BrachyNext 2014 Miami

Session E1: Science Is Proven Quality an Argument?

The Role of HDR Monotherapy for Intermediate and high risk patients

Disclosures

John K. Hayes, Jr, MS, MD, has received consulting fees for the Elekta Advisory Board and has contracted research for Elekta.

The Role of HDR Monotherapy for Intermediate-/High-risk Prostate Cancer

E1: Is Proven Quality an Argument?

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GammaWest Cancer Services
Salt Lake City, Utah

Special Thanks: C. Leland Rogers, M.D., Partner

HDR Monotherapy for Int./HR CaPr, Is Quality an argument?

- Ideal treatment for Prostate Ca?
- Consider various HDR approaches & dose regimens
- Report outcomes from GammaWest Cancer Services
- Need for Androgen suppression?
- HDR BT with other treatments?
- How do HDR Regimens compares to the ideal Rx?

HDR Monotherapy

Ideal Therapy for PrCa?

- Curative
- Short duration, short recovery
- Precise and accurate for every patient
- If procedural, low risk
- No androgen suppression
- Minimal acute/late symptoms
- Preserve normal anatomy
- No incontinence
- Preserve erectile function
- No risk for second malignant neoplasms
- No risk to others
- Affordable cost

bDFS – HDR Boost

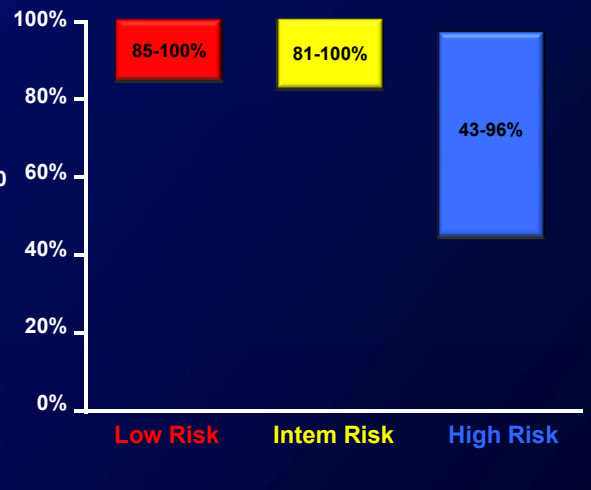
24 Studies

Patients:
total 5,955
range per study 35-1260

EBRT
typically 45-50Gy

HDR doses:
min 5.5 Gy x 3
max 15 Gy x 2

Follow-up:
range 26-105 mo



Yomada Y, Rogers L, Demanes DJ, Morton G, Prestidge B, Pouliot J, Cohen G, Zaider M, Ghilezan M, Hsu IC. American Brachytherapy Society consensus guidelines for HDR prostate brachytherapy. *Brachytherapy* 2012;11:20-32

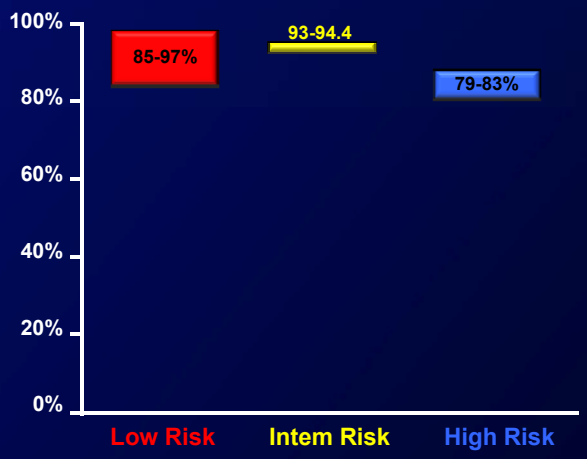
bDFS – HDR Monotherapy

7 Studies (2 Salvage*)

Patients:
total 976
range per study 6-298

HDR doses:
min 6 Gy x 2*
max 6 Gy x 9
9.5 Gy x 4

Follow-up:
range 26-105 mo



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bDFS – HDR Monotherapy

Author	n	FU (mo)	HDR Dose	Comments	Low Risk	Interm Risk	High Risk
Demanes	298	62	7Gyx6 9.5Gyx4	<1 % GI tox 3% G3 GU tox	97%		
Jabbari	6	26	6Gyx6	Prior APR no gr3 tox			
Lee	21	19	6Gyx6	Salvage tx of EBRT or LDR seed failure, 89% bNED at 2y			
Martinez/ Grills	248	58	9.5Gyx4/ 7Gyx6	Less urinary & GI tox compared to LDR boosts	97%		83%
Rogers	284	35.1	6.5Gyx6	2 sessions 6.5Gyx3. No urethral stricture 82.6% potency. No GI tox >gr 1		94.4%	
Tharp	7	58	6Gyx2/ 7Gyx3/ 9Gyx2	Salv HDR after LDR or EBRT failure, 5 pts devel strict, 71% bNED			
Yoshioka	112	65	6Gyx9 (5 days)	No >gr 3 toxicity	85%	93%	79%

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HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

GammaWest Cancer Services
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John K. Hayes, MD, MS

Rogers CL, Alder SC, Rogers RL, Hopkins SA, Platt, ML, Childs LC, Crouch RH, Hansen RS, Hayes JK.
High Dose Brachytherapy as Monotherapy for Intermediate Risk Prostate Cancer. *J Urol* 2012; 187:109-116

HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Intermediate-Risk Definition

AJCC Clinical Stage T2b - T2c
Gleason Score 7
and / or
PSA 10-20

Rogers CL, Alder SC, Rogers RL, Hopkins SA, Platt, ML, Childs LC, Crouch RH, Hansen RS, Hayes JK.
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HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Number of Patients
Length of Follow-up

2001 through 2009, 1260 patients treated with HDR-MT
Limiting analysis to intermed-risk & >1yr FU = 284 pts

Follow-up 12.1 – 96.1 mo, mean 35.2 mo
Scheduled at 3 mo, 6 mo, then every 6 mo
Patients reported IPSS, UBS, Pad usage, IIEF-5, each FU
Rectal effects were evaluated via RTOG criteria

Rogers CL, Alder SC, Rogers RL, Hopkins SA, Platt, ML, Childs LC, Crouch RH, Hansen RS, Hayes JK.
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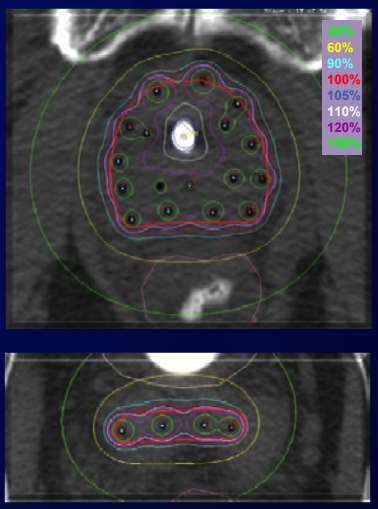
HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Intermed risk & >1y FU, 284 pts
2 brachytherapy procedures
1 night hospitalization each

6.5 Gy x 3 with each procedure
Total dose: 39 Gy in 6 fractions
Median 16 days, mean 19 days
range 6-35 days

Prostate volume	38.1 ± 15.7 cc
Planning target volume	68.7 ± 22.3 cc
Treatment volume	95.2 ± 29.6 cc



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HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

n = 284

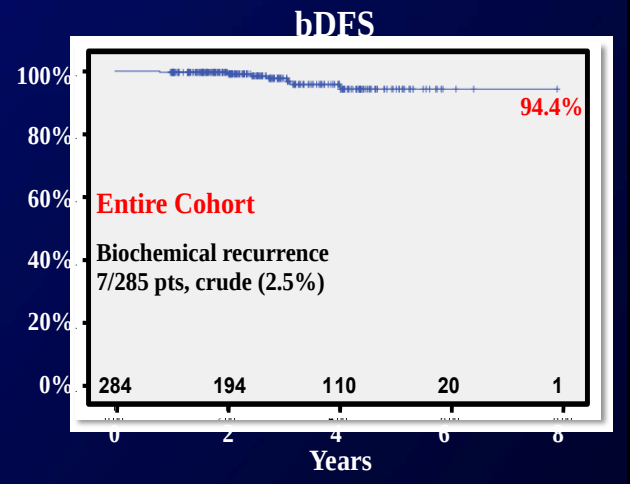
Mean values:

FU: 35.2 mo (12.1-96.1)

Age: 70.2 yr (47-85)

PSA: 8.4 (1.0-19.7)

Gleason Score: 6.6 (4-7)



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HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Univariate Analysis

Gleason score, PSA
No. of intermed-risk features
Age
Treatment duration
Prior TURP
Volume reduction HT (n=46/284, 16.2%)

Not significant

Clinical stage T2c
%PBCs 4th quartile (post-hoc)
PSA nadir
non-failure, mean 0.299
failure, mean 0.797
p=0.001

Significant

Owing to the constraints of an intermediate-risk cohort with only 7 events, multivariate analysis was deemed infeasible.

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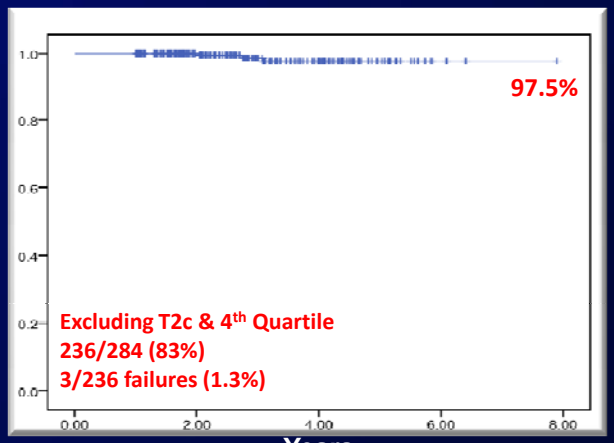
HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Biochemical Disease-Free Survival



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"HDR Monotherapy: Safe and Effective Brachytherapy for Patients Consistent Quality=high bPFS?

CET (UCLA) & WBH

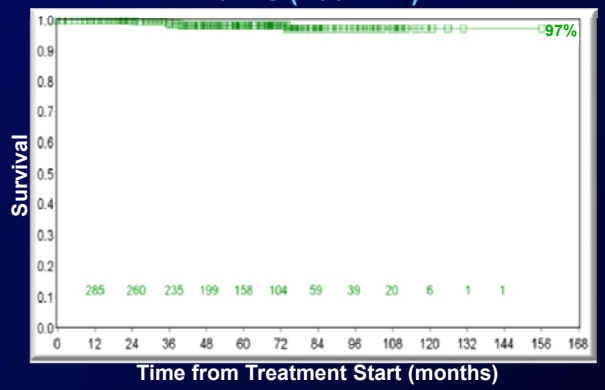
Patients n=298
CET 157
WBH 141

Mostly low-risk
Some "low-intermed-risk"
Stage: cT1 72%, cT2 23%
PSA: <10 91%, 10-15 8%
Gleason: ≤6 92%, 7 7.7%

CET: 7 Gy x 6 (TD 42 Gy)
2 procedures, 3 fx each
1 week apart

WBH: 9.5 Gy x 4 (TD 38 Gy)
1 procedure, 2 days

bPFS (Nadir + 2)



Demanes DJ, Martinez AA, Ghilezan M, Hill DR, Schour L, Brandt D, Gustafson G High-dose-rate monotherapy: Safe and effective brachytherapy for patients with localized prostate cancer. *IJROBP* 2011:81(5):1286-1292

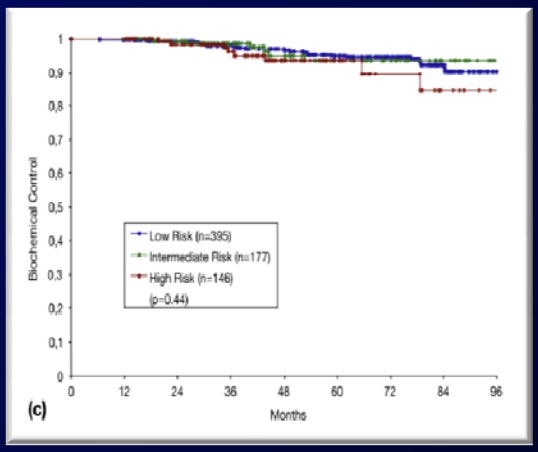
HDR Monotherapy

Offenbach, Frankfurt & Bremen, Germany

n = 718
Group A: 9.5 Gy x 4, 1 procedure
n=141
Group B: 9.5 Gy x 4, 2 procedures
2 wks apart, n=351
Group C: 11.5 Gy x 3, 3 procedures
3 weeks apart, n=226

Follow-up:
median 52.8 mo
Side effects:
grade 3 or 4 GU toxicity 3.7%
grade 3 or 4 GI toxicity 1.6%

Erectile function* retained in 81.1%
* suitable for intercourse"



Zamboglou N, Tselis N, Baltas D, Buhleier T, Martin T, Milickovic N, Papaioannou S, Ackermann H, Tann UW. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: Treatment evolution and mature results. *Int J Radiat Oncol Biol Phys* 2013;m85(3):672-678

HDR D_{90} = Dose to 90% Prostate

Is Quality an argument? Precise and Accurate in every patient

208 patients

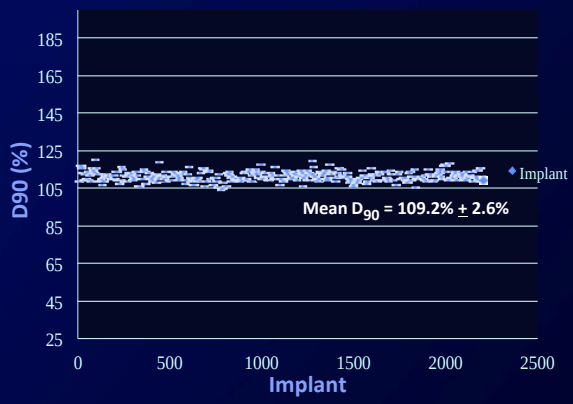
HDRB: 6 Gy x 4, then
39.6 Gy / 22 fx EBRT

HDR-MT: 7.25 Gy x 6

Mean V90, V100 , V150, V200
99.9%, 99.5%. 25.4%, 7.7%

Mean dose to OAR:

OAR	0.1cc	1cc	2cc
urethra:	107.3%,	101.1%,	47.9%
bladder:	79.5%,	69.8%,	66.3%
rectum:	76.3%,	70.2%,	66.3%



White E, Kamrave M, Memarco J, Park SJ, Steinberg M, Demanes DJ. Highly consistent dosimetry with prospectively planned image guided high-dose-rate intensity modulated prostate brachytherapy. ABS Annual Meeting 2011 (abst)

Seeds (^{103}Pd or ^{125}I) ± EBRT ± Horomes

Mount Sinai Hospital

Intermediate-Risk: PSA 10-20, GS 7, T2b (not T2c)

2,250 men treated w/ LDR brachy

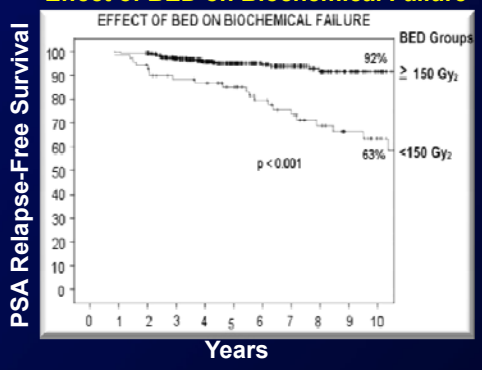
558 (25%) Intermediate-risk

risk fxs: 1 6.38%, 2 26.3%. 3 45%

EBRT median dose 45 Gy,
delivered 6-8 wk after brachy
target prost + SVs + 15-20mm

Hormones: LHRH ± anti-androgen
commonly for 6mo with LDR-MT
or 9mo with trimodality therapy

Effect of BED on Biochemical Failure



448 0f 588 (83%) received BED Gy2 ≥ 150

Ho AY, Burri RJ, Cesaretti JA, Stone NN, Stock RG. Radiation dose predicts for biochemical control in intermediate-risk prostate cancer patients treated with low-dose-rate brachytherapy. *IJROBP* 2009:75(1):16-22

"HDR Monotherapy: Safe and Effective Brachytherapy for Patients

Consistent Quality=high bPFS?

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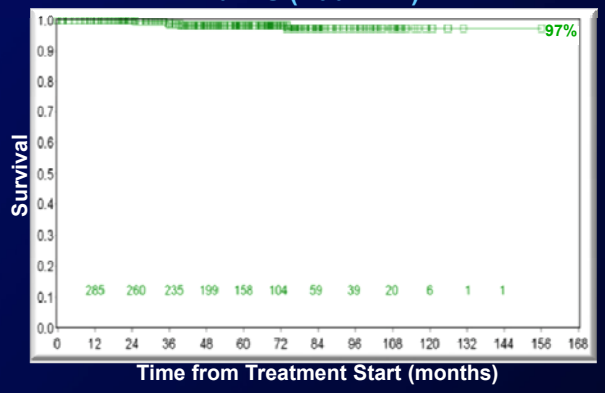

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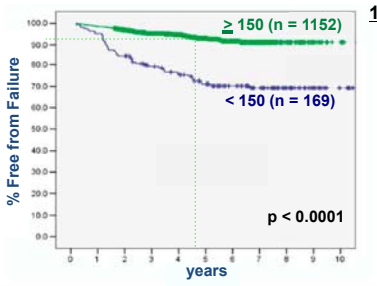
Seeds

Effect of BED on PSA FAILURE

1377 pts
I-125 or Pd-103
Brachy alone 571
Brachy + H 371
Trimodality 435



10- yr
91%
69%

Effect of BED cut-point of 150 on biochemical failure

448 of 588 (83%) received BED Gy2 ≥ 150

Stock RG *et al*. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and post-treatment biopsy results. IJROBP 2006; 64:527-533.

Ho AY, Burri RJ, Cesaretti JA, Stone NN, Stock RG. Radiation dose predicts for biochemical control in intermediate-risk prostate cancer patients treated with low-dose-rate brachytherapy. *IJROBP* 2009:75(1):16-22

External Beam Irradiation
Intermed-Risk Prostate Ca

Peter MacCallum Cancer Centre
Melbourne, Australia

2001-2006

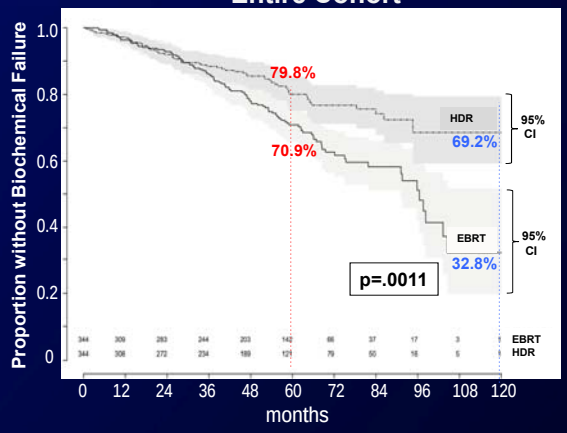
344 patients EBRT + HDR
46 Gy / 23 + 19.5 Gy / 3
344 matched cohort EBRT alone
74 Gy / 37

NCCN Risk Groups
Low – Risk none
Intermediate 203 each group
High - Risk 141 each group

Hormonal therapy 59% each arm

Median f/u 60.5 months

Entire Cohort



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NCCN Risk Groups
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Intermediate 203 each group
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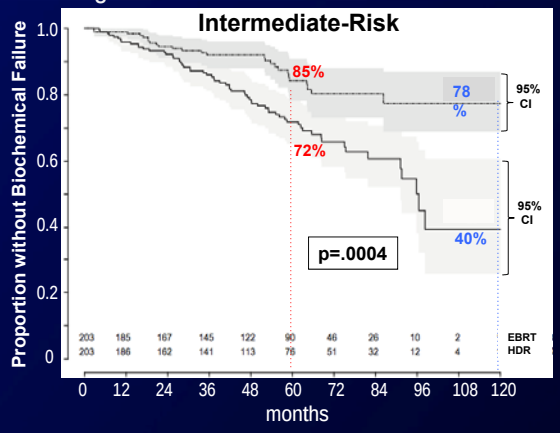
Hormonal therapy 59% each arm

Median f/u 60.5 months

Larger estimated treatment effect intermed-risk



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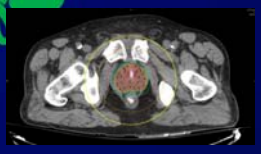
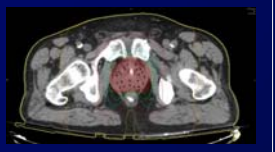
Is high quality dosimetry an argument for therapeutic Gain?

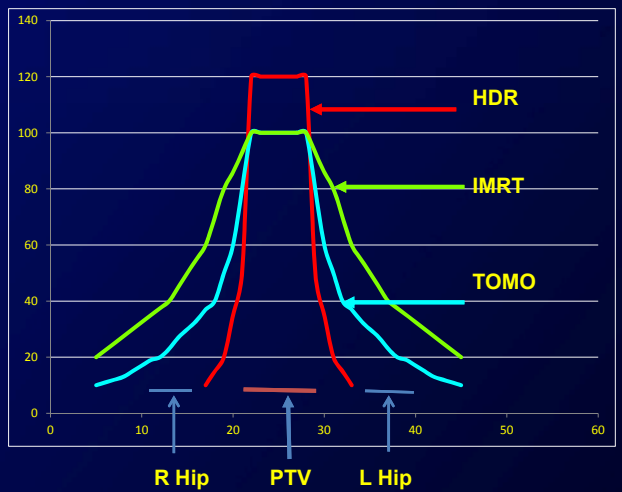


HDR



TOMO

IMRT



Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT

Israel Deutsch[1], Michael J. Zelefsky[1], Zhigang Zhang[2], Qianxing Mo[2], Marco Zaider[3], Gil'ad Cohen[3], Oren Cahlon[1], Yoshiya Yamada[1,*]

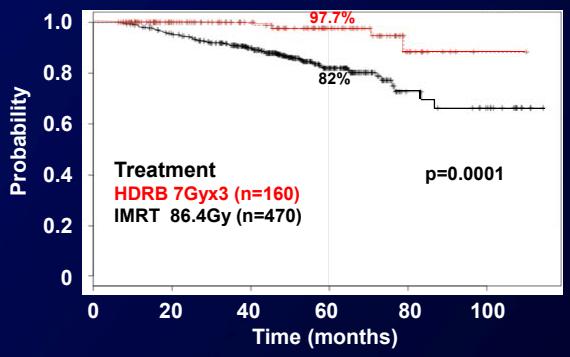
PSA Relapse-Free Survival (Nadir + 2)

MSKCC
IMRT 86.4Gy/48 (n=470) vs
HDRB 7Gyx3, then 1 mo later 50.4Gy/28 (n=160)

Med f/u: 53 mo IMRT
47 mo HDR + IMRT

Improved RFS on univariate analysis if: HDR, ↓T stage, ↓GS, ↓PSA, ↓NCCN risk group, no ADT

Improved on multivariate if: HDR, ↓NCCN risk group, age



Quality: Dose Escalation within the target is key!

Brachytherapy 2010;9:313-318

LDR Brachytherapy Intermediate Risk bDFS

			PSA Control (ASTRO)			
Study, (year)	n	FU (yrs)	All	Low	Intermed	High
Ragde (2000)	147	10	66%			
Blasko (2000)	279	5	94%			
Grimm (2001)	125	7	87%			
Beyer (2003)	551	4		85%	77%	55%
Kollmeier (2003)	243	6		88%	81%	65%
Potters (2005)	1,449	7	81%	89%	78%	63%
Merrick (2005)	180	5		97%	96%	
Stock (2006)	571	4	85%			
ADT v no ADT	371		91%			
Zelefsky (2007)	2,693	5	ASTRO:	82%	70%	48%
11 institutions			N + 2:	74%	61%	39%

Demanes DJ, Martinez AA, Ghilezan M, Hill DR, Schour L, Brandt D, Gustafson G High-dose-rate monotherapy: Safe and effective brachytherapy for patients with localized prostate cancer. *IJROBP* 2011:81(5):1286-1292

Systematic review

Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: A systematic review

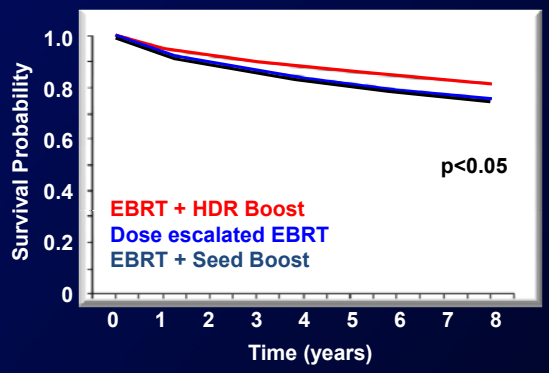
Bradley R. Pieters[a,*], Djuna Z. de Back[a], Caro C.E. Koning[a], Aeilko H. Zwinderman[b]

Biochemical Disease-Free Survival by Treatment

Systematic review 40 articles
bDFS and OS at 3,5, & 8 yrs

Treatment	HR bRecur
EBRT v HDR	1.40
95% CI	1.31-1.51
Seeds v HDR	1.37
95% CI	1.26-1.49

Treatment	HR OS
EBRT v HDR	1.50
95% CI	1.29-1.73
Seeds v HDR	2.33
95% CI	2.04-2.66



Radiotherapy and Oncology 2009;93:168-173

Does Quality Dosimetry=Better Survival?

Systematic review

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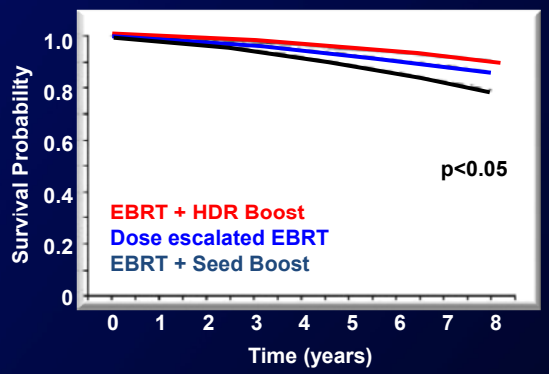
Overall Survival by Treatment

Systematic review 40 articles
bDFS and OS at 3,5, & 8 yrs

Treatment	HR bRecur
EBRT v HDR	1.40
95% CI	1.31-1.51
Seeds v HDR	1.37
95% CI	1.26-1.49

Treatment	HR OS
EBRT v HDR	1.50
95% CI	1.29-1.73
Seeds v HDR	2.33
95% CI	2.04-2.66



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HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Side Effects: IPSS Scores

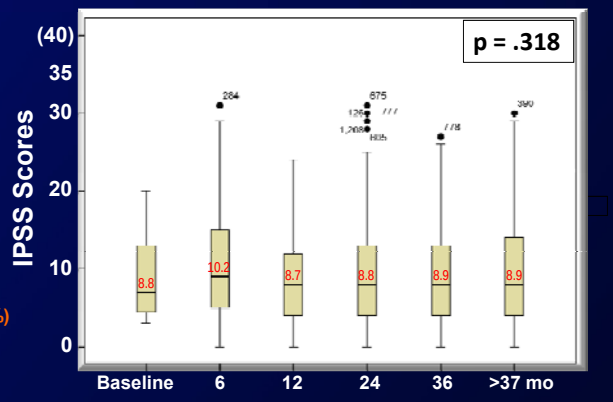
n = 284

Mean FU: 35.2 mo

(range 12.1-96.1)

Age: 70.2 yr (47-85)

PSA: 8.4 (1.0-19.7)



Box & Whiskers:
Box interquartile range (25-75%)
Line in the box is the median
Bottom of box 25th percentile
Top of Box is 75%

If no dots: Top whisker highest in range. Bottom whisker is the lowest value.
If there are dots: whiskers only allowed to be as long as 1.5x length of box.
Dots are any values that lie outside of that, i.e. are outliers

Mean IPSS scores

HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Side Effects: Incontinence (Pads)

New pad usage 22/284 (7.7%)

7 had TURP before HDR-MT (1 to 4 TURPs)

10 tremor, 2 stroke, and 1 had diffuse neuropathy

Grade 1	Grade 2	Grade 3	Grade 4
15 (68%)	5 (23%) †	2 (9%) ¶	0

† 4 of 5 had TURP or tremor

¶ 1 had 3 TURPs, the other 2 TURPs + tremor

7/284 (2.5%) with no TURP or neurologic compromise: 6 Gr 1, 1 Gr 2

Urinary Pad Grading Scale

Grade 0: none
Grade 1: occasional use of pads
Grade 2: ≤ daily intermittent use of pads
Grade 3: ≤ 2 pads/day, regular use of pads, self cath
Grade 4: Refractory, permanent catheter

Radical Prostatectomy vs Observation for Localized Prostate Cancer

PIVOT TRIAL

Phase III trial
731 men
Mean age 67
Med fit for RP
Life exp ≥ 10y
Med PSA 7.8
Low-Risk 40%
Intermed 34%
High-Risk 21%

Pt Reported Urinary, Erectile & Bowel Dysfunction at 2y

Dysfunction	Radical Prostatectomy (n=364)	Observation (n=367)	p-value
	number/total number (%)		
Urinary incontinence*	49/287 (17.2%)	12/284 (6.3%)	<0.001
Erectile dysfunction	231/285 (81.1%)	124/281 (44.1%)	<0.001
Bowel dysfunction	35/286 (12.2%)	32/282 (11.3%)	0.74

* Defined as "having a lot of problems with urinary dribbling," "lose larger amounts of urine than dribbling, but not all day," "have no control over urine," or "have an indwelling catheter"

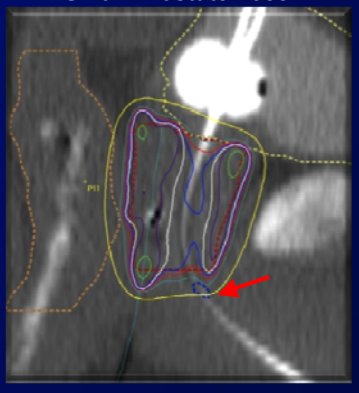
Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Gilhooly P, Grob BM, Nsouli I, Iyer JT *et al*. Radical prostatectomy versus observation for localized prostate cancer. NEJM 2012;367(3):203-213 (PIVOT TRIAL)

HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Side Effects

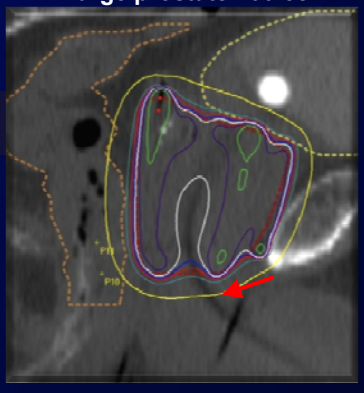
Bulbo-membranous Urethral Stricture

Small Prostate 15cc



150%
120%
110%
105%
100%
60%

Large prostate 100 cc



HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Side Effects

Bulbo-membranous Urethral Stricture

1st Author (Year Pub)	n	Treatment Modality	Time Frame	Stricture Rate	Stricture Time
Vicini (2000)	161	EBRT + HDR	"Late" (crude)	3%	_
Zelefsky (2000)	248	I-125 Seeds	5y actuarial	10%	18 mo
Zelefsky (2006)	561	IMRT (81Gy)	8y actuarial	Gr2 9% Gr3 3%	~20 mo per graph
Aluwini (2012)	264	EBRT + HDR	"After 7 years"	2.5%	_
Khor (2013)	344	EBRT + HDR	5y actuarial	Gr3 11.8%	_
Khor (2013)	344	EBRT (74 Gy)	5y actuarial	0.3%	_
Zamboglou (2013)	718	HDR-MT	"Late" (crude)	Gr3 1.8%	_

Vicini FA, Kestin LL, Martinez AA. Use of conformal high-dose rate brachytherapy for management of patients with prostate cancer: optimizing dose escalation. *Tech Urol* 2000;6(2):135-145
Zelefsky MJ, Hollister T, Raben A. Five-year biochemical outcome and toxicity with transperineal CT-planned permanent I-125 prostate implantation for patients with localized prostate cancer. *IJROBP* 2000;47:1261-1266
Zelefsky MJ, Chan H, Hunt M, Yomada Y, Shippy AM, Amols H. Long-term outcome of high dose intensity modulates radiation therapy for patients with clinically localized prostate cancer. *J Urology* 2006;176:1415-1419
Aluwini S, van Rooij PH, Kirkels WJ, Jansen PP, Praag JO, Bangma CH, Kolkman-Duerloo IKK. High-dose-rate brachytherapy and external beam radiotherapy for hormone naïve low- and intermediate-risk prostate cancer: A 7-year experience. *IJROBP* 2012;83(5):1480-1485
Khor R, Duchesne G, Tai KH, Foroudi F, Chander S, Van Dyk S, Garth M, Williams S. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external radiation therapy alone for prostate cancer. *IJROBP* 2013;85(3):679-685
Zamboglou N, Tselis N, Baltas D, Buhleier T, Martin T, Milickovic N, Papaioannou S, Ackermann H, Tunn UW. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: Treatment evolution and mature results. *IJROBP* 2013;85(3):672-678

Best HDR Fractionation Schedule

Bulbo-membranous Urethral Stricture

Peter MacCallum Cancer Centre, Melbourne, Australia

- 474 pts, organ confined prostate cancer, cT1-3 N0 M0, all risk groups
- 90% HDR-B, 10% HDR-MT
- HDRB: EBRT: 46Gy/23 (prostate + SVs) + HDR
  HDR-B: 19.5Gy/3, 20Gy/4, 16Gy/4, 14Gy/3, 10Gy/1
- HDR-MT: 30Gy/3, 31.5Gy/3, or 33Gy/3 (1 implant, 3 fxs over 3 days)
- Urethral doses ≤120%
- CTCAE ≥2 urethral stricture in 8% crude, 12% 6y act. 92% were bulbomembranous
- Median time 22 (range 10-68) months. 49% needed 2nd line therapy

Non-Predictive Factors: Age, PSA, GS, stage, risk category, smoking history, vasc event history, diabetes, androgen deprivation use, duration of urethral catheterization, total radiation dose

Univariate Predictors	p-value	Multivariate Predictors	HR	p-value
HDR dose per fraction	<0.001	HDR dose per fraction	1.33/Gy	0.008
Hypertension	0.002	Hypertension	2.83	0.005
$2GyNED_3$ [1]	0.005	Prior TURP(s) [2]	2.81	0.023
HDR monotherapy	0.029			
Prior TURP(s)	0.036			

[1] $2GyNED_3$ = nominal equivalent dose in 2Gy fractions using an α/β ratio of 3

[2] Of prior TURP pts who developed stricture, the most recent TURP was 62 - 134 (med 115) mo before HDR

Sullivan L, Williams SG, Tai KH, Foroudi F, Cleeve L, Duchesne GM. Urethral stricture following high dose rate brachytherapy for prostate cancer. *Radiotherapy & Oncology* 2009;91:232-236

Best HDR Fractionation Schedule

Bulbo-membranous Urethral Stricture

Mount Vernon Cancer Centre, Middlesex, UK

Nov 2003 - July 2009
Prospective study
"Locally advanced" prostate ca
- T1-T3b confirmed by MRI
- PSA <40
- normal bone scan

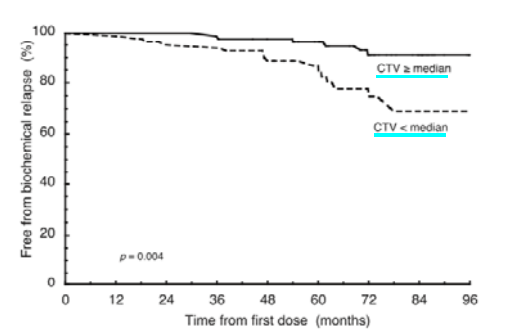
164 pts HDR monotherapy
- typically 1-night stay
- interfraction interval ≥6 h
  - 8.5 Gy x 4 (n=30)
  - 9 Gy x 4 (n=25)
  - 10.5 Gy x 3 (n=109)

Med FU 71.3 months

Gland size not considered in the selection criteria

Med prostate CTV 60 (15-208) cc

bDFS



No signif diff between the CTV groups in moderate to severe side effects including urethral stricture.
BUT 7y actuarial rate of urethral stricture treated surgically was 10% (9% for CTV ≥60cc, 11% <60cc)

Le H, Rojas A, Alonzi R, Hughes R, Ostler P, Lowe G, Bryant L, Hoskin P. The influence of prostate volume on outcome after high-dose-rate brachytherapy alone for localized prostate cancer. *IJROBP* 2013; 87(2):270-274

Best HDR Fractionation Schedule

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Gland size not considered in the selection criteria

Med prostate CTV 60 (15-208) cc

Table 1 Demographic details of patients treated with high-dose-rate brachytherapy alone

Variable	Category	CTV ≤median (n=82)	CTV >median (n=82)
Age (y)	Median	68	69
	Range	55-78	57-81
Gleason score	≤6	21 (13)	26 (16)
	=7	57 (35)	47 (29)
	≥8	4 (2.4)	9 (5.5)
PSA	<10	31 (19)	33 (20)
	10-20	33 (20)	25 (15)
	>20	18 (11)	24 (15)
Risk group	Low	2 (1)	6 (4)
	Intermediate	45 (28)	39 (24)
	High	35 (21)	37 (23)
ADT	No	9 (5)	23 (14)
	Yes	73 (45)	59 (36)
	Mean duration	12.1	15.3
Pretreatment IPSS	Median	6	5
	Moderate	25 (30)	24 (29)
	Severe	2 (2)	5 (6)

Le H, Rojas A, Alonzi R, Hughes R, Ostler P, Lowe G, Bryant L, Hoskin P. The influence of prostate volume on outcome after high-dose-rate brachytherapy alone for localized prostate cancer. *IJROBP* 2013; 87(2):270-274

Best HDR Fractionation Schedule

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Gland size not considered in the selection criteria

Med prostate CTV 60 (15-208) cc

Time to moderate to severe symptoms all patients

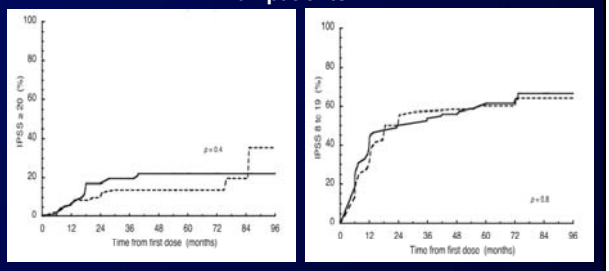


Table 2 Dosimetric parameters after high-dose-rate brachytherapy alone

Volumes	V100 mean	P value	D90 mean	P value	V150 mean	P value	Urethral D30 mean	P value
≤Median	93	.24	103.7	.14	29.0	.97	11.2	<.0001
>Median	94	-	104.7	-	28.9	-	10.6	-

Le H, Rojas A, Alonzi R, Hughes R, Ostler P, Lowe G, Bryant L, Hoskin P. The influence of prostate volume on outcome after high-dose-rate brachytherapy alone for localized prostate cancer. *IJROBP* 2013; 87(2):270-274

HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Side Effects: Erectile Function (IIEF-5)

Defining potency as IIEF-5 >10 (with or without aid), 67.9% were potent prior to HDR-MT. Of these 82.6% maintained potency at 2y

Mean decrease in IIEF-5 score 6.1

Erectile aid used by 9.2% before vs 95.7% after HDR-MT typically PDE-5 inhibitors alone

This result is similar to Vicini *et al* [1], who used 46Gy EBRT + HDRB, 5 Gy x 3 or 8.25-10.5 Gy x 2. With median f/u 2.8 y, potency was preserved in 73%.

1. Vicini FA, Kestin LL, Martinez AA. Use of conformal high-dose rate brachytherapy for management of patients with prostate cancer: optimizing dose escalation. Tech Urol 2000;6(2):135-145

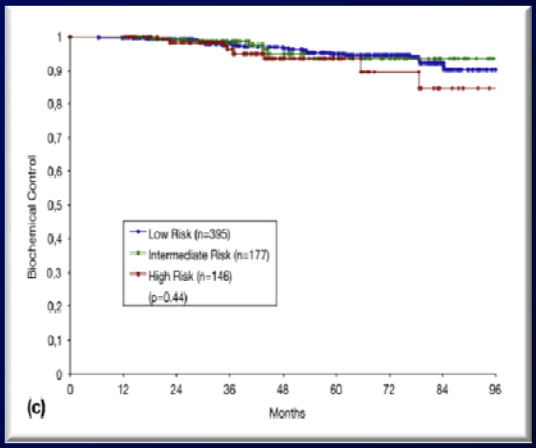
HDR Monotherapy

Offenbach, Frankfurt & Bremen, Germany

n = 718
Group A: 9.5 Gy x 4, 1 procedure
n=141
Group B: 9.5 Gy x 4, 2 procedures
2 wks apart, n=351
Group C: 11.5 Gy x 3, 3 procedures
3 weeks apart, n=226

Follow-up:
median 52.8 mo
Side effects:
grade 3 or 4 GU toxicity 3.7%
grade 3 or 4 GI toxicity 1.6%

Erectile function* retained in 81.1%
* suitable for intercourse"



Zamboglou N, Tselis N, Baltas D, Buhleier T, Martin T, Milickovic N, Papaioannou S, Ackermann H, Tann UW. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: Treatment evolution and mature results. *Int J Radiat Oncol Biol Phys* 2013;m85(3):672-678

Radical Prostatectomy vs Observation for Localized Prostate Cancer

PIVOT TRIAL

Phase III trial
731 men
Mean age 67
Med fit for RP
Life exp ≥ 10y
Med PSA 7.8
Low-Risk 40%
Intermed 34%
High-Risk 21%

Pt-reported Urinary, Erectile, & Bowel Dysfunction at 2y

Dysfunction	Radical Prostatectomy (n=364)	Observation (n=367)	p-value
	number/total number (%)		
Urinary incontinence	49/287 (17.2%)	12/284 (6.3%)	<0.001
Erectile dysfunction*	231/285 (81.1%)	124/281 (44.1%)	<0.001
Bowel dysfunction	35/286 (12.2%)	32/282 (11.3%)	0.74

* Defined as the inability to have an erection or an erection sufficient for vaginal penetration

Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Gilhooly P, Grob BM, Nsouli I, Iyer JT *et al*. Radical prostatectomy versus observation for localized prostate cancer. NEJM 2012;367(3):203-213 (PIVOT TRIAL)

HDR Brachytherapy as Monotherapy for Intermediate-Risk Prostate Cancer

Side Effects: Rectal Toxicity (RTOG/EORTC)

RTOG Grade 1 toxicity occurred in 12 patients (4.2%)
None experienced rectal toxicity beyond grade 1

ORGAN/ TISSUE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SMALL/LARGE INTESTINE	None	Mild diarrhea ~~Mild cramping~~ BM 5 times daily Slight rectal d/c ~~or bleeding~~	Moderate diarrhea and colic BM >5 times daily Excessive mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis Perforation Fistula

97.9% of patients remain Hemoccult® negative
No patient required GI intervention for an HDR side effect

Rogers CL, Alder SC, Rogers RL, Hopkins SA, Platt, ML, Childs LC, Crouch RH, Hansen RS, Hayes JK. High Dose Brachytherapy as Monotherapy for Intermediate Risk Prostate Cancer. *J Urol* 2012; 187:109-116

Radical Prostatectomy vs Observation for Localized Prostate Cancer

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Bowel dysfunction*	35/286 (12.2%)	32/282 (**11.3%**)	0.74

* Defined by patient reports as a "moderate" or "big" problem

Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Gilhooly P, Grob BM, Nsouli I, Iyer JT *et al*. Radical prostatectomy versus observation for localized prostate cancer. NEJM 2012;367(3):203-213 (PIVOT TRIAL)

Challenges, Anorectal Dysfunction with IMRT?

Chronic Radiation Proctitis*

50-65% at 5-years [1]

"Despite advances in EBRT technology, prevalence of CRP has not diminished."

26-73% acute toxicity with IMRT [2]

5-65% late toxicity with IMRT [2]

*Increased frequency, urgency of defecation fecal incontinence, rectal bleeding

There is also data from a randomized phase III trial demonstrating a lower rate of rectal toxicity with HDR boost than with IMRT alone.[3] Stay tuned.

1. Yeok E, Tam W, Shoeman M, Moore J, Thomas M, Botton R, Di Matteo A. Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. *Internat J Radiat Oncol Biol Phys* 2013; 87(5):954-e959.
2. Smeenk RJ. General Introduction. In External beam prostate radiotherapy: anorectal toxicity and the influence of endorectal balloons. Radboud University Nijmegen, p9-15, 2012.
3. Guix B, Bartrina I, Tello J, Lacorte T, Henriquez I, Sole J, Guix I, Galdron G, Espino M. Dose escalation with high-dose 3D-conformal radiotherapy (HD-3D-CRT) or low-dose 3D-conformal radiotherapy plus HDR brachytherapy (LD-3D-CRT+HDR-B) for intermediate-or high-risk prostate cancer: Higher PSA control with lower toxicity. *JCO*2011 (suppl 7; abstr 82). Also JCO 2010; 28:15s, abst 4633

Prospective, Longitudinal Study of Ano-Rectal Function after Conventional or Hypofx EBRT

Table 3 Percentage (proportion) of patients with anorectal symptoms 1 month after radiation therapy, as well as annually to 5 years after its completion in the whole patient group (n=34)

	1 mo	1 y	2 y	3 y	4 y	5 y
Stool frequency	38	35	32	33	29	24
Stool consistency	21	24	32	24	21	26
Rectal pain	32	9	3	6	0	9
Rectal mucous discharge	32	41	26	27	32	38
Urgency of defecation	41	38	35	36	38	44
Rectal bleeding	18	18	21	18	21	21
Effect on daily activities	53	56	59	60	56	48

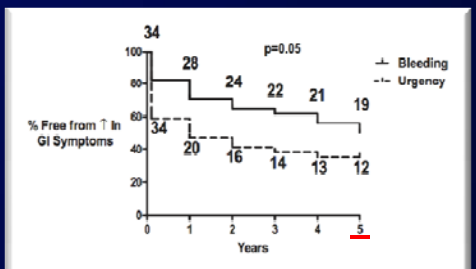


Fig. 1. Percent of patients free from urgency of defecation vs rectal bleeding 5 years after radiation therapy. GI = gastrointestinal.

At 5 years after EBRT:
48% of patients reported impairment of ADLs
44% reported urgency of defecation
21% reported rectal bleeding

"No differences in any of the GI symptoms or any anorectal functional and anal sphincter morphologic measurements between pts treated with the 2 radiation schedules (64Gy/32, 55Gy/20)"

Yeok EK, Holloway RH, Fraser RJ, Botton RJ, Di Matteo AC, Butters J. Pathophysiology and natural history of anorectal sequelae following radiation therapy for carcinoma of the prostate. *Internat J Radiat Oncol Biol Phys* 2012; 84(5):e593-e599.

MAB (4 mo)+ EBRT + HDR Boost for High-Risk Prostate Cancer

n = 588

T3-T4, GS 8-10, PSA ≥20

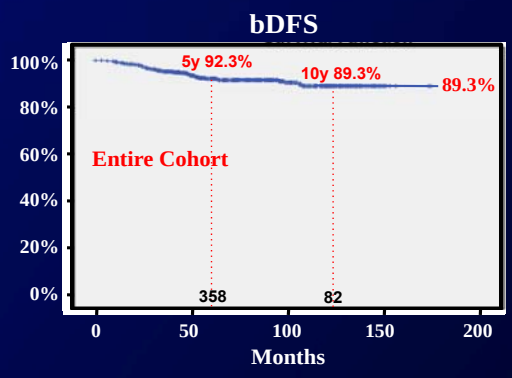
Mean age 71 (45-90) yr

Mean PSA 21.52 (1.7-353.9)

51% ≥T2c, 85% ≥GS7

Follow-up:

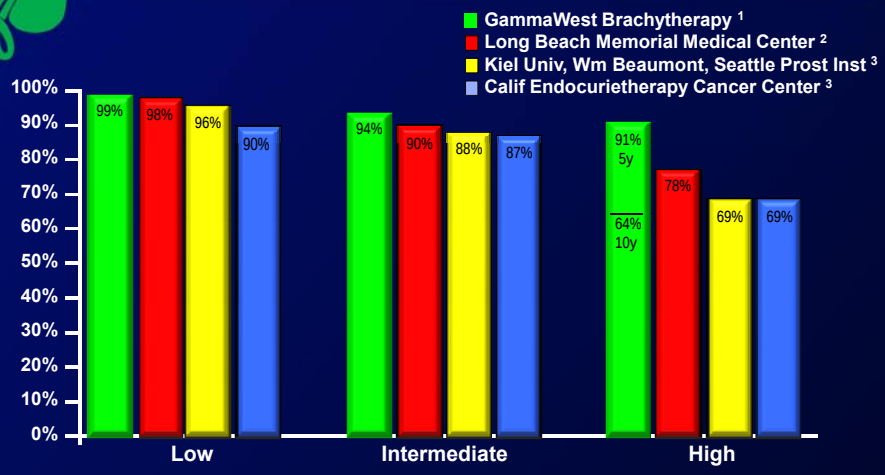
- minimum 36 mo
- mean 78.05 mo
- median 73.00 mo



# High-Risk Features	5-year bDFS
1	94.5%
2	87.7%
3	83.4%

Rogers CL, Alder SC, Rogers RL, Hopkins SA, Platt, ML, Childs LC, Crouch RH, Hansen RS, Hayes JK. Trimodality therapy incorporating HDR brachytherapy for high-risk prostate cancer Risk Prostate Cancer. In preparation

bDFS – HDR



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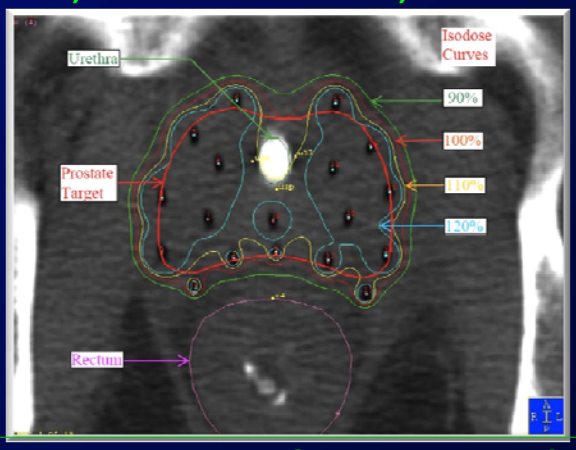
2. Phan TP, Syed AMN, Puthawala A, Sharma A, Khan F. High dose rate brachytherapy as a boost for the treatment of localized prostate cancer. *J Urol* 2007; 177:123-127

3. Yamada Y, Rogers L, Demanes DJ, Morton G, Prestidge B, Pouliot J, Cohen G, Zaider M, Ghilezan M, Hsu IC. American Brachytherapy Dose Rate Task Group Treatment Guidelines. *Brachytherapy*, 2012;11:20-32

HDR Monotherapy

Demanes, Martinez *et al* UCLA, Wm Beaumont



Is Quality an Argument? Yes! In terms of cure and freedom from complications

1. Demanes DJ, Martinez AA, Ghilezan M, Hill DR, Schour L, Brandt D, Gustafson G. High dose rate monotherapy : Safe and effective brachytherapy for patients with localized prostate cancer. IJROBP 2011; 81(5): 1286-1292

HDR Monotherapy

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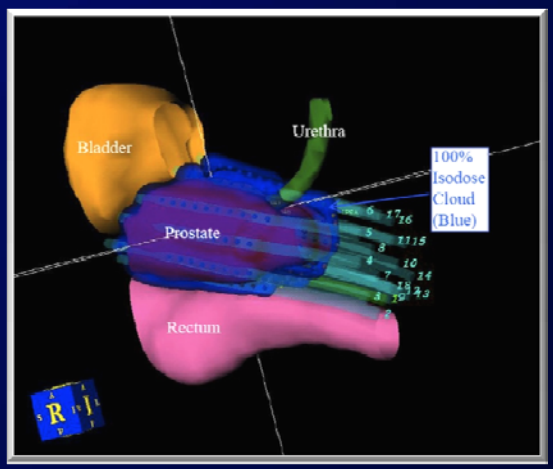

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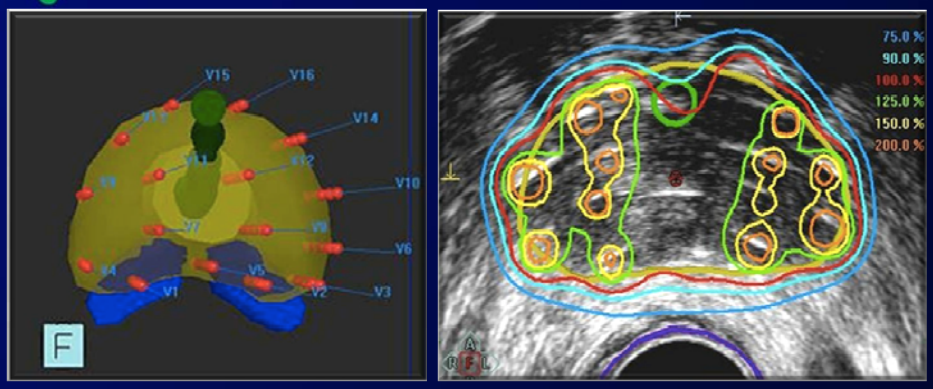

Real-time 3D image with preselected ideal template needle (red) trajectories, TRUS prostate contour (mustard yellow) & urethra (central green circle). Final mid-prostate dosimetry (100% red, 125% green, and 150% yellow). Most of the transition zone received 125% isodose and the anterior urethra <100%

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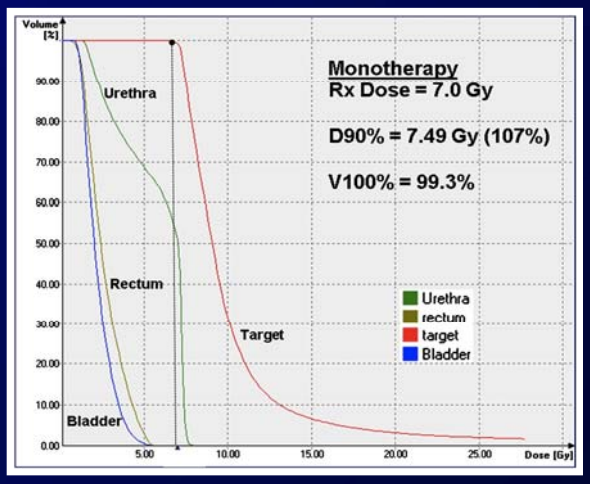

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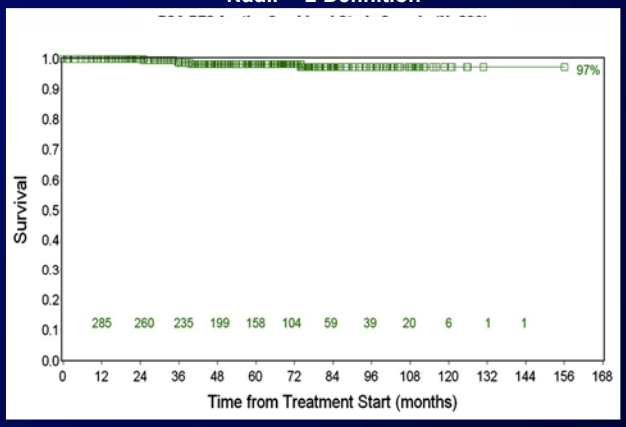
HDR Monotherapy

Demanes, Martinez *et al* UCLA, Wm Beaumont

PSA-PFS for the Combined Study Sample (n=298)
Nadir + 2 Definition



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IMRT vs. HDR, ALARA?

43 X 1.8 Gy = 77.4 Gy

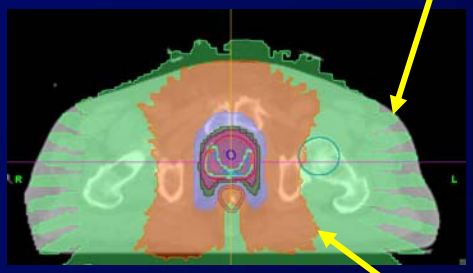
6 X 6.5 Gy = 39.0 Gy

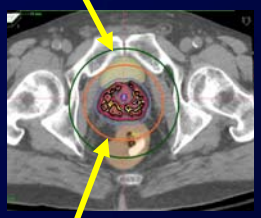
12.5 % of prescription dose

About 500-1000 pelvic CT scans

9.7 Gy (10.76 Gy_2)

4.9 Gy (6.85 Gy_2)





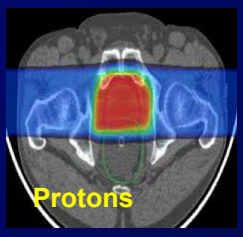
19.4 Gy (23.70 Gy_2)

9.75 Gy (17.67 Gy_2)

25% of prescription dose

Integral dose strongly favors of Brachytherapy in this comparison

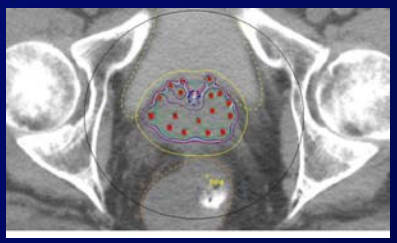
Proton Beam vs. HDR?
ALARA and Socioeconomics

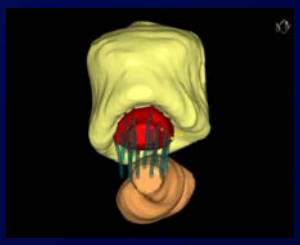


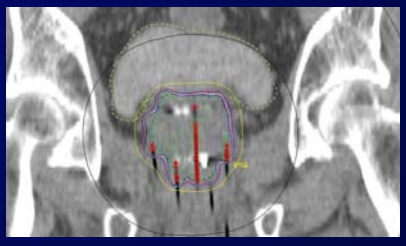
$75M

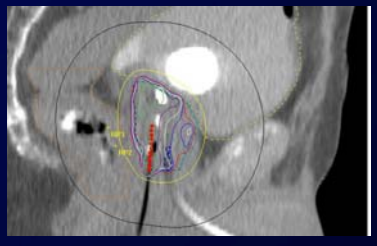
$0.5M

61 yo almost Proton Beamer who condescended for treatment in his home state of Utah









Is Quality An Argument? HDR as Monotherapy for Prostate Cancer

- Unmatched long-term biochemical control for the majority of patients with prostate cancer
- Very favorable side effect profile
- Few adverse events. Urinary incontinence is more likely in pts with TURP, or with neurologic compromise
- Every study, including randomized trials and a large systematic review, making a direct comparison has shown advantages to HDR brachytherapy
- Androgen ablation may be unimportant, less important, or appropriate in shorter courses (e.g. GW 4 months) with HDR. This will demand further study. RTOG 0815 will help
- HDR delivers superb outcomes, optimized dosimetry, limited side effects, lack of rad exposure to others, short tx course, min time out of work, and affordability.

Is Quality an Argument? HDR Monotherapy for Prostate Cancer

- Eliminates the need to clone Peter Grimm and Greg Merrick. I.E., the technique eliminates the need for brachytherapy superheroes. The technology can be transferred to brachytherapy teams while maintaining high quality.
- Adaptable to Multiple planning methods and techniques.
- Although very high dose-fractionation schedules have been reported, 45 Gy IMRT plus 3X6.5 Gy or 6X6.5 Gy HDR MT (or its BED GY2 equivalent, is sufficient to eradicate a very high percentage of prostate tumors. Dose escalation beyond that BED is therefore not recommended.
- Medicare and the USPSTF have failed the American public as regards HDR BT for Prostate Cancer (Gleason 7-10 = 50% of new prostate diagnoses in Utah)
- Radiation oncologists working with urologists can be a powerful public health team in the upcoming epidemic of advanced prostate cancer if they incorporate HDR BT into treatment.

Quality an Argument?Socioeconomics

- Doctor A 2002
- Age 56
- PSA 60 ng/ml
- Gleason 3+4, 3/6 sext.
- MAB+EBRT+HDR BT
- PSA 8/14/10 = 0.01 ng/ml

- Doctor B 2004
- Age 56
- PSA 13.7 ng/ml
- Gleason 3+3, 6/6 sext. 30-80% in each core
- MAB+EBRT+HDR BT
- PSA 10/07 = 0.03 ng/ml
- PSA 04/08 = 0.02
- PSA 03/10 = 0.01

Cost effective medicine? We have kept quite a few doctors in the trenches.

Quality an Argument? HDR Brachytherapy

- Truly Robotic vs. Robot Assisted
- Highly potent against CaP (Very favorable radiobiology, Brenner and Hall)
- In world, since 1986 vs. 1995 for IMRT
- Precise and Accurate? Yes
- Fewer Side effects than almost all treatments for prostate cancer