

# An Update on Radiation Therapy for Prostate Cancer

~ David C. Beyer, MD

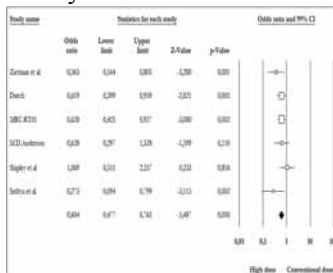
## An Update on Radiation Therapy for Prostate Cancer

David C. Beyer, MD, FACR, FACRO, FASTRO  
 Arizona Oncology Services  
 Phoenix, Arizona

### Objectives

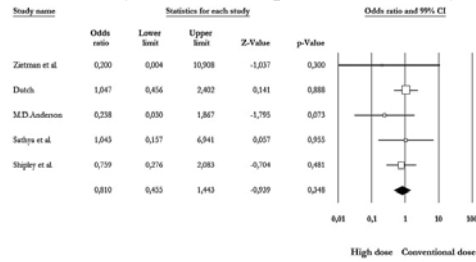
- Review significant new data
- Identify leading trends in PCa
  
- 2009 Issues for:
  - Dose and Fractionation
  - Post-operative radiation
  - Role of hormones

### XRT Dose Escalation (All Risk Groups) Meta-analysis of Biochemical Failure



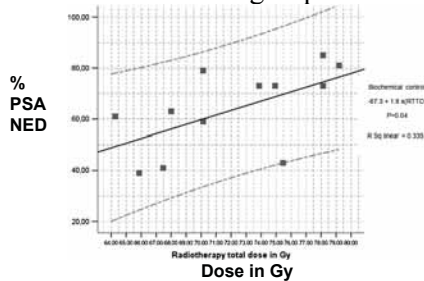
Viani, G. et al. IROBP V74(5):1405-1418, 2009

### XRT Dose Escalation (All Risk Groups) Meta-analysis of PCa Specific Mortality



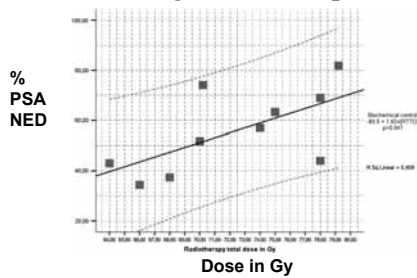
Viani, G. et al. JROBP V74(5):1405-1418, 2009

### Regression Analysis All Subgroups



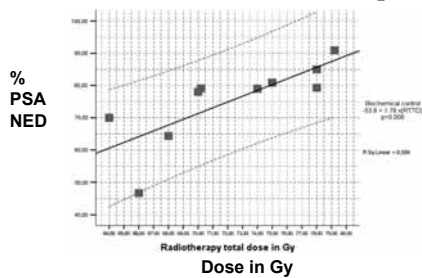
Viani, G. et al. JROBP V74(5):1405-1418, 2009

### Meta-regression Analysis High-Risk Group



Viani, et al. JROBP V74(5):1405-1418, 2009

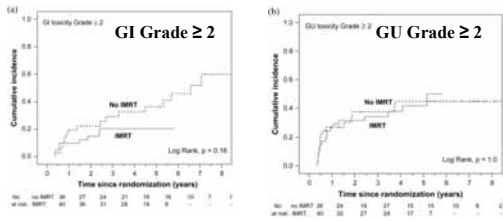
### Meta-regression Analysis Intermediate-Risk Group



Viani, G. et al. JROBP V74(5):1405-1418, 2009



### IMRT Reduces Late GI Toxicity



Al-Mamgani, A. et al. IJROBP. V73(3): 685-691, 2009.

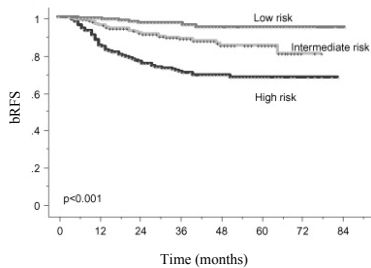
### Fractionation = Daily Radiation

- Based on radiobiology principles
  - ✓  $\alpha/\beta$  ratio determines optimal daily dose
  - ✓  $\alpha/\beta$  ratio not precisely known for PCA nor for OAR
- Conventional wisdom
  - ✓ Prostate cancer  $\alpha/\beta \sim 10$
  - ✓ For any biologically effective dose, daily fractions of 1.8-2.0 Gy/day reduces late complications
  - ✓ Steady increase from 33Fx to 45 Fx or more
  - ✓ 6 1/2 to 9+ weeks

### Radiobiology for Prostate Cancer

- But what if  $\alpha/\beta$  for prostate is  $< 3$ ??
- Then fewer fractions of higher daily dose =
  - Better or same cancer control
  - Fewer complications
  - Greater convenience
  - Better patient acceptance
  - Lower cost

### Hypofractionated Radiotherapy 70Gy = 250Gy x 28 Fx



Kupelian, P.A. et al. IJROBP. Aug 2007. V68(5); pp 1424-1430

### Hypofractionation in Prostate XRT

- Retrospective
- University of Wisconsin
- Patient choice (n=219)
  - 78 Gy / 2 Gy/day / 39 fractions / 55 elapsed days
  - 60 Gy / 3 Gy/day / 20 fractions / 33 elapsed days

Leborgne, F. et al. IJROBP V74(5): 1441-1446, 2009

### Five-year Actuarial Rates of bNED

Risk Group	Hypo (n=89)	Standard (n=130)	p
Low risk	96%	98%	0.64
Medium risk	84%	84%	0.75
High risk	85%	87%	0.97

Leborgne, F. et al. IJROBP V74(5): 1441-1446, 2009

### Late Complications Standard vs Hypofractionated XRT

Grade	Rectal		Bladder	
	Hypo	Standard	Hypo	Standard
1	22	17	1	2
2	4	5	2	2
3	1	1	2	1
4	0	1	0	0
5	0	0	0	0

Leborgne, F. et al. IJROBP V74(5): 1441-1446, 2009

### Phase III Confirmatory Data

- Randomized trial
- National Cancer Institute, Italy
- 168 high risk patients
- 9 months TAB
  - 80 Gy / 40 Fx's / 8 weeks
  - 62 Gy / 20 Fx's / 5 weeks

Arcangeli et al. IJROBP 75(3):S79, October 2009

### Hypofractionation 3 Year Results

	Control	Hypofractionated
PSA nadir <0.5	94%	100%
FBF	79%	87%
Late G2 GI toxicity	17%	16%
Late G2 GU toxicity	11%	14%

Arcangeli et al, IJROBP 75(3):S79, October 2009

### Stereotactic Body Radiation Therapy SBRT for Prostate Cancer

- Considered **Investigational** in 2009
  - ASTRO SBRT Task Force
  - Noridian (Medicare) payment policy
    - ✓Varies by locale

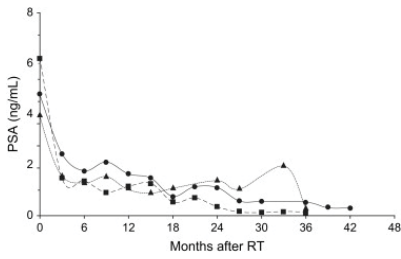
### Stereotactic Body Radiation Therapy SBRT

- Highly precise, and tight conformality
- Ablative doses
- ≤ 5 Fractions
- Image guidance / tracking
- Increased dose rate
- 725cGy x 5
- 900cGy x 4

### SBRT Prostate Early “Phase II” Results

- 44 patients with 3 year bNED 78%
  - ✓Choi et al, IJROBP 69(3):s375 2007
- 40 patients with 4 year bNED 70%
  - ✓Madsen et al, IJROBP 67(4):1099-1105, 2007
- 10 patients with decreasing PSA at 4 months
  - ✓Fuller et al, IJROBP 69(3):s358, 2007
- 22 patients with low toxicity (18 f/u> 1 month)
  - ✓Mantz et al, IJROBP 69(3): s334, 2007
- 23 patients with 9% acute grade ≥2 toxicity
  - ✓Pawlicki et al, IJROBP Front Rad Ther Onc, 40:395-406, 2007

PSA Bounce following SBRT



King, C. et al. *UROBP*. V73(4): 1043-1048, 2009.

---

---

---

---

---

---

---

---

---

---

% With Urinary QOL after SBRT

QOL score (IPSS)	Baseline	3 months	1 year	2 year
0-1	51%	37%	44%	92%
2-3	41%	58%	52%	8%
4-5	8%	-	4%	-
6	-	5%	-	-

King, C. et al. *UROBP*. V73(4): 1043-1048, 2009.

---

---

---

---

---

---

---

---

---

---

% With Rectal QOL after SBRT

QOL score (EPIC)	Baseline	3 months	1 year	2 year
0-1	89%	37%	46%	45%
2-3	11%	48%	50%	45%
4	-	16%	4%	9%
5	-	-	-	-

King, C. et al. *UROBP*. V73(4): 1043-1048, 2009.

---

---

---

---

---

---

---

---

---

---

Late Urinary & Rectal Toxicity on RTOG scale after SBRT

	RTOG grade				
	0	I	II	III	IV
Urinary, late % (no. patients)	30%	41%	24%	5%	-
Rectal, late % (no. patients)	51%	33%	15%	-	-

King, C. et al. *UROBP*. V73(4): 1043-1048, 2009.

---

---

---

---

---

---

---

---

---

---

### Late Urinary & Rectal Toxicity on MDA dose escalation trial

	RTOG grade				
	0	I	II	III	IV
Urinary, late toxicity % (no. patients)	76%	14%	7%	7%	-
Rectal, late toxicity % (no. patients)	47%	28%	19%	19%	-

King, C. et al. IJROBP. V73(4): 1043-1048, 2009.

### Comparison of QD vs QOD for SBRT

	QD	QOD	p=
GU QOL 4-6	19%	5%	0.34
Rectal (6mos), Any score 4-5	38%	0%	0.0035
Rectal QOL 4-5	24%	0%	0.048

King, C. et al. IJROBP. V73(4): 1043-1048, 2009.

### Phase I Dose Escalation SBRT

- Low to intermediate risk prostate cancer
- 5 fractions
- 2 weeks
- 45 Gy -- 47.5 Gy – 50 Gy
- With 12 month follow-up
  - 100% PSA control
  - No dose limiting toxicity

Boike et al. IJROBP 75(3):S80, October 2009

### Post-Operative Radiation Spectrum

- Immediate adjuvant
  - High risk
  - No gross residual / PSA
- Immediate salvage
  - Gross residual / PSA
- Late salvage
  - PSA failure
  - Documented recurrence
  - Hormone refractory

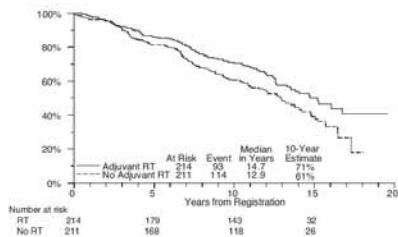


### Phase III Trials: Adjuvant RT after RRP

	EORTC 22911		SWOG 8794		ARO 9402	
	RT	Observation	RT	Observation	RT	Observation
<b>Eligibility</b>	PSA < 10 with PT3a, PT3b, or positive surgical margin		PT3b, margin status, Prior hormone therapy		PT3b with undetectable postoperative PSA	
<b>Standardization factors</b>	Institution, PSA, PT3b, margin status				PT stage, margin status, Gleason score, Prior hormone therapy	
<b>Number</b>	302	303	214	211	108	133
<b>Age (median)</b>	65	65	64.1	65.8	N/A	N/A
<b>Pre-op PSA (Median)</b>	12.3	12.4	< 10 31% ≥ 10 49%	< 10 39% ≥ 10 47%	N/A	N/A
<b>Post-op PSA (≤ 2)</b>	89.8%	87.5%	45%	48%	100%	100%
<b>Median follow-up</b>	5 yrs	5 yrs	10.2 yrs	10 yrs	3.3 yrs	3.2 yrs
<b>PSA free survival</b>	74% at 5 years	52.8% at 5 years	71% at 5 yrs 52% at 10 yrs	44% at 5 yrs 26% at 10 yrs	81% at 4 years	68% at 4 years
<b>Clonidine free survival</b>	85% at 5 yrs	77.5% at 5 yrs	84% at 5 yrs 69% at 10 yrs	69% at 5 yrs 49% at 10 yrs	N/A	N/A
<b>Metastasis-free survival</b>	93.9% at 5 years	93.9% at 5 years	89% at 5 yrs 71% at 10 yrs	84% at 5 yrs 62% at 10 yrs	N/A	N/A
<b>Freedom from ADT</b>	N/A	N/A	93% at 5 yrs	93% at 5 yrs	N/A	N/A
<b>Overall survival</b>	92.3% at 5 yrs	93.1% at 5 yrs	90% at 5 yrs 74% at 10 yrs	89% at 5 yrs 66% at 10 yrs	N/A	N/A

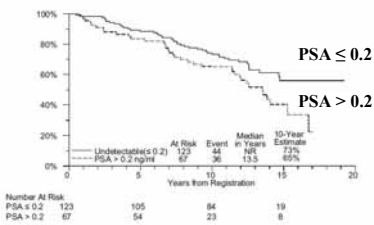
Bolla, M. et al. J. Clin. Oncol. 2002; 20: 1567-1575.  
Pacholke, H et al, J. Urology, 2004, 06, 020: 982-986

### SWOG 8794 Update Metastasis-free Survival



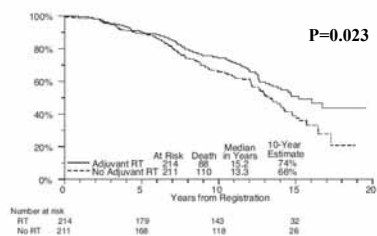
Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

### Adjuvant Radiotherapy Metastasis-free Survival Post Operative PSA



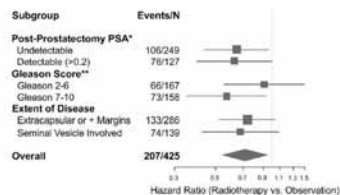
Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

### SWOG 8794 Overall Survival



Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

### Adjuvant Radiotherapy T3N0M0 Metastasis-free Survival HR



\* Missing for 49 patients. \*\* Missing for 100 Patients  
Size of box and diamond symbols are proportionate to sample size

Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

---

---

---

---

---

---

---

---

---

---

### Hormone Therapy for Prostate Cancer



---

---

---

---

---

---

---

---

---

---

### Hormones with Prostate Cancer

- In general
  - Improved outcomes with ADT
  - Long term better than short term
- Possible mechanism?
  - Eradicate subclinical microscopic disease
  - Synergy with XRT
    - ✓ Enhanced response to dose of XRT
  - Compensate for suboptimal local therapy
    - ✓ (65-70 Gy)

---

---

---

---

---

---

---

---

---

---

### 10 Year Results “Bolla” Study

- 415 patients treated EORTC 1987-1995
- XRT (pelvis + prostate) +/- 3 years  
Goserelin (concomitant and adjuvant)
- Median F/U 9.1 years

Bolla et al. IJROBP 72(1):s30-31, 2008

---

---

---

---

---

---

---

---

---

---

### EORTC 10 Year

	RT Alone	RT+LTAD	
Overall Survival	39.8%	58.1%	$p = 0.0004$
Clinical PFS	22.7%	47.7%	$p < 0.0001$
Distant PFS	30.2%	51.0%	$p < 0.0001$
PSA PFS	17.6%	37.9%	$p < 0.0001$

Bolla et al. IJROBP 72(1):s30-31, 2008

### EORTC 10 Year

	RT Alone	RT+LTAD	
PC Mortality	31%	11.1%	$p < 0.001$
CV Mortality	11.1%	8.2%	$p = 0.75$
Pathologic Fracture	0	2	

Bolla et al. IJROBP 72(1):s30-31, 2008

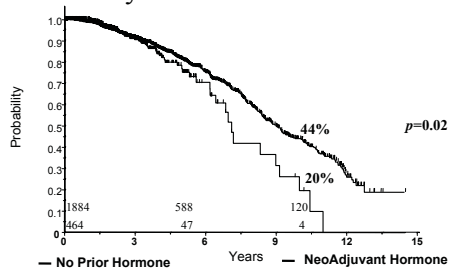
### Impact of NHT on Mortality

- 1709 brachytherapy monotherapy patients
  - 786 NHT median 3.5 months
- All Cause Mortality (ACM)

	Hazard Ratio	$p =$
NHT	1.2	0.04
Age	1.1	0.001
Gleason $\geq 7$	1.2	0.05

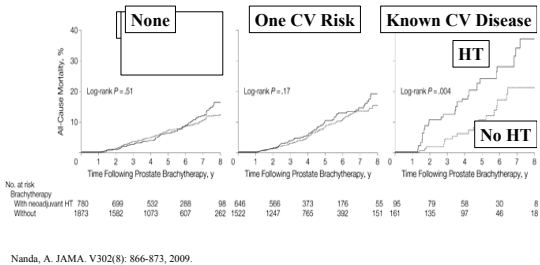
Dosoretz et al. IJROBP 72(1): s39, 2008 and USA Today 9/24/2008

### Overall Survival by Hormone Status



Beyer et al. IJROBP 61(5):1299-1305, 2005

Impact of Hormones and Comorbidity on All Cause Mortality Following Brachytherapy



Nanda, A. JAMA. V302(8): 866-873, 2009.

Value of Hormones with Dose Escalated XRT  
RTOG 0815

- Intermediate risk factors
  - Gleason 7
  - PSA 10-20
  - T2b-T2c
- Stratify for number of risk factors
  - Exclude if all 3 and >50% cores involved
- Endpoints
  - Survival
  - PSA
  - HRQOL
  - QALY

<http://rtog.org/members/protocols/0815/0815.pdf>

RTOG 0815

- XRT 79.2 Gy
  - @ 1.8/day
  - 3D or IMRT
- XRT 45 Gy + LDR implant
  - 110 Gy <sup>125</sup>I
  - 100 Gy <sup>103</sup>Pd
- XRT 45 Gy + HDR implant
  - 10.5 Gy x 2 fractions
  - ≥ 6 hour interval

<http://rtog.org/members/protocols/0815/0815.pdf>

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---