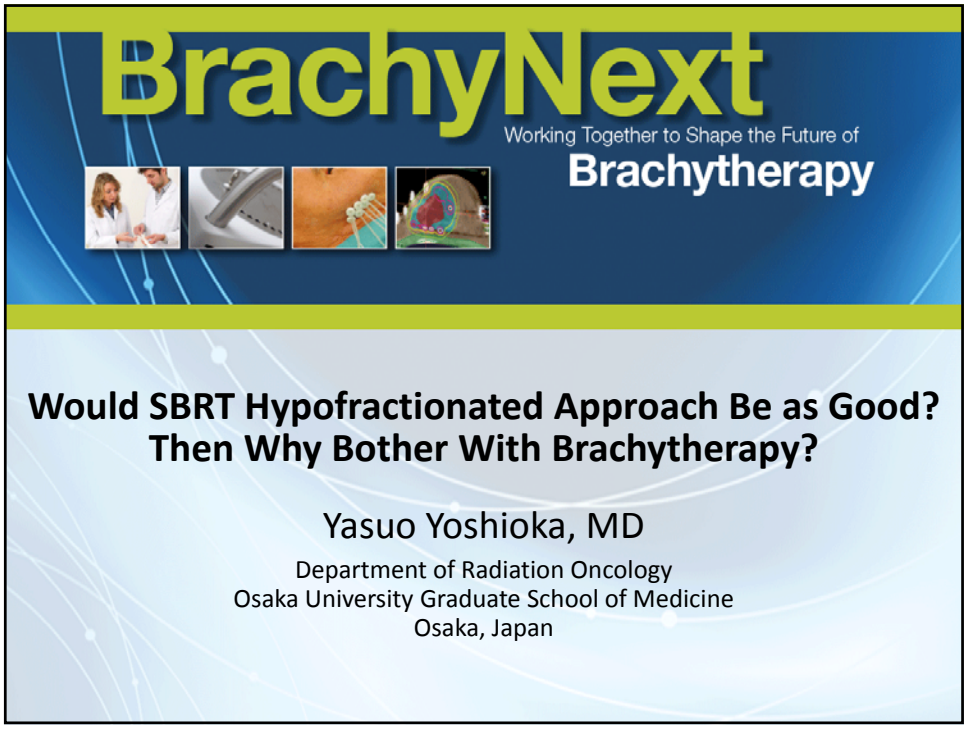



# Would SBRT Hypofractionated Approach Be as Good? Then Why Bother With Brachytherapy?

Yasuo Yoshioka, MD

Department of Radiation Oncology
Osaka University Graduate School of Medicine
Osaka, Japan

## Disclosure

Yasuo Yoshioka, MD, does not have any financial relationships or products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

## Background

Typical IMRT (1.8–2 Gy/fr) has problems of…

- Long treatment period of 2 months
  - Burden to patients
  - Burden to medical staff
  - Burden to machine resources
- Difficulty in controlling intra-fraction error
  - Wider margin
  - Toxicity concern
  - Moderate dose escalation
- Not utilizing low α/β ratio of prostate caner

HDR brachytherapy (especially monotherapy) solution

▸▸▸ SBRT solution??

## Aim

To discuss similarity and difference

between HDR monotherapy and SBRT,

in terms of

✓ radiation physics (dose distribution)
✓ radiobiology (dose, dose-fractionation)
✓ reported clinical results

in the context of extreme hypofractionation.

EXPERT REVIEWS

# Extreme hypofractionation for prostate cancer

Expert Rev. Anticancer Ther. 9(1), 61–65 (2009)

W Robert Lee
Duke University School of Medicine, Depu Radiation Onco Box 3085, Durh NC 27710, USA Tel.: +1 919 66 Fax: +1 919 66 w.robert.lee@d

In ideal circumstances the fractionation schedule of radiotherapy should match the fractionation sensitivity of the tumor relative to the nearby normal tissues. A number of recent publications

**Table 1. Results with high-dose-rate monotherapy.**

| Author (year) | Patients (n) | Fractionation schedule | Median FU (months) | 3-year FFBR (%) | Acute toxicity ≥ grade 3 (%) | | Late toxicity ≥ grade 3 (%) | | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | GI | GU | GI | GU | |
| Yoshioka *et al.* (2000, 2006) | 111 | 48 Gy/8 fx/5 days or 54 Gy/9 fx/5 days | 27 | 83 | 0 | 5 | 1 | 0 | [7,8] |
| Grills *et al.* (2004) | 65 | 38 Gy/4 fx/2 days | 34 | 98 | 0 | 10 | 0 | 6 | [11] |
| Martin *et al.* (2004) | 52 | 38 Gy/4 fx/2 days | 8 | NR | 0 | 4 | NR | NR | [14] |
| Corner *et al.* (2008) | 110 | 34 Gy/4 fx/2 days or 36 Gy/4 fx/2 days or 31.5 Gy/3 fx/2 days | 11.8–27 | NR | 0 | 6 | 0 | 2 | [15] |

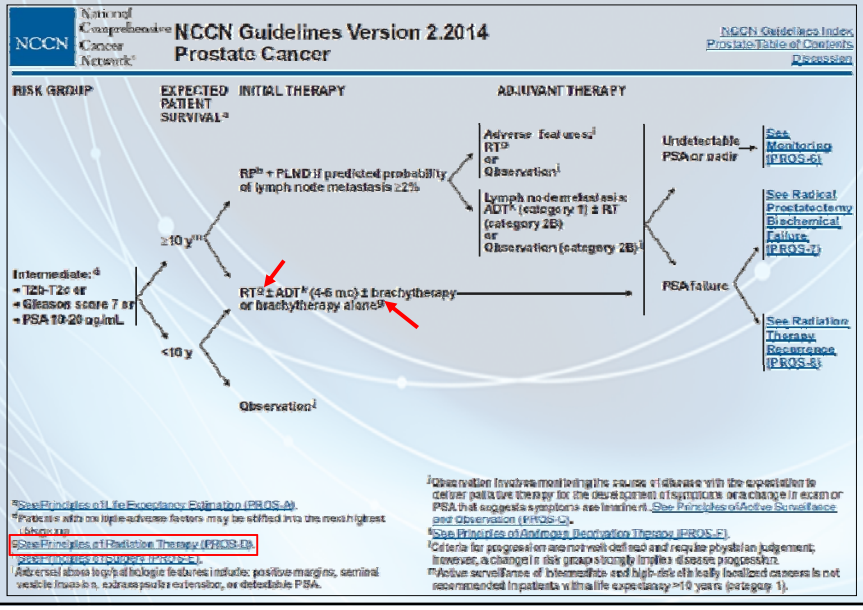
FFBR: Freedom from biochemical recurrence; FU: Follow-up; fx: Fractions; GI: Gastrointestinal; GU: Genitourinary; NR: Not reported.

**Table 2. Results with stereotactic body radiosurgery.**

| Author (year) | Patients (n) | Fractionation schedule | Median FU (months) | 5-year FFBR (%) | Acute toxicity ≥ grade 3 (%) | | Late toxicity ≥ grade 3 (%) | | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | GI | GU | GI | GU | |
| Madsen *et al.* (2007) | 40 | 33.5 Gy/5 fx/5 days | 41 | 70 | 0 | 2.5 | 0 | 0 | [16] |
| King *et al.* (2008) | 41 | 36.25 Gy/5 fx/5–10 days | 33 | 100 | 0 | 5 | 0 | 5 | [17] |

FFBR: Freedom from biochemical recurrence; FU: Follow-up; fx: Fractions; GI: Gastrointestinal; GU: Genitourinary; NR: Not reported.

# Where Are HDR and SBRT Standing?



# Where Are HDR and SBRT Standing?

NCCN Guidelines Version 2.2014
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion

**PRINCIPLES OF RADIATION THERAPY**

Primary External Beam Radiation Therapy (EBRT)

- 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 to 4 Gy per fraction over 4-5 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.
- Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2 to 3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4- to 6-mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques of IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.

Primary/Salvage Brachytherapy

- Permanent low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, consider combining brachytherapy with EBRT (40-50 Gy) ± 4- to 6-mo neoadjuvant/concomitant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 2 to 3 y neoadjuvant/concomitant/adjuvant ADT.
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity would be expected from ADT and prostate size may not decline.
- Post-implant dosimetry must be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for Iodine-125 and 125 Gy for Palladium-103. The corresponding boost doses after 40 to 50 Gy EBRT are 110 Gy and 90 to 100 Gy, respectively.
- High-dose rate (HDR) brachytherapy can be used alone or in combination with EBRT (40-50 Gy) instead of LDR. Commonly used boost regimens include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone includes 13.5 Gy x 2 fractions.
- Permanent LDR or temporary HDR brachytherapy can be used as treatment for a local recurrence following EBRT or primary brachytherapy. Radiation dose depends on the original primary external beam dose and ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

# "Classics" of Prostate Hypofractionation (Era of 2D or Early 3D. No IMRT)

Carcinoma of prostate treated by radical external beam radiotherapy using hypofractionation. Twenty-two years' experience (1962-1984).
Lloyd-Davies RW, et al. *Urology.* 1990;36:107-111.（UK）
36 Gy/6 fr (6 Gy/fr), n = 209

Randomized trial comparing two fractionation schedules for patients with localized prostate cancer.（Canada）
Lukka H, et al. *J Clin Oncol*. 2005;23:6132-6138.
52.5 Gy/20 fr (2.625 Gy/fr) vs 66 Gy/33 fr (2 Gy/fr), n = 936

Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial.（Australia）
Yeoh EE, et al. *Int J Radiat Oncol Biol Phys*. 2011;81:1271-1278.
55 Gy/20 fr (2.75 Gy/fr) vs 64 Gy/32 fr (2 Gy/fr), n = 217

## Moderate Hypofractionation (2.4–4 Gy/fr) "Modern" Clinical Trials, Using IGRT + 3D-CRT or IMRT

Table 1 Moderate Hypofractionation: Contemporary Superiority Trials

| Study (Author) | Sample Size | ADT (%) | Median Follow-up | Randomization Arms | Toxicity | Efficacy |
|---|---|---|---|---|---|---|
| Regina Elena (Arcangeli) | 168 | 100 | 5.8 years | 80 Gy/2 Gy<br>62 Gy/3.1 Gy | NS | NS |
| FCCC (Pollack) | 303 | 45 | 5.5 years | 76 Gy/2 Gy<br>70.2 Gy/2.7 Gy | Hypofractionation: worse GU effects | NS |
| MDACC (Kuban) | 204 | 21 | 4.7 years | 75.6 Gy/1.8 Gy<br>72 Gy/2.4 Gy | NS | NS |

Abbreviations: ADT, androgen deprivation therapy; FCCC, Fox Chase Cancer Center; GU, genitourinary; MDACC, MD Anderson Cancer Center; NS, no significant difference.

Table 2 Moderate Hypofractionation: Ongoing Noninferiority Trials

| Study (Group) | Sample Size | Risk Group | Randomization Arms |
|---|---|---|---|
| CHHiP (MRC) | 3216 | Intermediate/ low | 74 Gy/2 Gy<br>57 Gy/3 Gy<br>60 Gy/3 Gy |
| 0415 (RTOG) | 1067 | Low | 73.8 Gy/1.8 Gy<br>70 Gy/2.5 Gy |
| PROFIT (OCOG) | 1204 | Intermediate | 76 Gy/2 Gy<br>60 Gy/3 Gy |

Abbreviations: CHHiP, conventional or hypofractionated high-dose intensity-modulated radiotherapy in prostate cancer; MRC, Medical Research Council; OCOG, Ontario Clinical Oncology Group; PROFIT, Prostate Fractionated Irradiation Trial; RTOG, Radiation Therapy Oncology Group.

Cabrera AR, Lee WR. Hypofractionation for clinically localized prostate cancer. *Semin Radiat Oncol*. 2013;23:191-197.

In near future, 70 Gy/2.5 Gy or 60 Gy/3 Gy（IGRT + IMRT) may become the standard

## Extreme Hypofractionation Trials （6 Gy/fr or More, Excluding HDR Brachy）

Table 3 Extreme Hypofractionation: Phase I/II Studies

| Author (Institution) | Sample Size (Risk Group) | Median FU (Months) | Regimen | Grade 2+ Toxicity (%) | FFBR (%) |
|---|---|---|---|---|---|
| Madsen (VMMC) | 40 (Low) | 41 | 33.5 Gy/6.7 Gy | GU: 20<br>GI: 7.5 | 90 |
| King (Stanford) | 67 (Low to low-intermediate) | 32 | 36.25 Gy/7.25 Gy | GU: 8.5<br>GI: 2 | 94 |
| Friedland (Naples) | 112 (Low > intermediate > high) | 24 | 35 Gy/7 Gy | <10 | >95 |
| Katz (Wiathrop) | 304 (Low > intermediate > high) | 30<br>17 | 35 Gy/7 Gy<br>36.25 Gy/7.25 Gy | <10 | >95 |
| McBride (multicenter) | 45 (Low) | 44.5 | 37.5 Gy/7.5 Gy<br>36.25 Gy/7.25 Gy | GU: 19<br>GI: 12 | 98 |
| Boike (multicenter) | 45 (60% intermediate, 40% low) | 30<br>18<br>12 | 45 Gy/9 Gy<br>47.5 Gy/9.5 Gy<br>50 Gy/10 Gy | GI: 18<br>GU: 31 | 100 |

Abbreviations: FFBR, freedom from biochemical recurrence; FU, follow-up; GU, genitourinary; GI, gastrointestinal; VMMC, Virginia Mason Medical Center.

Cabrera AR, Lee WR. Hypofractionation for clinically localized prostate cancer. *Semin Radiat Oncol*. 2013;23:191-197.

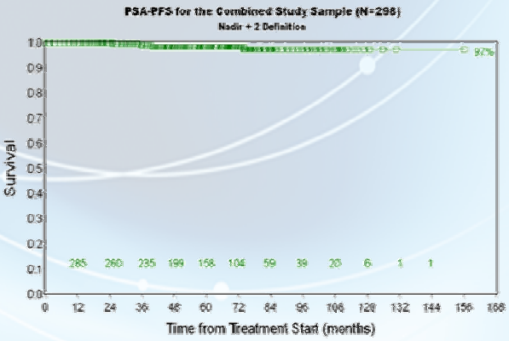
CLINICAL INVESTIGATION — Prostate

## HIGH-DOSE-RATE MONOTHERAPY: SAFE AND EFFECTIVE BRACHYTHERAPY FOR PATIENTS WITH LOCALIZED PROSTATE CANCER

D. Jeffrey Demanes, M.D.,* Alvaro A. Martinez, M.D.,† Michel Ghilezan, M.D.,† Dennis R. Hill, M.D.,‡ Lionel Schour, M.D.,‡ David Brandt, M.S.,‡ and Gary Gustafson, M.D.‡

*California Endocurietherapy at UCLA, Department of Radiation Oncology, David Geffen School of Medicine of the University of California at Los Angeles, Los Angeles, CA; †William Beaumont Hospital, Royal Oak, MI; and ‡California Endocurietherapy, Oakland, CA

N = 298
42 Gy/6 fr. CET
38 Gy/4 fr. WBH
Median follow-up: 5.2 years
97% biochemical control at 8 years
3% GU Grade 3
10% GU Grade 2
<1% GI

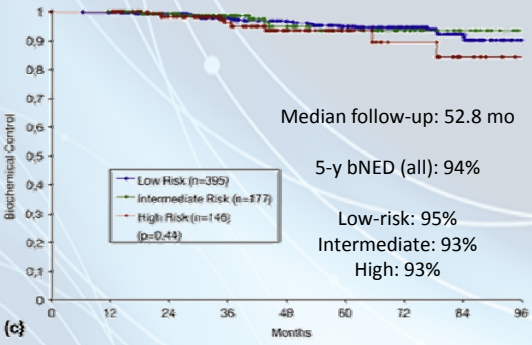



Demanes DJ, Martinez AA, et al. *Int J Radiat Oncol Biol Phys.* 2011;81:1286-1292.

## Largest Series of HDR Monotherapy for Low-, Intermediate-, and High-Risk Prostate Cancer

718 patients (low-high risk) treated by HDR monotherapy

9.5 Gy x 4 fr (1 implant) (2 days) → 9.5 Gy x 4 fr (2 implants) (2 weeks) → 11.5 Gy x 3 fr (3 implants) (3 weeks)




Median follow-up: 52.8 mo

5-y bNED (all): 94%

Low-risk: 95%
Intermediate: 93%
High: 93%

Hormone therapy (median mo [range])

Low: 4 (3-6)
Inter: 6 (6-10)
High: 9 (9-14)

Overall: 9 (3-14)

Toxicity (per event)

Acute GU G3: 5.4%
Acute GI G3: 0.2%
Late GU G3: 3.5%
Late GI G3: 1.6%
(None G4-5)

Zamboglou N, et al. *Int J Radiat Oncol Biol Phys.* 2013;85:672-678. (Offenbach, Germany)

## HDR Monotherapy for Intermediate-/High-Risk Prostate Cancer: the Longest Follow-up Series

Patient characteristics

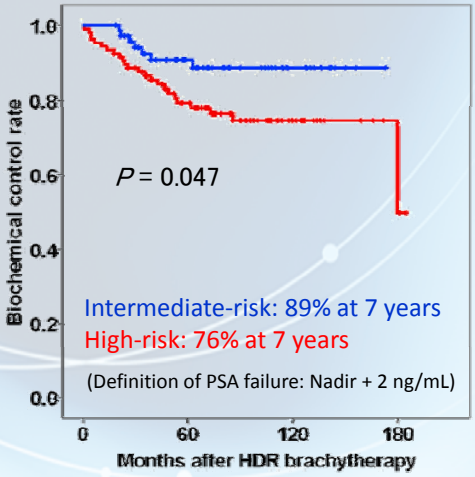
| | |
|---|---|
| Treatment period | 1995-2011 |
| No. of patients | 177 |
| Risk category | |
| Intermediate | 71 (40%) |
| High | 106 (60%) |
| Hormone | |
| Yes | 133 (75%) |
| No | 44 (25%) |
| Follow-up period (years) | |
| Median | 6.8 |
| Range | 1.5-17.4 |

Definitions of
intermediate: T2b-c, GS=7 or 10≤PSA<20
high: T3-4, GS≥8 or PSA≥20

HDR monotherapy regimen

| | |
|---|---|
| 1995-1996 | 48 Gy/8 fr/ 5 days |
| 1996-2005 | 54 Gy/9 fr/ 5 days |
| 2005-2011 | 45.5 Gy/7 fr/ 5 days |

Biochemical control rate




Presented at ESTRO 2014 (Vienna)
by Yoshioka Y (Osaka, Japan)

## Literature on HDR Monotherapy for Intermediate-/High-Risk Prostate Cancer

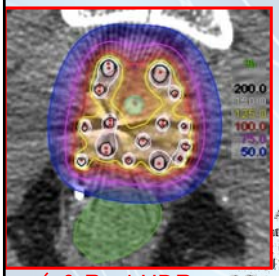
| Author [Country] | Total dose/ Fractions | No. of patients | Follow-up (y) | PSA control rate/ Risk group | Late toxicity ≥ Grade 2* GU | Late toxicity ≥ Grade 2* GI |
|---|---|---|---|---|---|---|
| Rogers [USA] | 39 Gy/6 Fr. | 284 | 2.7 | 94% (5y)/Intermediate | 7.7% | 0.0% |
| Zamboglou [Germany] | 38 Gy/4 Fr. | 141 | 4.4 | 95% (5y)/Low<br>93% (5y)/Intermediate<br>93% (5y)/High | 27.5% | 2.6% |
| | 38 Gy/4 Fr. | 351 | | | | |
| | 34.5 Gy/3 Fr. | 226 | | | | |
| Hoskin [UK] | 34 Gy/4 Fr. | 34 | 3.5 | 95% (3y)/Intermediate<br>87% (3y)/High | 33.0% | 13.0% |
| | 36 Gy/4 Fr. | 25 | | | 40.0% | 4.0% |
| | 31.5 Gy/3 Fr. | 55 | | | 34.0% | 7.0% |
| Present study [Japan] | 48 Gy/8 Fr.<br>54 Gy/9 Fr.<br>45.5 Gy/7 Fr. | 177 | 6.8 | 89% (7y)/Intermediate<br>76% (7y)/High | 12.4% | 4.5% |

*Scored per event not per patient.

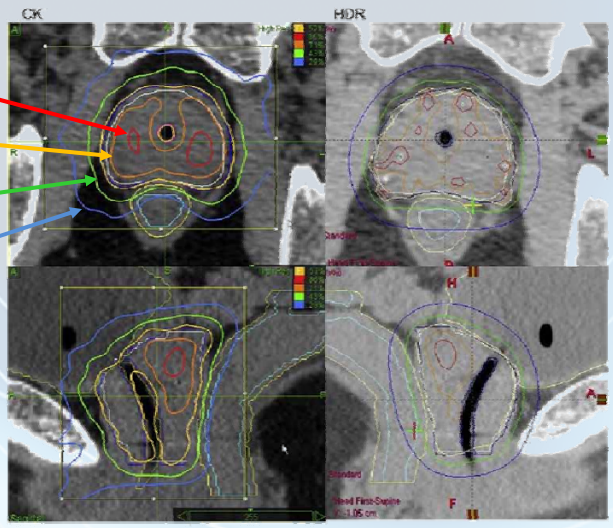
Rogers CL, et al. *J Urol*. 2012;187:109-116.
Zamboglou N, et al. *Int J Radiat Oncol Biol Phys*. 2013;85:672-678.
Hoskin P, et al. *Int J Radiat Oncol Biol Phys*. 2012;82:1376-1384.

## "Virtual HDR" (CyberKnife)

Indeed, this arrangement of isodose lines resembles HDR…



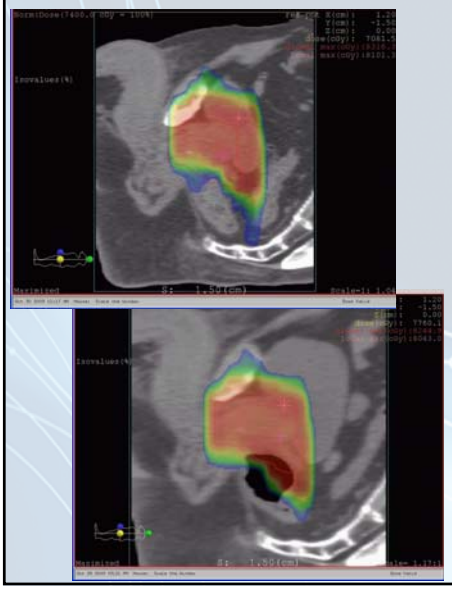
(cf. Real HDR at Osaka Univ.)

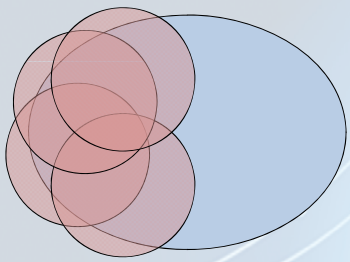



Axial and sagittal comparison: CyberKnife (CK) vs. simulated high-dose-rate (HDR) dosimetry. White line = prostatic contour; dark blue line = 2-mm planning target volume expansion. Isodose lines shown as follows: 150%, red; 125%, 100%, yellow (very light on HDR image); 75%, green; and 50%, blue. Note similar morphologic characteristics of 125%, and 150% coverage lines, with partial exclusion of the urethra from 100% isodose volume coverage with CK (left) and lower rectal wall and mucosa 75% and 50% isodose volume with CK (left).

Fuller, et al. *Int J Radiat Oncol Biol Phys. 2008;*70;1588-1597.

## Influence of "Interplay Effect" 2D < 3D-CRT < IMRT < SBRT+IMRT?





Small field (segment) irradiation would be easily influenced by interplay effect, which never be adjusted by re-registration before irradiation

Stanford 2008

Intrafractional motion of the prostate during hypofractionated radiotherapy.

Xie Y, et al. *Int J Radiat Oncol Biol Phys.* 2008;72:236-246.

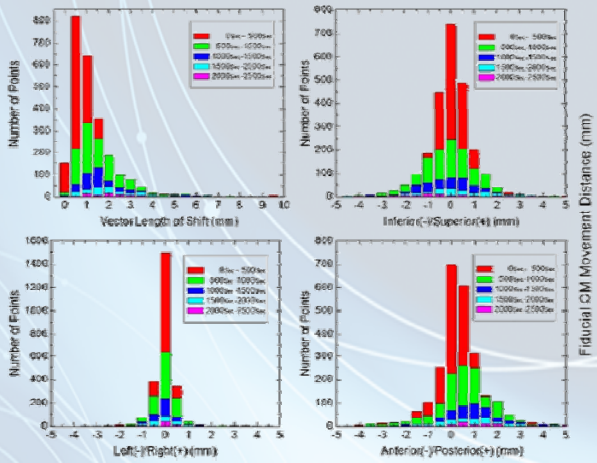



Fig. 4. A smaller shift observed for a shorter interval (red), whereas a larger shift for a longer interval (green, blue)

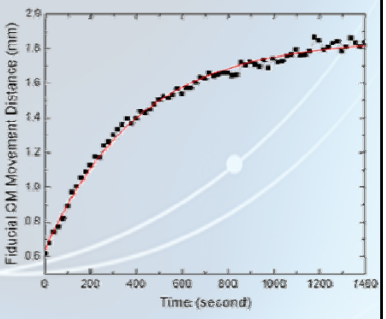



Fig. 5. The amount of shift increases according to time

## Intra-fractional Motion Is Not Constant

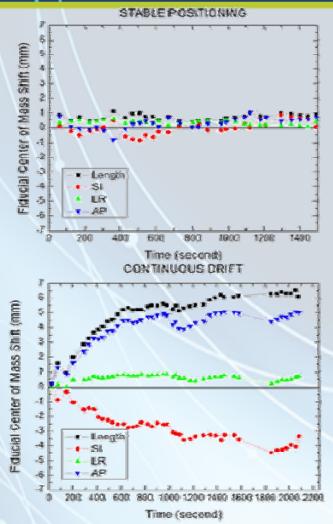



Fig. 6(a), (b).Different patterns among different patients

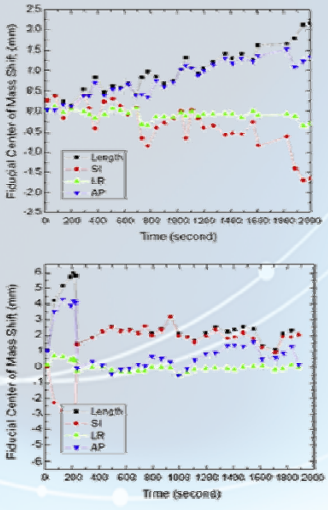



Fig. 7(d), (j). Different patterns among different fractions <u>in the same patient</u>

Xie Y, et al. *Int J Radiat Oncol Biol Phys*. 2008;72:236-246.

## "Ignorance Is Bliss" — What You Don't Know Never Hurts You —

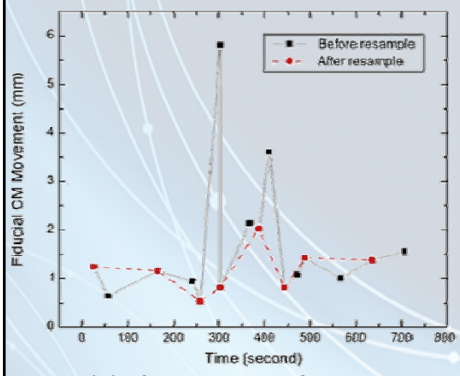



Fig. 9(b). If the interval of imaging becomes twice (ie, shot frequency is 1/2), the shift looks smaller significantly

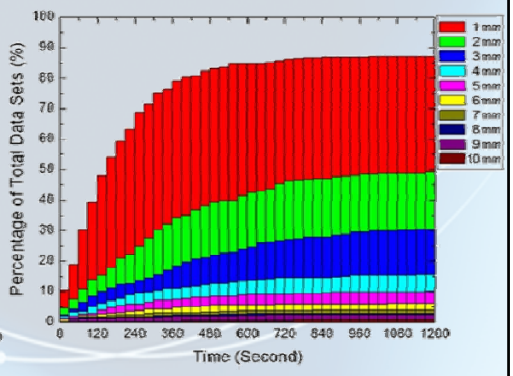



Fig. 10. Shorter interval imaging is needed to detect a smaller shift with less probability

Xie Y, et al. *Int J Radiat Oncol Biol Phys*. 2008;72:236-246.

Radiotherapy and Oncology 109 (2013) 217–221

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]

Table 1
Patient and treatment characteristics (n= 1100[†]).

| Risk group | N (%) | 35 Gy | 36.25 Gy | 38–40 Gy | ADT use | FU[‡] |
|---|---|---|---|---|---|---|
| Low | 641 (58%) | 254 (40%[*]) | 319 (50%) | 68 (11%) | 50 (8%) | 36 |
| Intermediate | 334 (30%) | 108 (32%) | 188 (56%) | 38 (11%) | 49 (15%) | 30.5 |
| High | 125 (11%) | 23 (18%) | 82 (66%) | 20 (16%) | 48 (38%) | 23 |
| Total | 1100 | 385 (35%) | 589 (54%) | 126 (11%) | 147 (14%) | |

[†] Participating institutions:
Flushing Radiation Oncology, Flushing, NY.
Naples Radiation Oncology, Naples, FL.
Dept. of Radiation Oncology, Beth Israel Deaconness, Boston, MA.
Radiosurgery Medical Group, San Diego, CA.
Division of Radiation Oncology, San Bortolo Hospital, Vicenza, Italy.
Dept. of Radiation Oncology, Stanford, CA.
Dept. of Radiation Oncology, Georgetown University, Washington DC.
Dept. of Radiation Oncology, Swedish Medical Center, Seattle, WA.
[*] % calculated with respect to the total number of patients within each respective risk-group.
[‡] Median follow-up (in months).

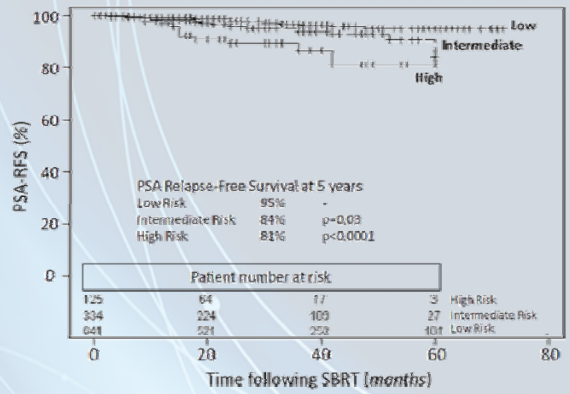


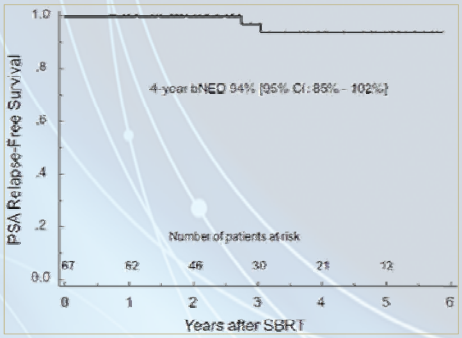

Table 3
Comparisons of 5-year PSA relapse-free survival rates by risk group and substratified by use of ADT or total dose.

| | 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 |

NE, no events.
Reference group.

King, et al. *Radiother Oncol*. 2013;109;217-221.

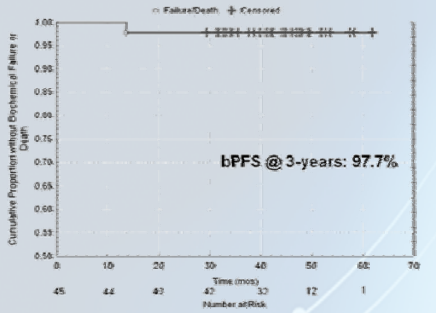
Stanford 2012
King CR, et al. *Int J Radiat Oncol Biol Phys*. 2012;82:877-882




2003-2009
67 low-risk patients
Median follow-up: 2.7 years

36.25 Gy/5 fractions
(7.25 Gy/fraction)

Harvard, others (multicenter) 2012
McBride SM, et al. *Cancer*. 2012;118:3681-3690




4 centers, phase I trial
45 low-risk patients
34 pts: 7.5 Gy x 5 fractions
9 pts: 7.25 Gy x 5 fractions
2 pts: other regimens
Median follow-up: 44.5 months
bPFS rate at 3 years: 97.7%
G3 late GU: 1 pt (stricture→TUR-P)
G3 late GI: 2 pts (rectal bleed→APC)
G2 late GU: 7 pts (17%)
G2 late GI: 3 pts (7%)

UCSF 2012

Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response.

Jabbari S, et al. *Int J Radiat Oncol Biol Phys.* 2012;82:228-234.

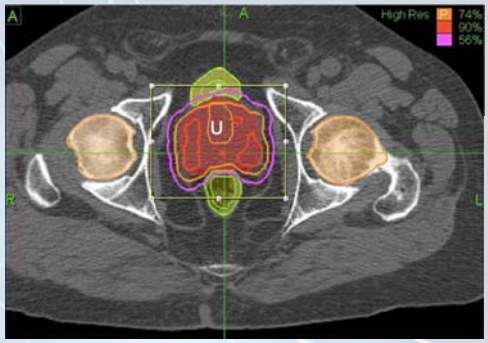


Table 3. Maximum late GU and GI toxicity for all SBRT patients

| | |
|---|---|
| Max. reported late GU toxicity | |
| 0 | 32 (84%) |
| 1 | 1 (3%) |
| 2 | 3 (8%) |
| 3 | 2 (5%) |
| Max. reported late GI toxicity | |
| 0 | 35 (92%) |
| 1 | 2 (5%) |
| 2 | 1 (3%) |

38 prostate cancer (low-high risk)
Median follow-up: 18.3 months
100% biochemical control
（hormone used for 47% pts）

20 patients (mainly low-intermediate risk):
9.5 Gy x 4 fractions

18 patients (mainly high-risk):
Whole-pelvis IMRT 45-50 Gy
+ 9.5 Gy x 2 fractions

Margin: 0/0 mm for first 15 pts,
2/0-2 mm for latter 23 pts

60-80% isodose line prescription

## Reported Clinical Results of Robotic SBRT

| Author | Institution | No. of patients | Median Follow-up (years) | Biochemical control/ Risk group | Late toxicity ≥ Grade 2 | |
|---|---|---|---|---|---|---|
| | | | | | GU | GI |
| King | Stanford | 67 | 2.7 | 94% at 4y/Low | 9% | 2% |
| McBride (multicenter, Prospective) | 4 centers | 45 | 3.7 | 98% at 3y/Low | 19% | 12% |
| Katz | Flushing | 50 | 6 | 97% at 5y/Low, 91% at 5y/Inter, 74% at 5y/High | 4% | 2% |
| | | 254 | 5 | | 11% | 5% |
| Ju | Georgetown | 41 | 1.8 | 98% at 2y/Inter | 44% | 7% |
| King (multicenter, pooled） | 8 centers | 1100 | 3 | 95% at 5y/Low, 84% at 5y/Inter, 81% at 5y/High | NA | NA |

**Representative Dose-fractionations and BEDs of SBRT or HDR**

| | | Physical dose | | | BED (Gy) | | $EQD_{2Gy}$ (Gy) | |
|---|---|---|---|---|---|---|---|---|
| Method | Author | Dose/fr (Gy) | No. of fractions | Total dose (Gy) | α/β =1.5 | α/β =3.0 | α/β =1.5 | α/β =3.0 |
| SBRT | McBride (multicenter, prospective) | 7.25 | 5 | 36.25 | 211 | 124 | 91 | 74 |
| | | 7.5 | 5 | 37.5 | 225 | 131 | 96 | 79 |
| SBRT | Katz | 7 | 5 | 35 | 198 | 117 | 85 | 70 |
| | | 7.25 | 5 | 36.25 | 211 | 124 | 91 | 74 |
| SBRT | King (multicenter, pooled) | 7-8, Median 7.25 | 5 | 35-40, Median 36.25 | 198 | 117 | 85 | 70 |
| | | | | | 253 | 147 | 109 | 88 |
| HDR | Yoshioka | 6 | 9 | 54 | 270 | 162 | 116 | 97 |
| HDR | Yoshioka | 6 | 8 | 48 | 240 | 144 | 103 | 86 |
| HDR | Yoshioka | 6.5 | 7 | 45.5 | 243 | 144 | 104 | 86 |
| HDR | Rogers | 6.5 | 6 | 39 | 208 | 124 | 89 | 74 |
| HDR | Demanes | 7 | 6 | 42 | 238 | 140 | 102 | 84 |
| HDR | Mark | 7.5 | 6 | 45 | 270 | 158 | 116 | 95 |
| HDR | Martinez | 9.5 | 4 | 38 | 279 | 158 | 119 | 95 |
| HDR | Zamboglou | 11.5 | 3 | 34.5 | 299 | 167 | 128 | 100 |
| HDR | Hoskin | 13 | 2 | 26 | 251 | 139 | 108 | 83 |
| HDR | Ghilezan | 13.5 | 2 | 27 | 270 | 149 | 116 | 89 |
| HDR | Hoskin | 19 | 1 | 19 | 260 | 139 | 111 | 84 |
| IMRT | Zelefsky | 1.8 | 48 | 86.4 | 190 | 138 | 81 | 83 |

## Clinical Trial: Robotic SBRT Mimicking HDR Dose Distribution and Fractionation

Official Title:
Virtual HDR CyberKnife Radiosurgery for Localized Prostatic Carcinoma: A Phase II Study

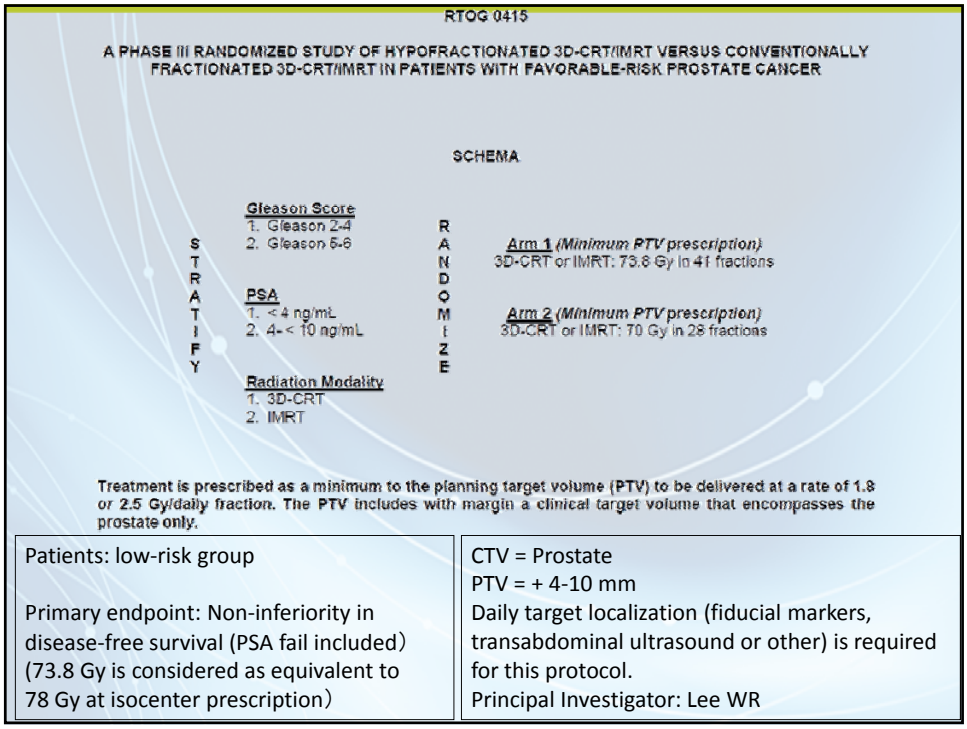
Intervention Radiation:
CyberKnife Radiosurgery 38 Gy in 4 fractions of 9.5 Gy/fx, over 4-5 days

Status Recruiting:
Start date: 2006-03
Primary completion date: 2014-12 (Anticipated)

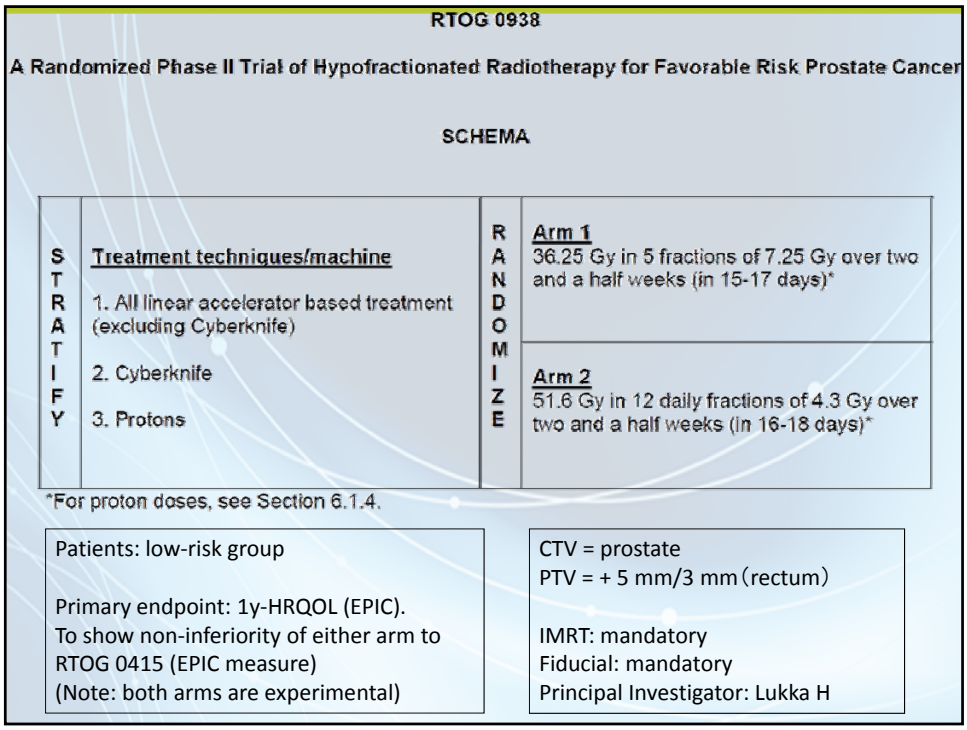
Inclusion Criteria:
T1b–T2b, NX/N0, M0
Gleason Sum <7
Prostate-specific antigen <10 ng/mL
Prostate volumes by TRUS ≤80 cc

Principal Investigator:
Donald B Fuller, MD, CyberKnife Centers of San Diego/Radiation Medical Group

http://clinicaltrials.gov/ct2/show/record/NCT01045148




| | |
|---|---|
| Patients: low-risk group<br><br>Primary endpoint: Non-inferiority in disease-free survival (PSA fail included)<br>(73.8 Gy is considered as equivalent to 78 Gy at isocenter prescription) | CTV = Prostate<br>PTV = + 4-10 mm<br>Daily target localization (fiducial markers, transabdominal ultrasound or other) is required for this protocol.<br>Principal Investigator: Lee WR |




| | |
|---|---|
| Patients: low-risk group<br><br>Primary endpoint: 1y-HRQOL (EPIC).<br>To show non-inferiority of either arm to RTOG 0415 (EPIC measure)<br>(Note: both arms are experimental) | CTV = prostate<br>PTV = + 5 mm/3 mm (rectum)<br><br>IMRT: mandatory<br>Fiducial: mandatory<br>Principal Investigator: Lukka H |

# Cost Comparison (USA)


**Figure 4: Cost Comparisons for All Prostate Cancer Treatments**—Medicare allowables for brachytherapy (Brachy), external-beam radiation therapy (EBRT), conventional radical prostatectomy (Surgery), robotic surgery (Robot), intensity-modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic body radiotherapy (SBRT).

Technologic evolution in the treatment of prostate cancer. Clinical, financial, and legal implications for managed care organizations. Quang TS, et al. *Oncology*. 2007;21:1598-600,1602-1604.

**Table 1. Treatment Options for Clinically Localized Prostate Cancer.***

| Treatment | Description | Claim Code† | Mean Cost Estimate‡ |
|---|---|---|---|
| Radical prostatectomy§ | Complete removal of the prostate gland is performed with the use of one of three surgical approaches: radical retropubic prostatectomy, laparoscopic radical prostatectomy, or robot-assisted prostatectomy; the latter two are less invasive. | 55801, 55810, 55812, 55815, 55821, 55831, 55840, 55842, 55845, 55866, and 55899 | $16,762¶ |
| Brachytherapy§ | Brachytherapy with the use of low-dose-rate isotopes involves permanent implantation of seeds that emit a low dose of radiation over a period of several months. Some patients also receive a boost of external-beam radiation therapy or androgen-deprivation therapy. | 55875, 55862, 55865, 77778, 77784, and 77787 | $17,076¶ |
| IMRT | This advanced form of three-dimensional radiation therapy involves the use of a computer-driven machine that revolves around the patient as it delivers radiation. Radiation beams are aimed at the prostate from multiple angles. Intensity can be adjusted to maximize the dose targeted at the cancerous tissue and minimize the dose to surrounding healthy tissue. | 77418 | $31,574¶ |
| Androgen-deprivation therapy | This hormone treatment reduces the effects of testosterone, thereby slowing the growth of prostate cancer. Medications are administered orally or injected to reduce or block circulating androgens. | 54520, J1950, J9217, J9218, J9219, and J9202 | $2,112‖ |
| Active surveillance | This active plan to postpone intervention typically involves monitoring with office visits every 6 months, prostate-specific antigen testing, digital rectal examination, and prostate biopsy. | NA | $4,228** |
| Less common procedures | | | |
| Cryosurgery | Liquid nitrogen or liquid carbon dioxide is used to freeze tissue in order to destroy abnormal cells. | 55873 | — |
| Stereotactic body radiation therapy | This type of external-beam radiation therapy involves the use of special equipment to position a patient and precisely deliver radiation to tumors in the body (except the brain). The total dose of radiation is divided into smaller doses given over a period of several days. This type of radiation therapy helps spare normal tissue. | G0339 and G0340 during 2005–2006 and 77435 during 2007–2010 | — |
| External-beam radiation therapy as a three-dimensional conformal treatment | Also called three-dimensional radiation therapy and three-dimensional conformal radiation therapy, this procedure uses a computer to create a three-dimensional picture of the tumor, allowing doctors to give the highest possible dose of radiation to the tumor, while sparing as much of the normal tissue as possible. | 77401–77404, 77406–77409, 77411–77413, and 77416 | $20,588¶ |

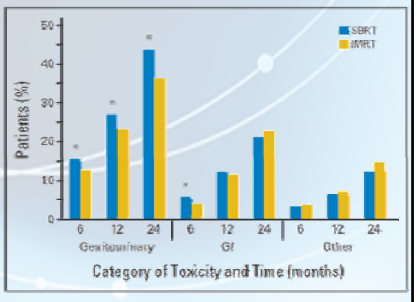
Urologists' use of intensity-modulated radiation therapy for prostate cancer. Mitchell JM. *N Engl J Med*. 2013;369:1629-1637.

VOLUME 32 · NUMBER 12 · APRIL 20 2014
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*

Samples from Medicare beneficiaries age ≥66
1,335 SBRT patients
2,670 IMRT patients
$13,645 SBRT cost
$21,023 IMRT cost
GU toxicity at 24 months
43.9% (SBRT) vs 36.3% (IMRT) (*P* = 0.001)
(measured by Medicare claims)




**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.

JOURNAL OF CLINICAL ONCOLOGY
E D I T O R I A L

# Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Less Cost at the Expense of More Genitourinary Toxicity Is a Concerning But Testable Hypothesis

Anthony V. D'Amico, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA

See accompanying article on page 1135

In conclusion, despite the potential limitations of the study by Yu et al[17] including the lack of adjustment for important patient and treatment factors in the model and the inability to assess the grade of the GU complications, the results of the current study should raise our awareness that the potential for an increase in clinically significant GU toxicity with SBRT as compared with IMRT exists. As the authors allude to in their concluding remarks, I would also recommend that until the results of the Swedish RCT[16] are available to provide data about the relative efficacy and toxicity among men treated with IMRT versus accelerated RT, accelerated RT regiments utilizing cyberknife or SBRT for PC should only be performed in the setting of well-designed clinical trials.

## Conclusion: SBRT or HDR?

| 【Key words at the forefront of EBRT】 | 【SBRT solution】 | 【HDR solution】 |
|---|---|---|
| IGRT (image-guided radiotherapy) | OK with device | OK |
| SBRT (stereotactic body radiotherapy) | OK | OK |
| Inter-fraction error [organ motion] | OK | Need applicator adjustment |
| Intra-fraction error [organ motion] | Fiducial tracking? | OK |
| Gating or Chasing | Robot? | OK |
| [Extreme] Hypofractionation [>6 Gy/fr.] | (Clinical results) Coming after, but rapidly growing | (Clinical results) Preceding, but slow accumulation |
| Optimal dose-fractionation? | Slightly low? | Optimal or high? |

Any unknown uncertainty?
Or perfect substitute for HDR?