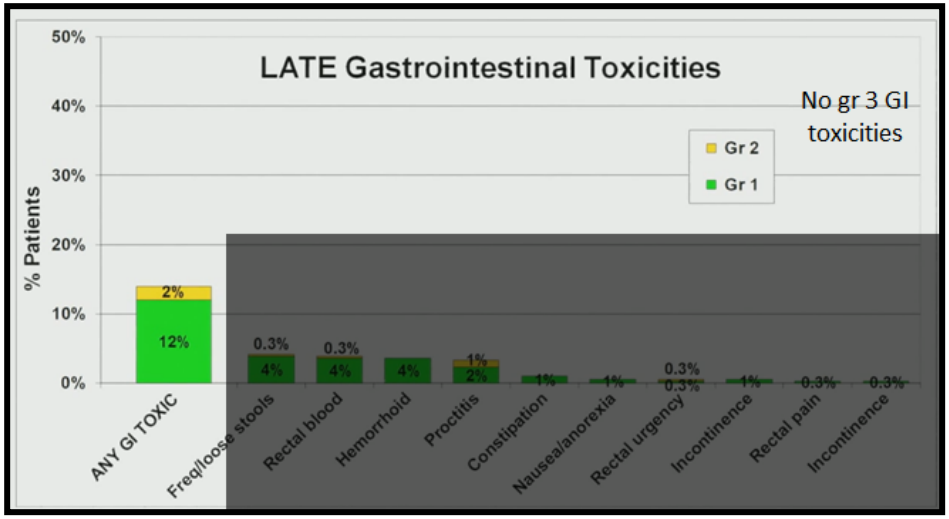

## Intermediate-risk Patients

**5-yr Nadir+2 Disease-Free Survival**

5yr DFS

- Favorable 100%
- Unfavorable 93.1%

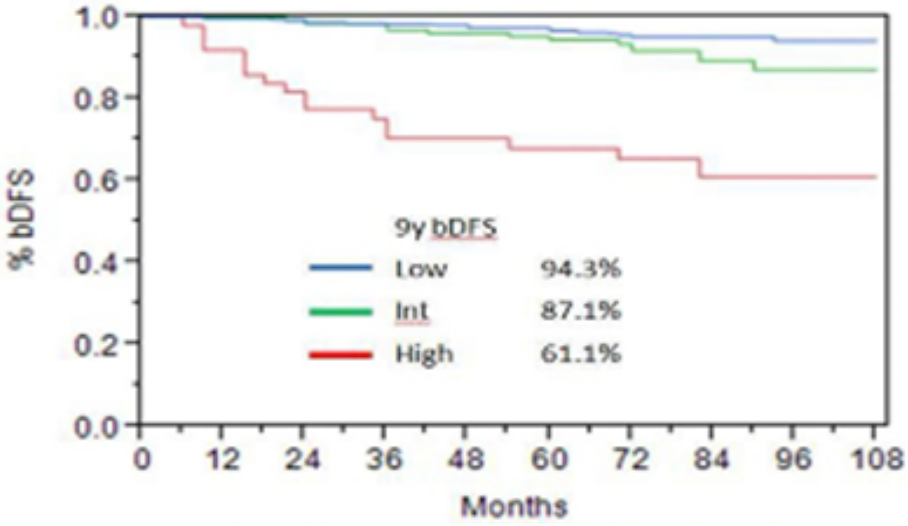



Robert Meier, MD 2016 ASTRO

# 9yr Outcomes, Katz et al

GU ASCO, Jan 2016




515 pts, median f/u of 84mos

9-year freedom from biochemical failure

- 94.3% for low-risk men
- 87.1% for intermediate-risk men
- 61.1% for high-risk men

No difference in biochemical control for the lower (35)vs. the higher (36.25) radiation dose

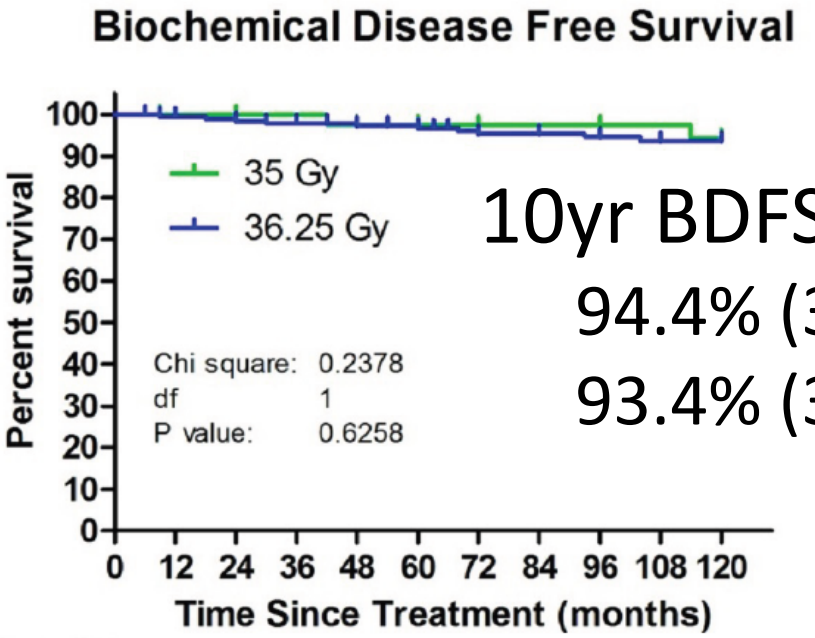
Cureus Open Access Original Article DOI: 10.7759/cureus.1668

# Stereotactic Body Radiotherapy for Low-Risk Prostate Cancer: A Ten-Year Analysis

Alan Katz [1]

1. Flushing radiation

**Corresponding author:** Alan Katz, akatzmd@msn.com
Disclosures can be found in Additional Information at the end of the article




Patients at Risk

| Months | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3500 | 41 | 41 | 40 | 40 | 38 | 37 | 36 | 36 | 35 | 35 | 31 |
| 3625 | 190 | 186 | 182 | 176 | 173 | 161 | 149 | 142 | 132 | 87 | 26 |

10yr BDFS

94.4% (35Gy)

93.4% (36.25Gy)

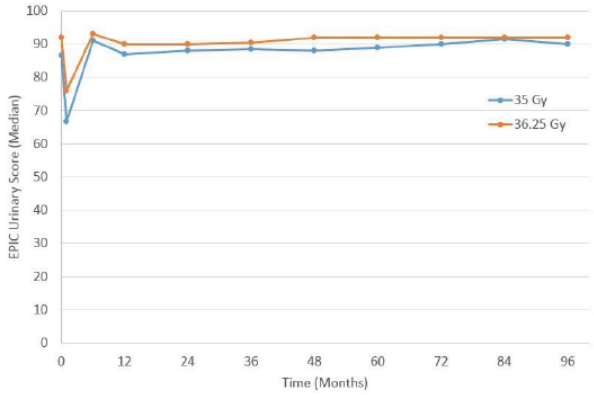



**FIGURE 3: Expanded Prostate Cancer Index Composite (EPIC) urinary quality of life as a function of time since the treatment for the 35 and 36.25 Gy cohorts.**

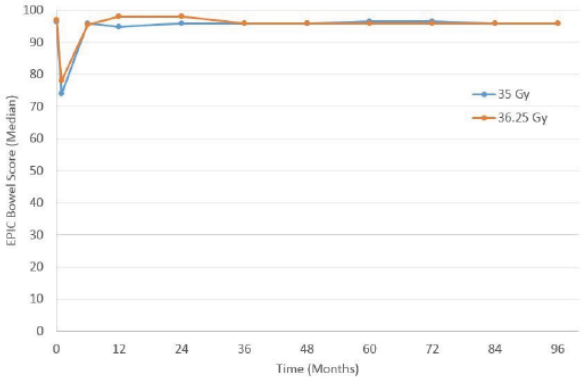
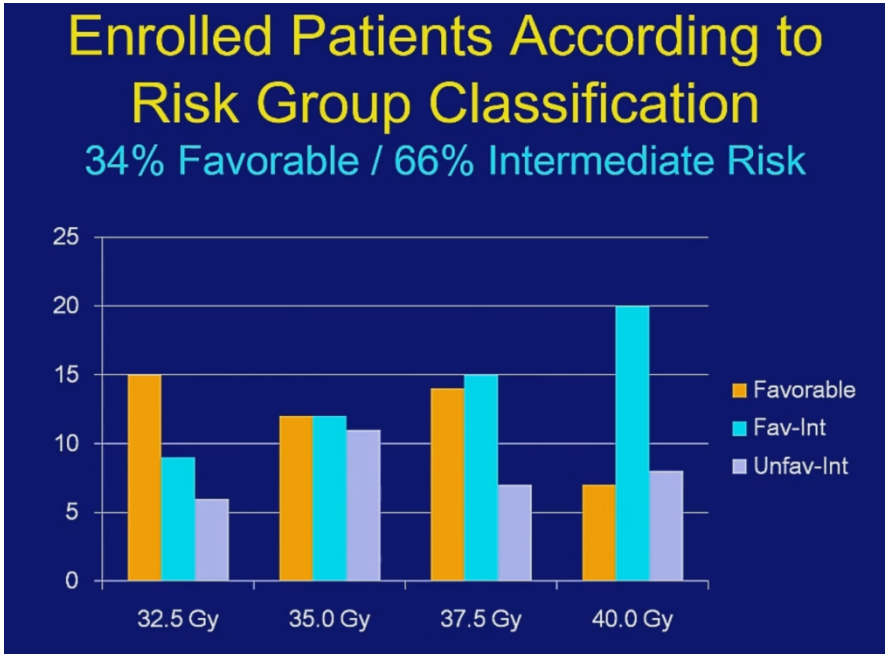


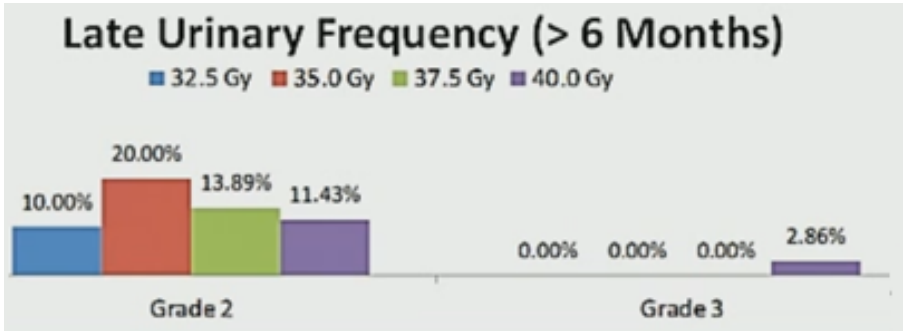

**FIGURE 4: Expanded Prostate Cancer Index Composite (EPIC) bowel quality of life as a function of time since the treatment of 35 and 36.25 Gy cohorts.**

# MSKCC SBRT Dose Escalation

## Zelefsky M, et al, ASTRO 2017

| Dose level | Dose | Median f/u |
|---|---|---|
| 6.5Gy x 5 | 32.5Gy | 60 mos |
| 7.0Gy x 5 | 35.0Gy | 60 mos |
| 7.5Gy x 5 | 37.5Gy | 44 mos |
| 8.0Gy x 5 | 40.0Gy | 33 mos |



## Crude PSA Failure Rate and 2-year Biopsy Outcomes

| dose | % PSA failure (Nadir +2 Definition) | %Positive Biopsy |
|---|---|---|
| 32.5 Gy | 20% (6/30) | 48% (10/21) |
| 35 Gy | 2.9% (1/35) | 19% (5/26) |
| 37.5 Gy | 0% (0/36) | 17% (4/24) |
| 40 Gy | 2.9% (1/35) | 8% (2/25) |

## Biopsy Outcomes Based on Risk Group

| Dose Arm | Low Risk | Favorable Intermediate | Unfavorable Intermediate |
|---|---|---|---|
| 32.5 Gy | 27% (3/11) | 40% (2/5) | 100% (5/5) |
| 35 Gy | 0% (0/9) | 25% (2/8) | 33% (3/9) |
| 37.5 Gy | 13% (1/8) | 25% (3/12) | 0% (0/4) |
| 40 Gy | 0% (0/7) | 0% (0/13) | 40% (2/5) |

- How many would convert to neg bx @3yrs?
- Clinical significance of low PSA and positive bx?
- How do these findings compare w EBRT 81-86.4Gy?
- CK uses non-coplanar beams
  - lower IDL
  - Deliver higher dose

# MSKCC SBRT Dose Escalation

Zelefsky M, et al, ASTRO 2017

| Dose | Median f/u | PSA failure | Positive Biopsy % | Fav Int Risk positive Bx | Unfav Int Risk positive Bx |
|---|---|---|---|---|---|
| 32.5 Gy | 60 mos | 20% | 48% | 40% | 100% |
| 35 Gy | 60 mos | 2.9% | 19% | 25% | 33% |
| 37.5 Gy | 44 mos | 0% | 17% | 25% | 0% |
| 40 Gy | 33 mos | 2.9% | 8% | 0% | 40% |

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 2, pp. 527–533, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2005.07.981

**CLINICAL INVESTIGATION** **Prostate**

## BIOLOGICALLY EFFECTIVE DOSE VALUES FOR PROSTATE BRACHYTHERAPY: EFFECTS ON PSA FAILURE AND POSTTREATMENT BIOPSY RESULTS

RICHARD G. STOCK, M.D.,* NELSON N. STONE, M.D.,† JAMIE A. CESARETTI, M.D.,* AND BARRY S. ROSENSTEIN, PH.D.*

| BED groups | Number of patients | Percent positive | |
|---|---|---|---|
| ≤100 | 33 | 24% | |
| >100–120 | 20 | 15% | |
| >120–140 | 33 | 6% | |
| >140–160 | 52 | 6% | |
| >160–180 | 82 | 7% | |
| >180–200 | 72 | 1% | |
| >200 | 131 | 3% | $p < 0.0001$ |

*Abbreviation:* BED = biologically effective dose.

# Agenda

- Rationale for Hypofx for Prostate Ca
- Hypofx Prospective and RCTs
- SBRT
  - Virtual HDR?  How does it compare?
  - Retrospective Series: Biochemical Control
  - QOL Series, Cost Effectiveness Models
- ASTRO/NCCN and RCTs
- NYU-Winthrop Hospital

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

*James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross*

See accompanying editorial doi: 10.1200/JCO.2014.55.2380

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, and Cary P. Gross, Yale School of Medicine, [illegible]

A B S T R A C T

**Table 3.** Adjusted Random Effects Logit Model of Subcategories of Genitourinary Toxicity

| Toxicity | Duration of Follow-Up: 6 Months OR* | 6 Months P† | 12 Months OR* | 12 Months P† | 24 Months OR* | 24 Months P† |
|---|---|---|---|---|---|---|
| Diagnostic procedures to investigate incontinence or obstruction | **1.80** | **< .001** | **1.64** | **< .001** | **2.23** | **< .001** |
| Urethritis, urethral strictures, and bladder outlet obstruction | 1.25 | .14 | **1.45** | **.002** | **1.78** | **< .001** |
| Therapeutic procedures to correct urinary incontinence | 0.71 | .22 | 1.00 | 1.00 | 1.33 | .09 |
| Other genitourinary toxicity | 0.77 | .45 | 1.14 | .58 | 0.73 | .23 |
| Infections | 1.01 | .99 | 2.30 | .11 | 2.42 | .15 |
| Erectile dysfunction | 1.46 | .03 | 1.15 | .28 | 1.13 | .35 |

**Results**

The study sample consisted of 1,335 SBRT patients matched to 2,670 IMRT patients. The mean treatment cost was $13,645 for SBRT versus $21,023 for IMRT. In the 6 months after treatment initiation, 15.6% of SBRT versus 12.6% of IMRT patients experienced GU toxicity (odds ratio [OR], 1.29; 95% CI, 1.05 to 1.53; $P = .009$). At 24 months after treatment initiation, 43.9% of SBRT versus 36.3% of IMRT patients had GU toxicity (OR, 1.38; 95% CI, 1.12 to 1.63; $P = .001$). The increase in GU toxicity was due to claims indicative of urethritis, urinary incontinence, and/or obstruction.

**Conclusion**

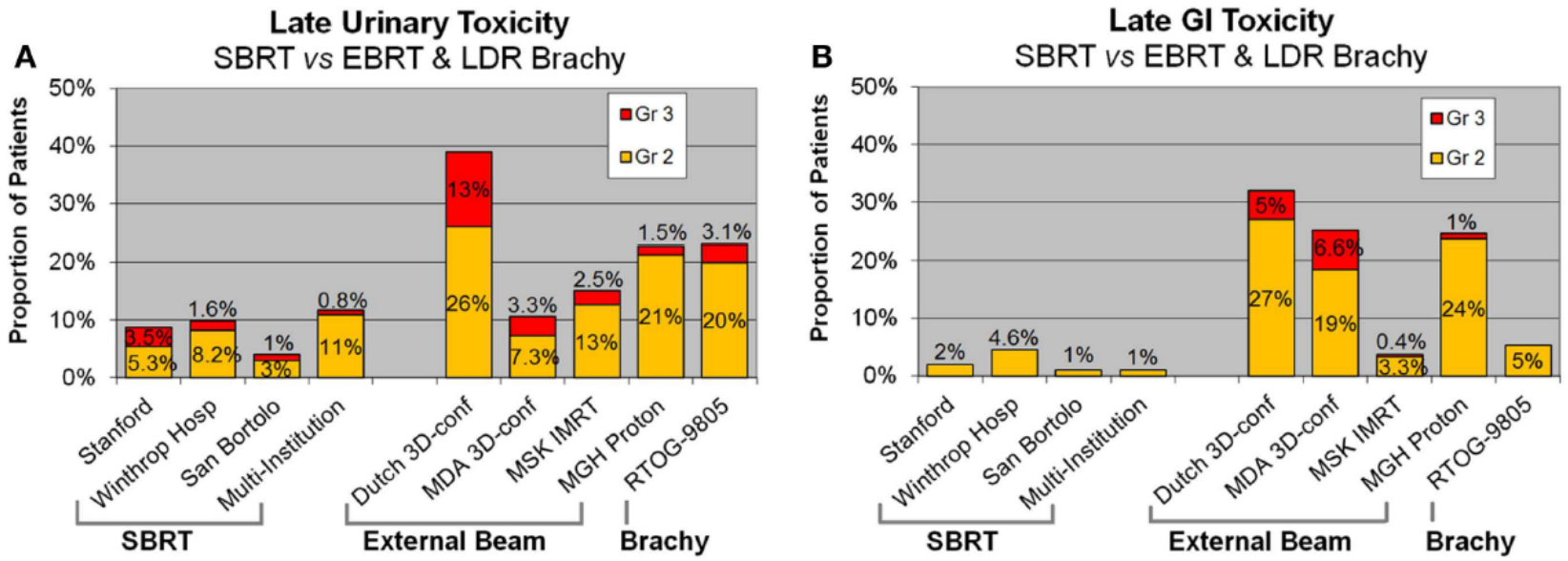
Although SBRT was associated with lower treatment costs, there appears to be a greater rate of GU toxicity for patients undergoing SBRT compared with IMRT, and prospective correlation with randomized trials is needed.

Translational Science (J.B.Y.), and by the NIH Roadmap for Medical Research.

The study sponsor (National Institutes of Health) did not play a role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Terms in blue are defined in the glossary, found at the end of this article

*J Clin Oncol 32.* 




chemical relapse rates which compare favorably to IMRT. Rates of late GU toxicity are similar to those seen with IMRT, and rates of late rectal toxicity may be less than with

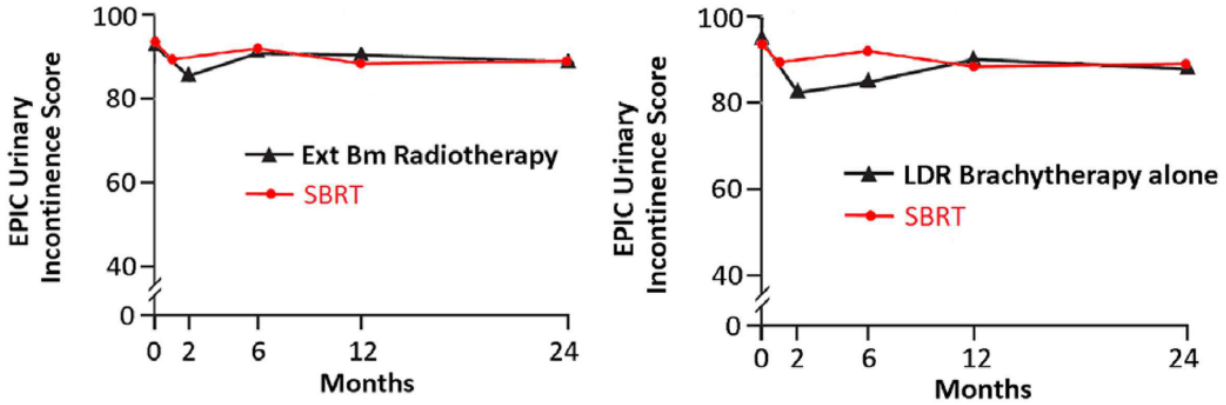



**FIGURE 3 | EPIC urinary incontinence scores at baseline and at various intervals following treatment (months) from Sanda (96) (black: left graph is for external beam RT and right is for brachytherapy) and SBRT (red)**. SBRT, stereotactic body radiotherapy; RT, radiation therapy.

Meier et al, *Frontiers*, 2015

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Patient reported outcome measures

# Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy

Joseph R. Evans [a,1], Shuang Zhao [a,1], Stephanie Daignault [b], Martin G. Sanda [c], Jeff Michalski [d], Howard M. Sandler [e], Deborah A. Kuban [f], Jay Ciezki [g], Irving D. Kaplan [h], Anthony L. Zietman [i], Larry Hembroff [j], Felix Y. Feng [a], Simeng Suy [k], Ted A. Skolarus [l,m], Patrick W. McLaughlin [a], John T. Wei [l], Rodney L. Dunn [l], Steven E. Finkelstein [n], Constantine A. Mantz [n], Sean P. Collins [k], Daniel A. Hamstra [a,*], and the PROSTQA Study Consortium

[a] *Department of Radiation Oncology, University of Michigan, Ann Arbor;* [b] *Department of Biostatistics, University of Michigan;* [c] *Department of Urology, Emory University, Atlanta;* [d] *Department of Radiation Oncology, Washington University Medical Center, St. Louis;* [e] *Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles;* [f] *Department of Radiation Oncology, M.D. Anderson Cancer Center, Houston;* [g] *Department of Radiation Oncology, Cleveland Clinic;* [h] *Beth Israel Deaconess Medical Center;* [i] *Department of Radiation Oncology, Massachusetts General Hospital, Boston;* [j] *Michigan State University, East Lansing;* [k] *Georgetown University, Washington;* [l] *Department of Urology, University of Michigan;* [m] *HSR&D Center for Clinical Management Research, VA Ann Arbor Healthcare System; and* [n] *21st Century Oncology, Ft Meyers, United States*

- 803 pts tx'd at multiple institutions w LDR brachy, IMRT, or SBRT
- 1200 EPIC questionnaires for year 0-2
- Minimal clinically detectable (MCD) thresholds for QOL domains
  - 6 urinary irritation/obstruction
  - 7.5 urinary incontinence
  - 5 bowel and vitality/hormonal
  - 11 sexual domain

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Patient reported outcome measures Radiotherapy and Oncology 116 (2015) 179–184

# Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy

Joseph R. Evans [a,1], Shuang Zhao [a,1], Stephanie Daignault [b], Martin G. Sanda [c], Jeff Michalski [d]

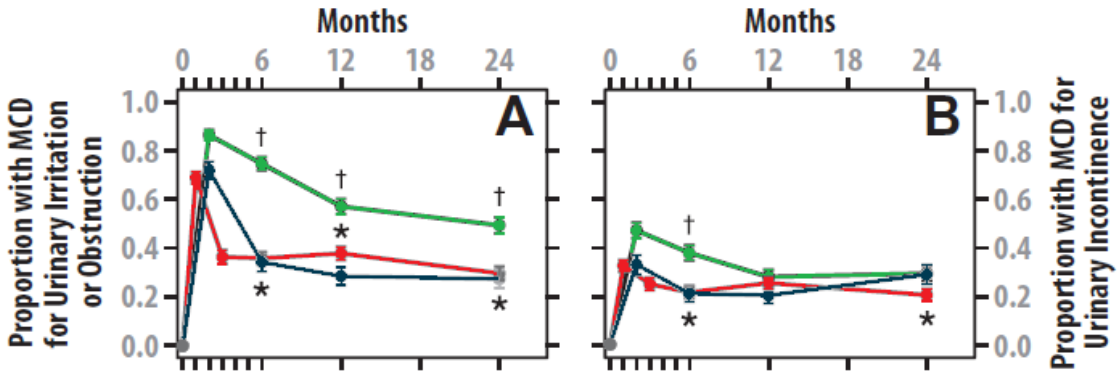



**Table 1**
Multivariate analysis.

| | Multivariate analysis | |
|---|---|---|
| | *p*-Value | Coefficient |
| *Urinary irritation or obstruction* | | |
| Brachytherapy (vs. IMRT) | <0.0001* | −6.8 (−9.9,−3.6) |
| SBRT (vs. IMRT) | 0.55 | −1 (−4.4,2.3) |
| SBRT (vs. Brachy) | 0.00051* | 5.8 (2.5,9) |
| *Urinary incontinence* | | |
| Brachytherapy (vs. IMRT) | 0.21 | −2.4 (−6.1,1.4) |
| SBRT (vs. IMRT) | 0.74 | 0.68 (−3.3,4.7) |
| SBRT (vs. Brachy) | 0.11 | 3 (−0.73,6.8) |
| *Bowel* | | |
| Brachytherapy (vs. IMRT) | 0.48 | 1.1 (−2,4.3) |
| SBRT (vs. IMRT) | 0.00014* | 6.7 (3.2,10) |
| SBRT (vs. Brachy) | 0.001* | 5.5 (2.2,8.8) |

# SBRT Cost Effectiveness

frontiers in ONCOLOGY

ORIGINAL RESEARCH ARTICLE
published: 20 August 2012
doi: 10.3389/fonc.2012.00081

## Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer

*Anju Parthan[1]*, Narin Pruttivarasin[1], Diane Davies[2], Douglas C. A. Taylor[1], Vivek Pawar[3], Akash Bijlani[2], Kristen Hassmiller Lich[4] and Ronald C. Chen[4]*

- 65yo w localized Prostate Cancer declined or ineligible for surgery
- Markov Model

| | Total per patient | |
|---|---|---|
| | **Costs** | **QALYs** |
| **PAYER PERSPECTIVE** | | |
| SBRT | $24,873 | 8.11 |
| IMRT | $33,068 | 8.05 |
| PT | $69,412 | 8.06 |

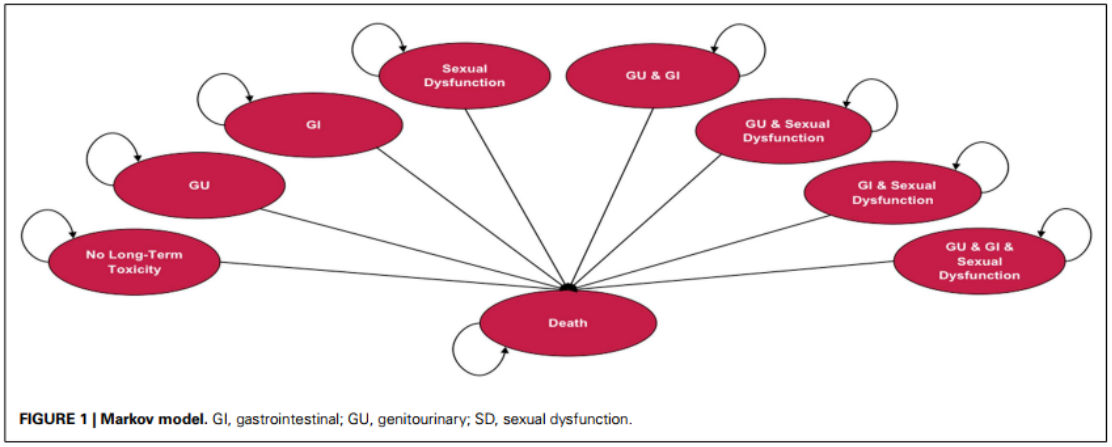



**FIGURE 1 | Markov model.** GI, gastrointestinal; GU, genitourinary; SD, sexual dysfunction.

# Agenda

- Rationale for Hypofx for Prostate Ca
- Hypofx Prospective and RCTs
- SBRT
  - Virtual HDR?  How does it compare?
  - Retrospective Series: Biochemical Control
  - QOL Series, Cost Effectiveness Models
- ASTRO/NCCN and RCTs

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2015
# Prostate Cancer

**PRINCIPLES OF RADIATION THERAPY**

**Primary External Beam Radiation Therapy**

- **Highly conformal RT techniques should be used to treat prostate cancer.**
- **Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.**
- **Moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.**

ASTRO Model Policies

## STEREOTACTIC BODY RADIATION THERAPY (SBRT)

**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.

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0938**

# A RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED RADIOTHERAPY FOR FAVORABLE RISK PROSTATE CANCER

| STRATIFY | | RANDOMIZE | |
|---|---|---|---|
| | **Treatment techniques/machine**<br><br>1. All linear accelerator based treatment (excluding Cyberknife)<br><br>2. Cyberknife<br><br>3. Protons | | **Arm 1**<br>36.25 Gy in 5 fractions of 7.25 Gy over two and a half weeks (in 15-17 days)*<br><br>**Arm 2**<br>51.6 Gy in 12 daily fractions of 4.3 Gy over two and a half weeks (in 16-18 days) |

# Phase 3 SBRT Trials

| Institution/study | Eligibility | Arms | Primary outcomes |
|---|---|---|---|
| Curie Institute Poland, NCT01839994 | T1–T3a N0 M0 | 76–78 Gy, 2 Gy/fx<br>50 Gy EBRT + 10 Gy × 2 SBRT/HDR boost | bDFS, toxicity |
| University of Miami, NCT01794403<br>**HEAT trial** | T1–T2 N0 M0, low-, intermediate-risk | 70.2 Gy, 2.7 Gy/fx IMRT<br>36.25 Gy, 5 fxs SBRT | 2-year bDFS |
| University Hosp Geneva, NCT01764646 | T1–T3a N0 M0 | 36.25 Gy SBRT 9 days<br>36.25 Gy SBRT once/week | Acute, late toxicity |
| Swedish HYPO-RT-PC, ISRCTN45905321 | Intermediate-risk | 78 Gy, 2 Gy/fx RT<br>42.7 Gy, 6.1 Gy/fx | bDFS |
| Royal Marsden PACE, CRUKE/12/025<br>**PACE trial** | T1–T2 N0 M0 | Prostatectomy vs. SBRT (36.25–38 Gy, 4–5 fxs)<br>SBRT vs. conventional RT (78 Gy, 2 Gy/fx) | 5-year bDFS |

- Additional dose-escalation and phase 2 studies continue to explore MTDs and varying schedules of prostate SBRT

# Conclusion

- Prostate Cancer has a unique biology that appears to favor higher doses/fx with external RT
- There is mature data regarding Hypo-fx RT for prostate cancer→ Standard of care
- SBRT is a(n) ~~cautious validated~~ alternative
  - Should be performed at “high volume” centers with expertise
  - Promising early results, limited long-term data
  - Mixed QOL parameters must continue to be explored with greater follow-up

# Thank you

# Hypofractionated Experience

- 1960s-1980s, St. Thomas Hospital London, 209pts
  - 55Gy/12fx's, then
  - 36Gy/6fx's (Lloyd Davies)
    - No PSA, low rectal, urologic toxicity

# 7yr Outcomes, Katz et al

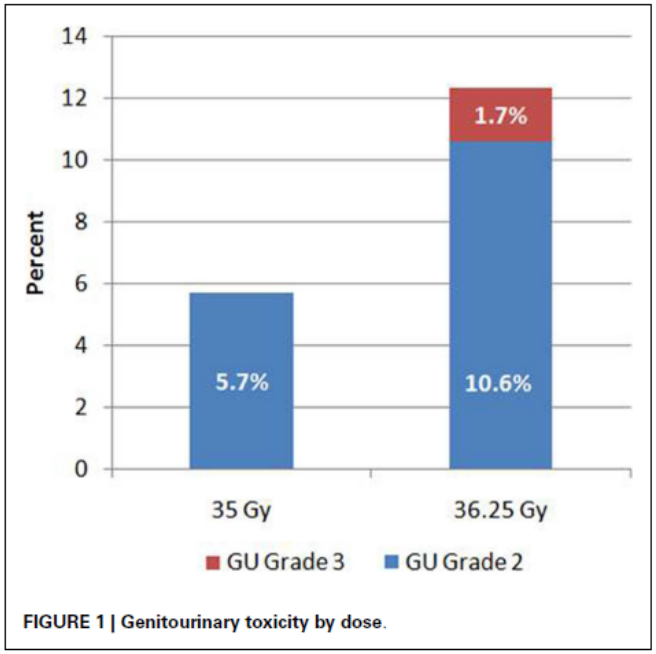


FIGURE 1 | Genitourinary toxicity by dose.

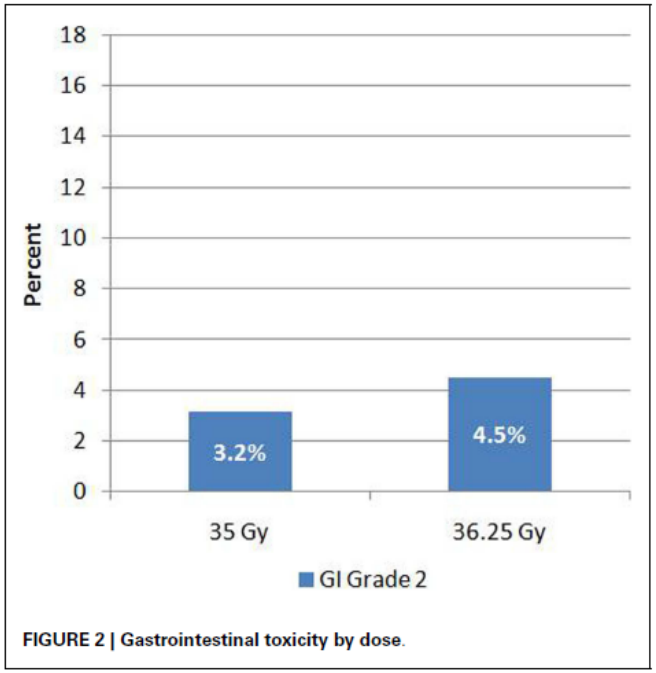


FIGURE 2 | Gastrointestinal toxicity by dose.

- 7.25Gy/fx on steep part of curve?
  - Daily vs. QOD fractionation

Katz et al, Frontiers, 2014

# SBRT

- BUT
  - Contours must be pristine, as if through TRUS
    - Thin CT slices
    - 3T MRI fusion
    - Define base-v-bladder neck, apex accurately
      - Not just “rules of thumb”
  - Intrafraction prostatic motion must be accounted for
    - Translation +/- Rotation

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Clinical Investigation: Genitourinary Cancer

# 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 in revised form Aug 17, 2013. Accepted for publication Aug 19, 2013.

- 864 patients treated w SBRT, 2005-2012
  - Self-reported QOL prospectively measured
  - Phase 2 clinical trials of SBRT for localized dz

- Transient decline in urinary and bowel domains w/in 3 mos post Tx
  - returned to baseline w/in 6 mos and remained so at 5yrs

**Table 1** Mean baseline Expanded Prostate Cancer Index Composite scores and change over time relative to baseline for all patients following prostate stereotactic body radiation therapy

| Time | Number of patients | Urinary domain | Bowel domain | Sexual domain |
|---|---|---|---|---|
| Baseline | 864 | 89 ± 12 | 95 ± 9 | 53 ± 28 |
| 1-3 mo | 826 | −8.7 [−9.5 to −7.8] | −12 [−13.1 to −11] | −5.1 [−6.5 to −3.7] |
| 6 mo | 500 | −0.95 [−1.9 to 0.01] | −3.5 [−4.5 to −2.5] | −4.2 [−5.8 to −2.5] |
| 9 mo | 388 | −2.9 [−4.1 to −1.7] | −4.0 [−5.1 to −2.9] | −6.1 [−8.1 to −4] |
| 12 mo | 658 | −2.5 [−3.4 to −1.6] | −3.2 [−4.2 to −2.3] | −5.5 [−7 to −4] |
| 24 mo | 489 | −0.6 [−1.5 to 0.3] | −1.1 [−2 to 0.2] | −6.1 [−7.9 to −4.4] |
| 36 mo | 388 | 0.4 [−0.6 to 1.3] | −0.85 [−2.2 to 0.5] | −7.3 [−9.3 to −5.3] |
| 48 mo | 271 | 1.9 [0.9 to 2.8] | 0.6 [−0.3 to 1.4] | −10.6 [−12.4 to −8.7] |
| 60 mo | 194 | 1.8 [0.7 to 2.9] | 0.9 [0 to 1.9] | −13.1 [−14.9 to −11.3] |
| 72 mo | 63 | 2.3 [0.9 to 3.7] | 1.8 [0.6 to 3] | −13.7 [−16.2 to −11.1] |

Negative values indicate a decline and positive values indicate an improvement over baseline scores. The 95% confidence interval is given in brackets.

Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):939-45

International Journal of Radiation Oncology biology • physics

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Clinical Investigation: Genitourinary Cancer

# Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,† Christopher Straka, BS,* Alana Christie, MS,‡ Yair Lotan, MD,§ David Pistenmaa, MD,* Brian D. Kavanagh, MD,‖ Akash Nanda, MD, PhD,¶ Patrick Kueplian, MD,# Jeffrey Brindle, MD,** Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD,‖ Xian-Jin Xie, PhD,‡ and Robert D. Timmerman, MD*

**Table 2** Worst acute and delayed rectal toxicity in patients by radiation prescription dose level

| | 45 Gy (n=15) | | 47.5 Gy (n=15) | | 50 Gy (n=61) | |
|---|---|---|---|---|---|---|
| Grade | Acute | Late | Acute | Late | Acute | Late |
| 0 | 9 (60.0) | 10 (66.7) | 7 (46.7) | 8 (53.3) | 23 (37.7) | 20 (32.8) |
| 1 | 6 (40.0) | 4 (26.7) | 4 (26.7) | 2 (13.3) | 23 (37.7) | 21 (34.4) |
| 2 | 0 | 1 (6.7) | 4 (26.7) | 5 (33.3) | 13 (21.3) | 15 (24.6) |
| 3 | 0 | 0 | 0 | 0 | 1* (1.6) | 3 (4.9) |
| 4 | 0 | 0 | 0 | 0 | 1 (1.6) | 2 (3.3) |

# MSKCC SBRT Dose Escalation

Zelefsky M, et al, ASTRO 2017

| Dose | Median f/u | PSA failure | Positive Biopsy % | Fav Int Risk positive Bx | Unfav Int Risk positive Bx |
|---|---|---|---|---|---|
| 32.5 Gy | 60 mos | 20% | 48% | 40% | 100% |
| 35 Gy | 60 mos | 2.9% | 19% | 25% | 33% |
| 37.5 Gy | 44 mos | 0% | 17% | 25% | 0% |
| 40 Gy | 33 mos | 2.9% | 8% | 0% | 40% |

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 2, pp. 527–533, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2005.07.981

**CLINICAL INVESTIGATION** **Prostate**

## BIOLOGICALLY EFFECTIVE DOSE VALUES FOR PROSTATE BRACHYTHERAPY: EFFECTS ON PSA FAILURE AND POSTTREATMENT BIOPSY RESULTS

RICHARD G. STOCK, M.D.,* NELSON N. STONE, M.D.,† JAMIE A. CESARETTI, M.D.,* AND BARRY S. ROSENSTEIN, PH.D.*

| BED groups | Number of patients | Percent positive | |
|---|---|---|---|
| ≤100 | 33 | 24% | |
| >100–120 | 20 | 15% | |
| >120–140 | 33 | 6% | |
| >140–160 | 52 | 6% | |
| >160–180 | 82 | 7% | |
| >180–200 | 72 | 1% | |
| >200 | 131 | 3% | $p < 0.0001$ |

*Abbreviation:* BED = biologically effective dose.

## THE CLINICAL SIGNIFICANCE OF A POSITIVE POST-IRRADIATION PROSTATIC BIOPSY WITHOUT METASTASES

BRADLEY R. PRESTIDGE, M.D.,* IRVING KAPLAN, M.D.,† RICHARD S. COX, PH.D.† AND MALCOLM A. BAGSHAW, M.D.†

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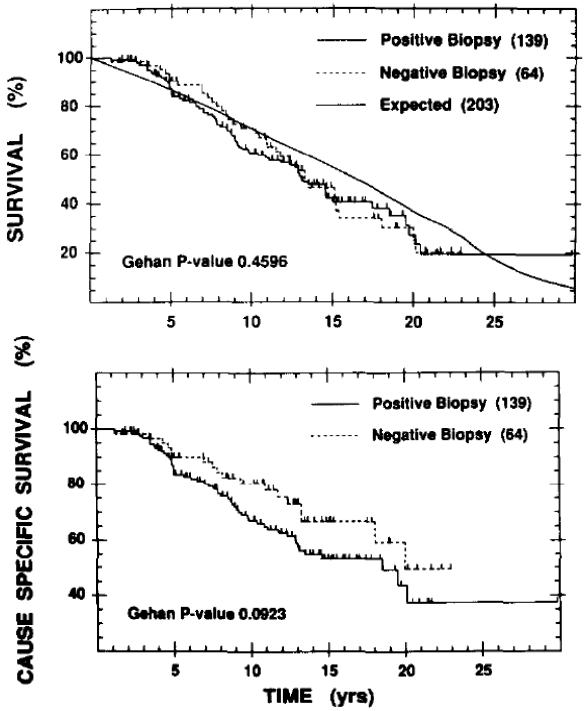
†Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA

*Int. J. Radiation Oncology Biol. Phys.*, Vol. 24, pp. 403–408 1992

**To define the prognostic value of a post-irradiation prostatic biopsy, the outcome of 203 previously irradiated patients who underwent post-treatment biopsy was analyzed. The majority of patients were selected for biopsy based on an abnormal digital rectal exam or elevated prostate specific antigen. Patients with distant metastases found at the time of biopsy were excluded from further analysis. One hundred thirty-nine (139) of these had a positive biopsy and 64 were negative. Those with a positive biopsy tended to present with more locally-advanced (Stage B2/C) tumors (61%) compared to those with negative biopsies (42%). The 10- and 15-year survival and cause-specific survival from the time of initial presentation were similar for both groups. However, those with a negative biopsy had a more favorable survival and cause-specific survival from the time of post-treatment biopsy and were less likely to develop distant metastases than the positive biopsy group. These data suggest that a positive prostatic biopsy is associated with a greater likelihood of subsequent distant relapse and decreased survival following biopsy relative to patients with negative biopsies. Since a positive post-treatment biopsy is more likely among patients presenting with locally-advanced disease, perhaps more aggressive initial therapy (i.e., interstitial boost or hyperthermia) would benefit this subgroup.**




- Stanford, 1956-1989, 139pts w pos bx
  - 40 observed
  - 99 received various secondary therapies

# 7yr Outcomes, Katz et al

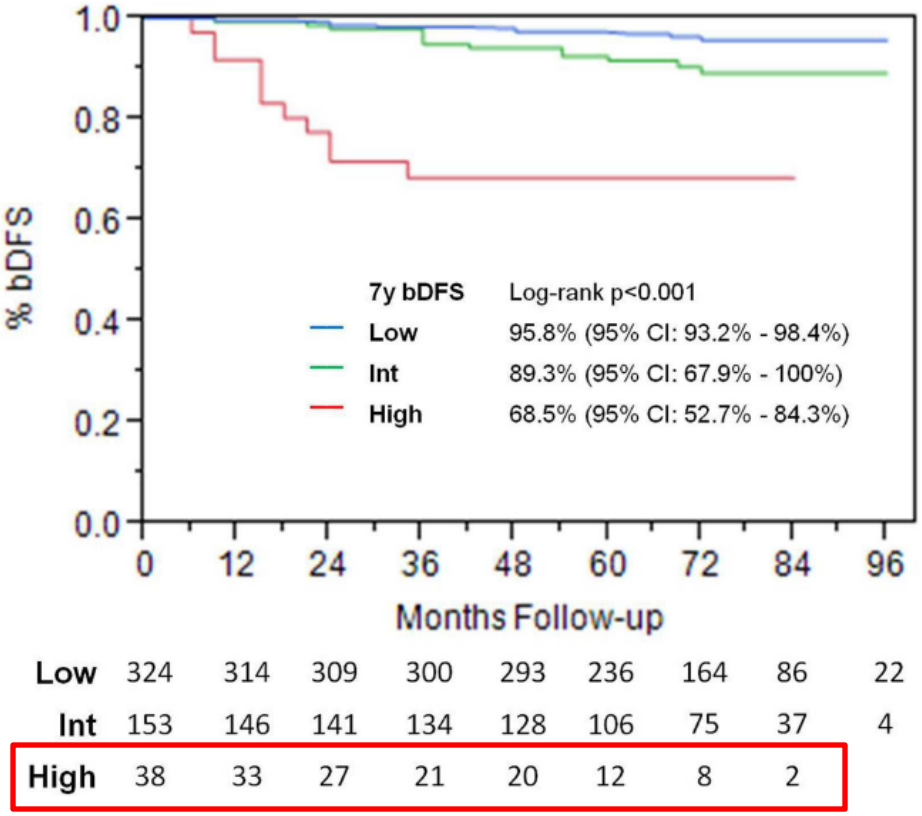



**Table 2 | Univariate (UVA) and multivariate (MVA) logistic regression analyses looking at patient characteristics and the effect on Grade 2 or higher late GU toxicity.**

| Factor | UVA | MVA | |
|---|---|---|---|
| | *p* | *p* | RR (95% CI) |
| Prostate size (above or below 60 cc) | 0.03 | 0.03 | 0.86 (0.66–1.13) |
| Dose (35 versus 36.25 Gy) | 0.051 | <0.0001 | 3.31 (2.17–5.35) |
| Baseline GU EPIC score (above or below 90) | 0.39 | 0.58 | 0.93 (0.71–1.21) |

Katz et al, Frontiers, 2014