

# The Role of Radiotherapy in the Post-Prostatectomy Setting

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# Disclosures

Accuray, Advisory Board

# Agenda

- Clinical Significance of biochemical failure
  - *Pound et al, JAMA*
  - Prediction Tools/Nomograms
- Salvage Radiation
  - Retrospective series
- Adjuvant Radiation
  - Retrospective series
  - EORTC 2291, *Lancet*
  - ARO/AUO 96-02, *JCO*
  - SWOG 8794, *JAMA*
- Consensus Guidelines: “Do you Concur?”
- Meta Level Considerations

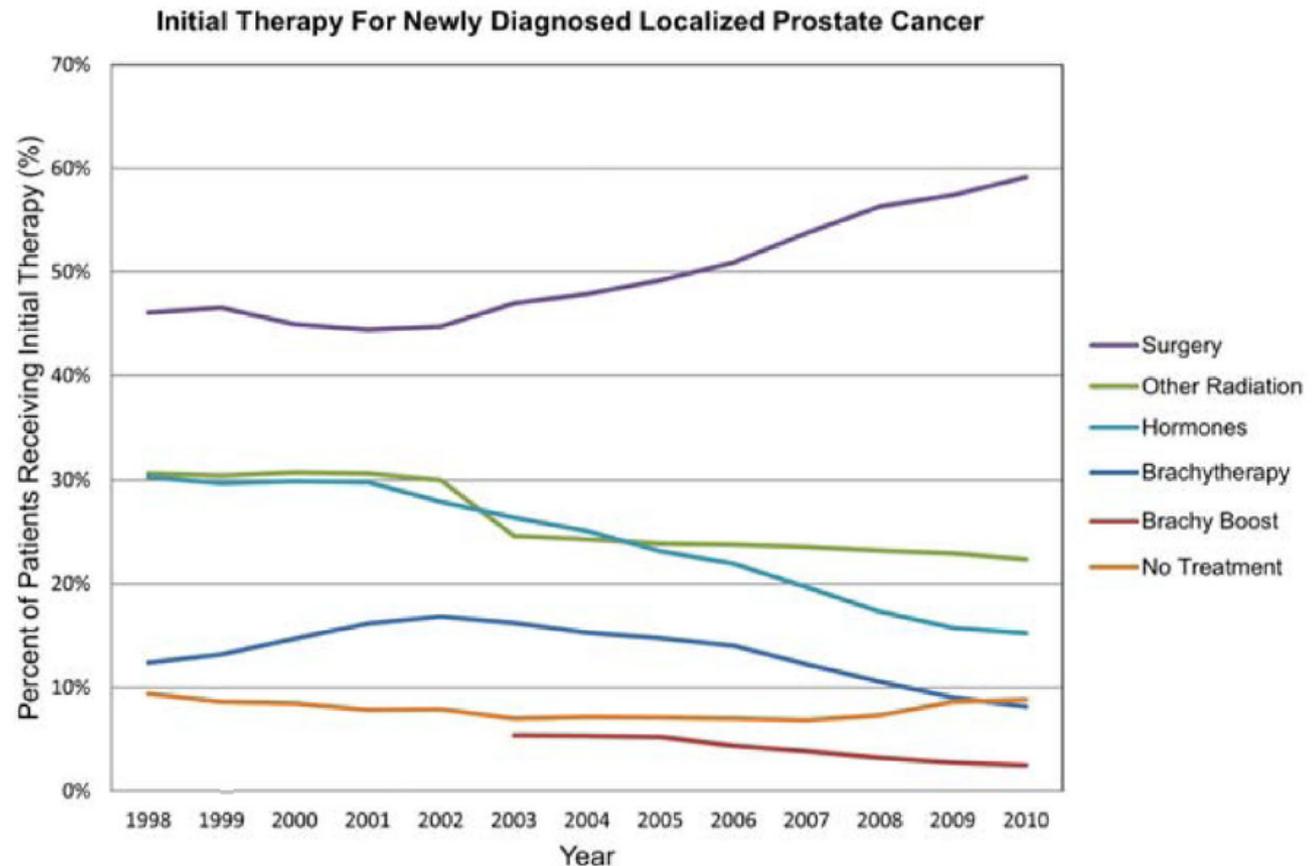


# Prostatectomy

- Radical/Laparoscopic/Robotic prostatectomy
  - established Tx option for the curative treatment of clinically localized prostate ca

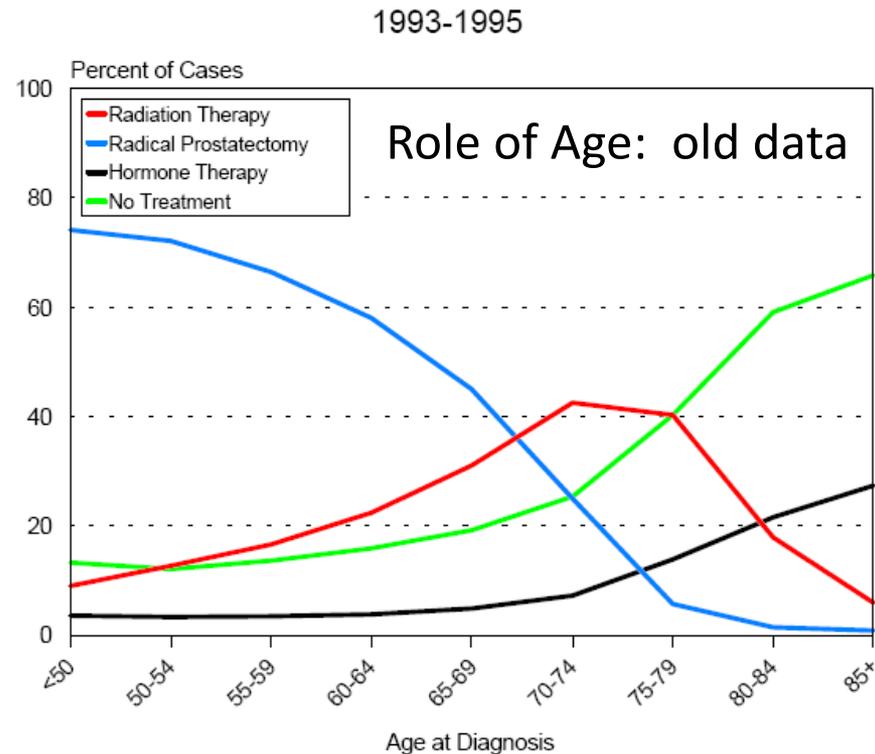
NCDB

1,547,941 cases  
prostate cancer:  
1998-2010



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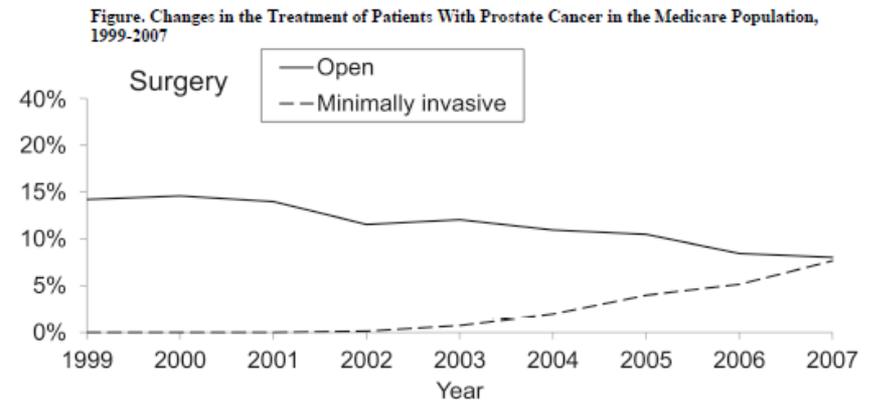
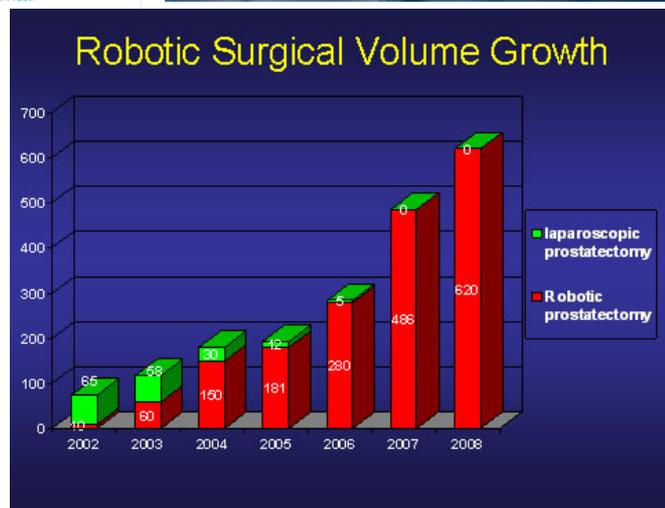
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Dinan MA et al, Int J Radiat Oncol Biol Phys. 2012 Apr 1;82(5):e781-6

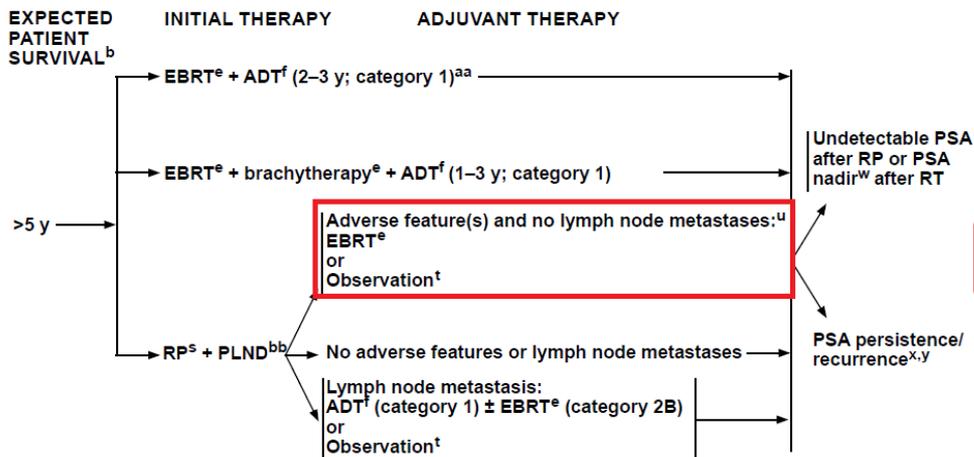
# Prostatectomy

- Radical/Laparoscopic/Robotic prostatectomy
  - established Tx option for the curative treatment of clinically localized prostate ca
- Appropriate Modality for Any Localized form of PCa
  - Like with any tx (MRM, IMRT, CK, Brachy), tx failures
- Post-RP results
  - ~30% pts have biochemical relapse at 5 years<sup>¥</sup>
    - 52% if Gleason 8 dz\*
    - 74% if Gleason 9-10 dz\*
  - ~30,000 men annually in the US
    - 65% of these men will develop bone mets within 10 years.

<sup>¥</sup> Han et al. 2003, Stephenson et al. 2007

\* Epstein J et al, Eur Urol. 2016 Mar;69(3):428-35.

**HIGH OR VERY HIGH RISK GROUP**



Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

**Adjuvant or Salvage Therapy after Radical Prostatectomy**

Most patients who have undergone radical prostatectomy are cured of prostate cancer. However, some men will suffer pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult.

Although observation after radical prostatectomy is appropriate, adjuvant EBRT after recuperation from operation is likely beneficial in men with adverse laboratory or pathologic features, which include positive surgical margin, seminal vesicle invasion, and/or extracapsular extension as recommended in the guideline by the American Urological Association (AUA) and ASTRO.<sup>354</sup> Positive surgical margins are unfavorable especially if diffuse (>10-mm margin involvement or ≥3 sites of positivity) or associated with persistent serum levels of PSA. The defined target volumes include the prostate bed.<sup>355</sup> The value of whole pelvic irradiation is unclear due to a lack of benefit in progression-free survival in 2 trials (RTOG 9413 and GETUG-01)<sup>356-358</sup>; whole pelvic radiation may be appropriate for selected patients.

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- Meta Level Considerations

ORIGINAL CONTRIBUTION

# Natural History of Progression After PSA Elevation Following Radical Prostatectomy

Charles R. Pound, MD

Alan W. Partin, MD, PhD

Mario A. Eisenberger, MD

Daniel W. Chan, PhD

Jay D. Pearson, PhD

Patrick C. Walsh, MD

**R**ADICAL PROSTATECTOMY PROVIDES excellent cancer control in most men with clinically localized disease. However, approximately 35% of men will experience a detectable serum prostate-specific antigen (PSA) elevation within 10 years following surgery.<sup>1-5</sup> At this early sign of biochemical recurrence, patients want to know what this means, whether they will survive, and if not, how

**Context** In men who develop an elevated serum prostate-specific antigen level (PSA) after having undergone a radical prostatectomy, the natural history of progression to distant metastases and death due to prostate cancer is unknown.

**Objective** To characterize the time course of disease progression in men with biochemical recurrence after radical prostatectomy.

**Design** A retrospective review of a large surgical series with median (SD) follow-up of 5.3 (3.7) years (range, 0.5-15 years) between April 1982 and April 1997.

**Setting** An urban academic tertiary referral institution.

**Patients** A total of 1997 men undergoing radical prostatectomy, by a single surgeon, for clinically localized prostate cancer. None received neoadjuvant therapy, and none had received adjuvant hormonal therapy prior to documented distant metastases.

**Main Outcome Measures** After surgery, men were followed up with PSA assays and digital rectal examinations every 3 months for the first year, semiannually for the second year, and annually thereafter. A detectable serum PSA level of at least 0.2 ng/mL was evidence of biochemical recurrence. Distant metastases were diagnosed by radionuclide bone scan, chest radiograph, or other body imaging, which was performed at the time of biochemical recurrence and annually thereafter.

**Results** The actuarial metastasis-free survival for all 1997 men was 87% (95% con-

- 1997 consecutive men underwent prostatectomy and followed
- No adjuvant hormonal therapy given at time of biochemical failure

# *Pound et al, JAMA*

- at mean f/u 5.3 years, 15% of patients (304) developed biochemical failure (PSA  $\geq$  0.2 ng/ml)
  - 103/304 developed mets
- Median time from first PSA elevation to development of mets  $\rightarrow$  8 years
- Median time to ***death*** after mets  $\rightarrow$  5 years

# After biochemical failure

- Factors predictive of probability and time to DM
  - time to biochemical progression ( $P < .001$ )
  - GS ( $P < .001$ )
  - PSA doubling time ( $P < .001$ )
- If time to biochemical failure  $< 2$  years,  $GS \geq 8$ , and PSA dt  $< 10$  mos
  - Prob of DM's 65% at 5 years
- Time interval to appearance of DM was predictive of time until death

# Strata of Extraprostatic Dz

+ Lymph Nodes

Seminal Vesicle Invasion

+ Surgical Margins

Pathologic Extension beyond  
Prostate

- + Lymph Nodes
- Seminal Vesicle Invasion
- + Surgical Margins
- Pathologic Extension beyond Prostate

# Recurrence-free rates

Han, Partin et al 2001

	Actuarial Percentage (95% CI)		
	5 year	10 year	15 year
Organ Confined	97 (95-98)	93 (90-95)	84 (77-90)
ECE+, GS<7, SM-	97 (94-98)	93 (89-96)	84 (70-92)
ECE+, GS<7, SM+	89 (80-94)	73 (61-82)	58 (41-71)
ECE+, GS $\geq$ 7, SM-	80 (75-85)	61 (52-68)	59 (50-67)
ECE+, GS $\geq$ 7, SM+	58 (49-66)	42 (32-52)	33 (23-44)
SV+, (LN-)	48 (38-58)	30 (19-41)	17 (5-35)
LN+	26 (19-35)	10 (5-18)	0

2404 men, 2123 with available pre-op PSA

EPE = extra-prostatic extension; GS = Gleason score; SM = surgical margin; SV = seminal vesicle, LN = lymph node involvement

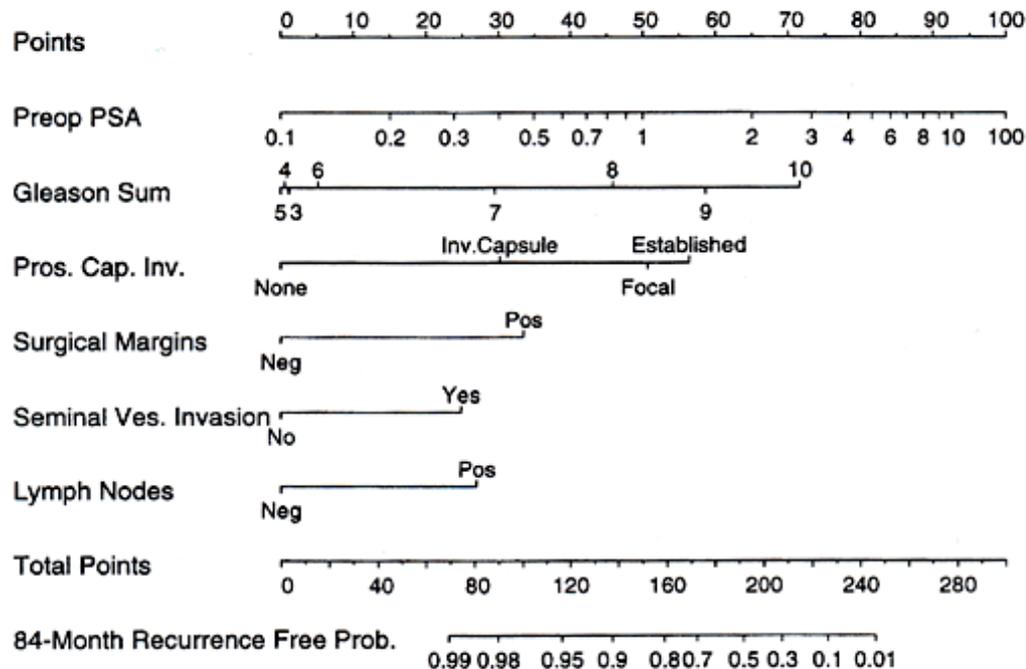
- + Lymph Nodes
- Seminal Vesicle Invasion
- + Surgical Margins
- Pathologic Extension beyond Prostate

# bRFS by Path features at RPE

	Washington University <sup>1</sup>	Baylor <sup>2</sup>	Johns Hopkins <sup>3</sup>	Cleveland Clinic <sup>4</sup>
<b>Follow-up, years</b>	7	10	10	8
<b>Biochemical RFS, all patients at last follow-up</b>	81	73	68	76
<b>Pathologic Stage</b>				
OC (ECE-)	81	92	85	92
ECE+, MS-	76			77
ECE+, MS+	57			50
SV+	26	33	43	34
LN +	19	16	0	0

1. Catalona, WJ et al. J Urol 1998; 160:2428.
2. Eastham, JA, Scardino, PT. Radical prostatectomy for clinical stage T1 and T2 prostate cancer. In: Comprehensive textbook of Genitourinary Oncology, ed 2 Vogelzang, NJ, Scardino, PT, Shipley, WU, Coffey, DS (Eds), Lippincollt, Williams, and Wilkins, Philadelphia, 1999.
3. Walsh, PC, et al. J Urology 1994; 152:1831.
4. Clark, PE, et al. The Prostate Journal, 2001.

# Postoperative Nomogram for Prostate Cancer Recurrence



**Instructions for clinician:**

Locate the patient's PSA on the PSA axis. Draw a line straight upwards to the **Points** axis to determine how many points towards recurrence the patient receives for his PSA. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to find the patient's probability of remaining recurrence-free for 84 months assuming he does not die of another cause first.

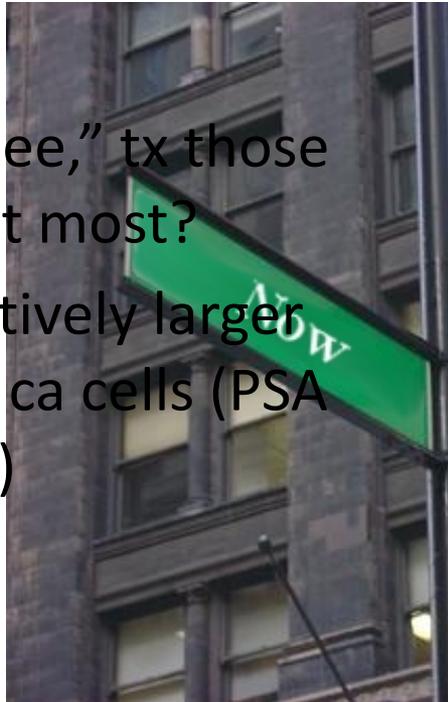
**Instructions to patient:**

"Mr. X, if we had 100 men exactly like you, we would expect between <predicted percentage from nomogram - 10 percent> and <predicted percentage + 10 percent> to remain free of their disease at 7 years following radical prostatectomy, and recurrence after 7 years is very rare".



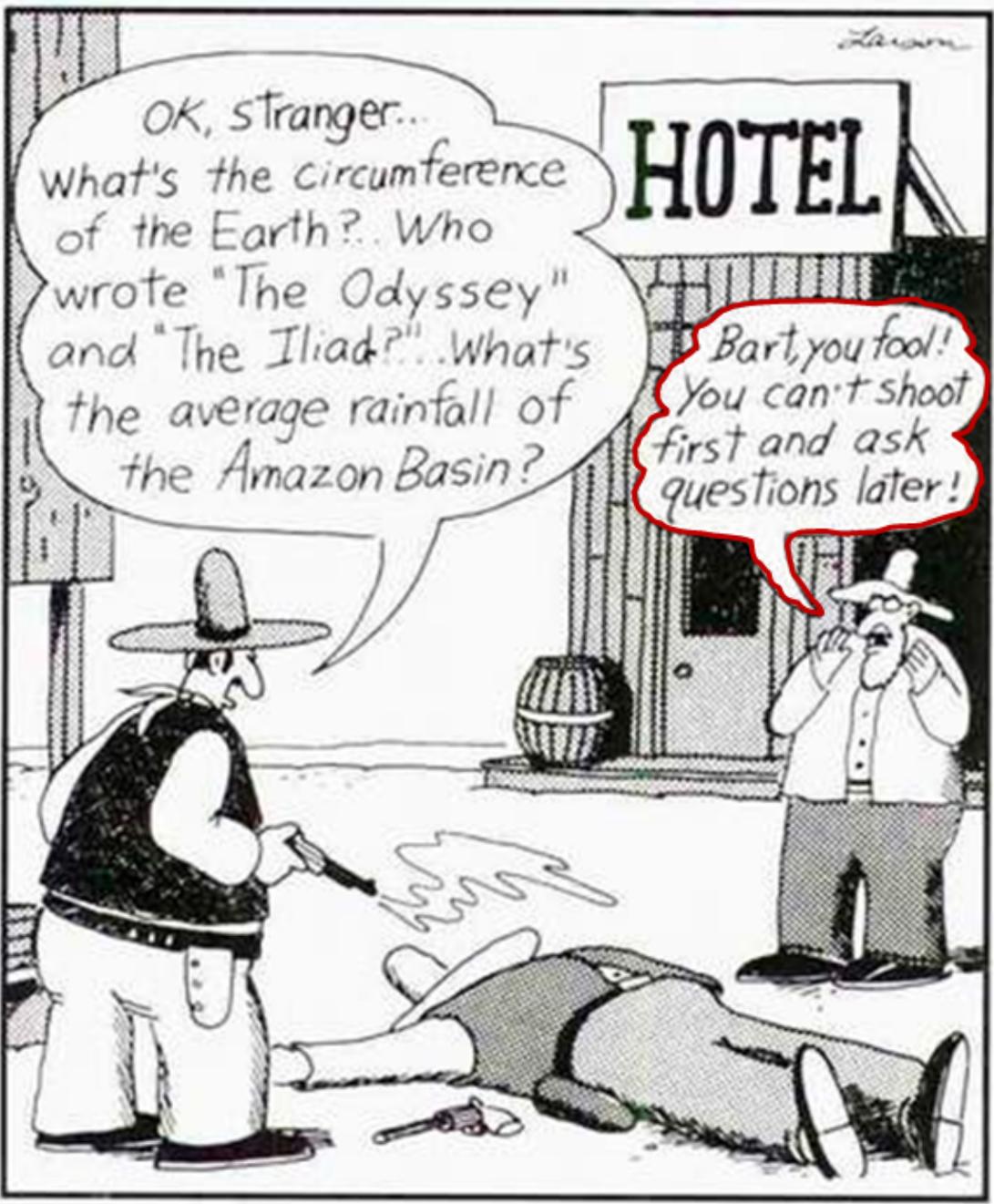
# Adjuvant or Salvage?

- “Wait & See,” tx those that need it most?
- Treat relatively larger number of ca cells (PSA detectable)



- treats relatively smaller # of ca cells (too small to be detected by PSA)
- over-treat a percentage of patients

Larson



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# Salvage RT

- Typical scenario
  - Persistent detectable PSA post-operatively
  - OR
  - Previously undetectable PSA, now detectable and slowly rising
- The earlier the initiation of Salvage RT, the better the biochemical-free survival



# Freedom from Biochemical Failure

Institution	Year	# pts	F/U	FFBF (%)
MSKCC	1997	42	2 yrs	<b>53 %</b>
Wayne S.	1998	78	3 yrs	<b>62 %</b>
Jefferson	1998	27	3 yrs	<b>44 %</b>
UCSF	1999	69	4 yrs	<b>45 %</b>
MGH	2002	54	5 yrs	<b>35 %</b>
Mayo	2003	60	5 yrs	<b>45 %</b>



# Salvage Radiotherapy for Recurrent Prostate Cancer After Radical Prostatectomy

Andrew J. Stephenson, MD

Shahrokh F. Shariat, MD

Michael J. Zelefsky, MD

Michael W. Kattan, PhD

E. Brian Butler, MD

Bin S. Teh, MD

Eric A. Klein, MD

Patrick A. Kupelian, MD

Claus G. Roehrborn, MD

David A. Pistenmaa, MD

Heather D. Pacholke, MD

Stanley L. Liauw, MD

Matthew S. Katz, MD

Steven A. Leibel, MD

Peter T. Scardino, MD

Kevin M. Slawin, MD

**Context** Salvage radiotherapy may potentially cure patients with disease recurrence after radical prostatectomy, but previous evidence has suggested that it is ineffective in patients at the highest risk of metastatic disease progression.

**Objective** To delineate patients who may benefit from salvage radiotherapy for prostate cancer recurrence by identifying variables associated with a durable response.

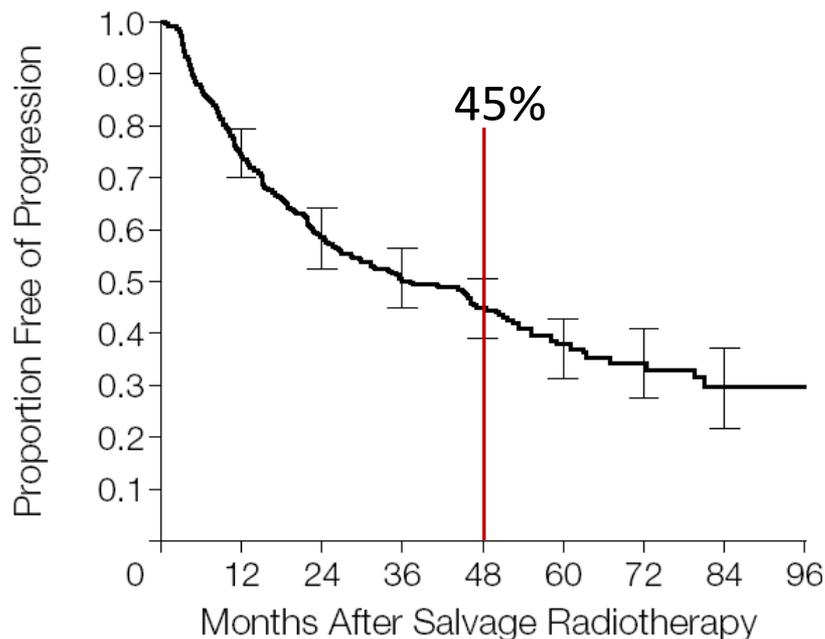
**Design, Setting, and Patients** Retrospective review of a cohort of 501 patients at 5 US academic tertiary referral centers who received salvage radiotherapy between June 1987 and November 2002 for detectable and increasing prostate-specific antigen (PSA) levels after radical prostatectomy.

**Main Outcome Measure** Disease progression after salvage radiotherapy, defined as a serum PSA value  $\geq 0.1$  ng/mL above the postradiotherapy PSA nadir confirmed by a second PSA measurement that was higher than the first by any amount, by a continued increase in PSA level after treatment, or by the initiation of androgen deprivation therapy after treatment.

**Results** Over a median follow-up of 45 months, 250 patients (50%) experienced disease progression after treatment, 49 (10%) developed distant metastases, 20 (4%) died from prostate cancer, and 21 (4%) died from other or unknown causes. The 4-year progression-free probability (PFP) was 45% (95% confidence interval [CI], 40%-50%). By multivariable analysis, predictors of progression were Gleason score of 8 to 10 (hazard ratio [HR], 2.6; 95% CI, 1.7-4.1;  $P < .001$ ), preradiotherapy PSA level greater than 2.0 ng/mL (HR, 2.3; 95% CI, 1.7-3.2;  $P < .001$ ), negative surgical margins (HR, 1.9; 95% CI, 1.4-2.5;  $P < .001$ ), PSA doubling time (PSADT) of 10 months or less (HR, 1.7; 95% CI, 1.2-2.2;  $P = .001$ ), and seminal vesicle invasion (HR, 1.4; 95% CI, 1.1-1.9;  $P = .02$ ). Patients with no adverse features had a 4-year PFP of 77% (95% CI, 64%-91%). When treatment was given for early recurrence (PSA level  $\leq 2.0$  ng/mL), patients with Gleason scores of 4 to 7 and a rapid PSADT had a 4-year PFP of 64% (95% CI, 51%-76%) and of 22% (95% CI, 6%-38%) when the surgical margins were positive and negative, respectively. Patients with Gleason scores of 8 to 10, positive

APPROXIMATELY 30 000 MEN ANNUALLY in the United States will have recurrence of prostate cancer after radical prostatectomy.<sup>1</sup> Initially, for most of these pa-

- 501 patients from 5 institutions treated with salvage RT
- Disease progression defined at  $>0.1$  ng/ml



## Predicting the Outcome of Salvage Radiation Therapy for Recurrent Prostate Cancer After Radical Prostatectomy

Andrew J. Stephenson, Peter T. Scardino, Michael W. Kattan, Thomas M. Pisansky, Kevin M. Slawin, Eric A. Klein, Mitchell S. Anscher, Jeff M. Michalski, Howard M. Sandler, Daniel W. Lin, Jeffrey D. Forman, Michael J. Zelefsky, Larry L. Kestin, Claus G. Roehrborn, Charles N. Catton, Theodore L. DeWeese, Stanley L. Liauw, Richard K. Valicenti, Deborah A. Kuban, and Alan Pollack

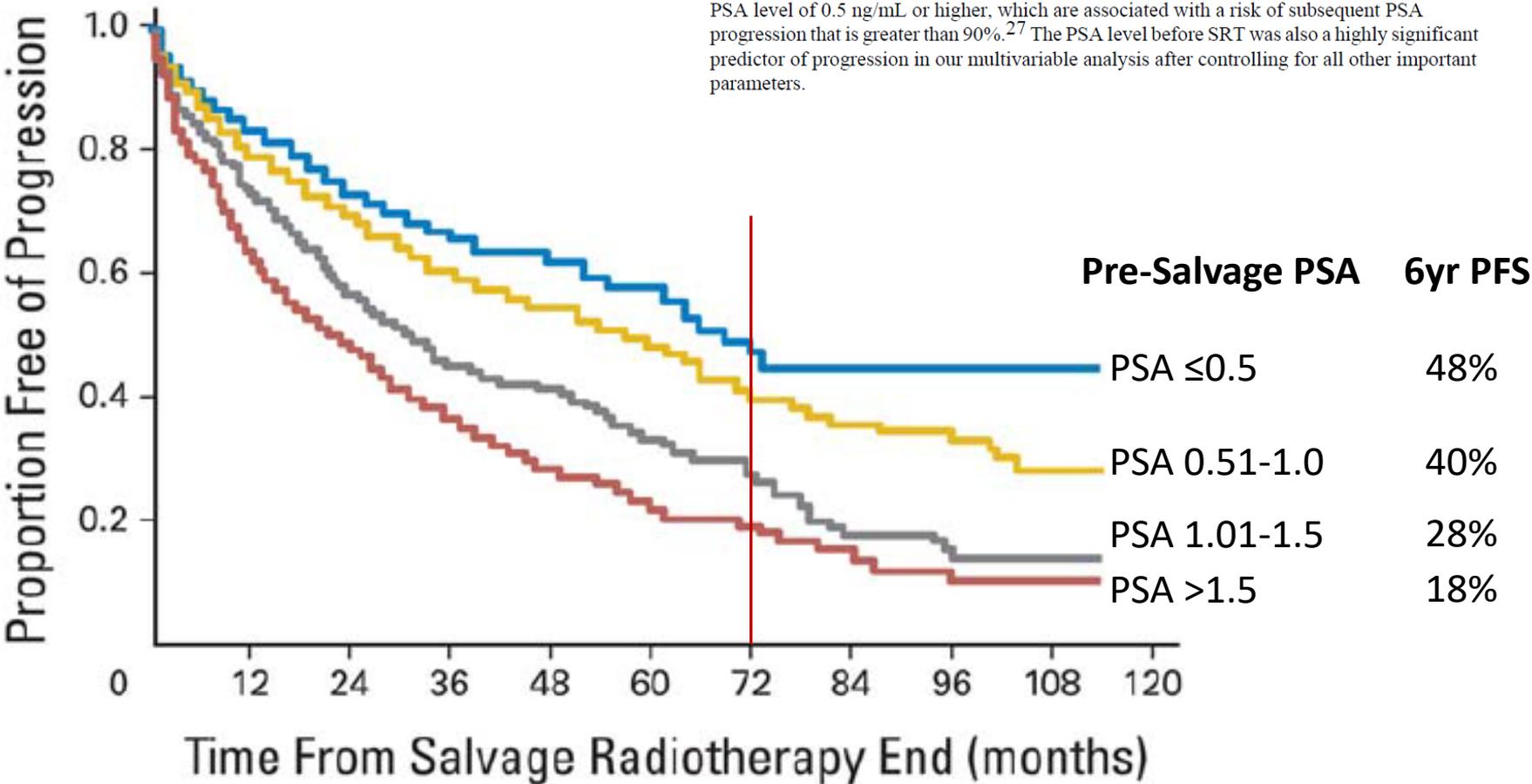
*From the Cleveland Clinic Foundation, Cleveland, OH; Memorial Sloan-Kettering Cancer Center, New York, NY; Mayo Clinic College of Medicine, Rochester, MN; Baylor College of Medicine; The University of Texas M.D. Anderson Cancer Center, Houston; The University of Texas Southwestern Medical Center, Dallas, TX; Duke University School of Medicine, Durham, NC; Washington University School of Medicine, St Louis, MO; University of Michigan Medical Center, Ann Arbor, MI; University of Washington School of Medicine, Seattle, WA; Wayne State University School of Medicine, Detroit, MI; William Beaumont Hospital, Royal Oak, MI; Princess Margaret Hospital,*

- 1603pts from 17 centers
- Salvage RT, 1987-2005
  - “Pure” SRT: *Analysis excluded pts who received ADT*
- Overall 6yr PFS: 32%

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The favorable outcome associated with SRT at lower PSA levels suggests that intervention when the cancer burden is lowest and most amenable to therapy, and before systemic dissemination, leads to improved outcome. Alternatively, this favorable result may be explained by the indolent natural history of PSA recurrence in some patients with a single PSA elevation between 0.2 and 0.39 ng/mL.<sup>27,38</sup> However, we included in our analysis only patients who experienced two or more PSA rises at levels of 0.2 ng/mL or higher or a single PSA level of 0.5 ng/mL or higher, which are associated with a risk of subsequent PSA progression that is greater than 90%.<sup>27</sup> The PSA level before SRT was also a highly significant predictor of progression in our multivariable analysis after controlling for all other important parameters.



# Prostate Cancer–Specific Survival Following Salvage Radiotherapy vs Observation in Men With Biochemical Recurrence After Radical Prostatectomy

Bruce J. Trock, PhD

Misop Han, MD

Stephen J. Freedland, MD

Elizabeth B. Humphreys, MS

Theodore L. DeWeese, MD

Alan W. Partin, MD, PhD

Patrick C. Walsh, MD

**N**EARLY 60 000 MEN (27% OF newly diagnosed cases) will have undergone radical prostatectomy in 2007.<sup>1</sup> Although surgery provides excellent cancer con-

**Context** Biochemical disease recurrence after radical prostatectomy often prompts salvage radiotherapy, but no studies to date have had sufficient numbers of patients or follow-up to determine whether radiotherapy improves survival, and if so, the subgroup of men most likely to benefit.

**Objectives** To quantify the relative improvement in prostate cancer–specific survival of salvage radiotherapy vs no therapy after biochemical recurrence following prostatectomy, and to identify subgroups for whom salvage treatment is most beneficial.

**Design, Setting, and Patients** Retrospective analysis of a cohort of 635 US men undergoing prostatectomy from 1982-2004, followed up through December 28, 2007, who experienced biochemical and/or local recurrence and received no salvage treatment (n=397), salvage radiotherapy alone (n=160), or salvage radiotherapy combined with hormonal therapy (n=78).

**Main Outcome Measure** Prostate cancer–specific survival defined from time of recurrence until death from disease.

- Retrospective review, 635pts from Johns Hopkins
  - No Salvage (n=397)
  - Salvage RT (n=160)
  - Salvage RT + ADT (n=78)

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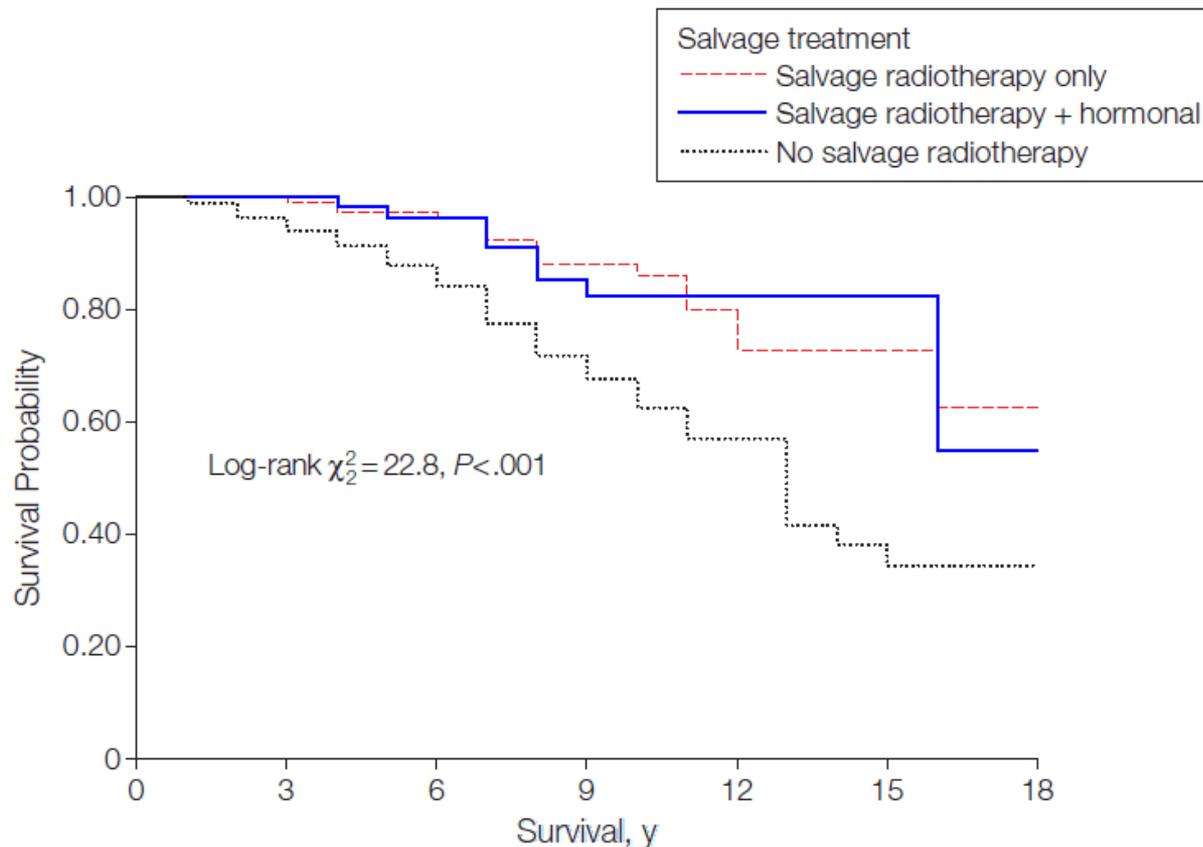
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- Salvage RT only: 3-Fold increase in PCa-specific survival (HR 0.32,  $p < .001$ )
  - Limited to men w PSA DT <6mos and
  - if Salvage RT given within 2yrs of biochem failure
- ADT no benefit on PCa-specific survival

# Salvage Radiation in Men After Prostate-Specific Antigen Failure and the Risk of Death



Shane E. Cotter, MD, PhD<sup>1</sup>; Ming Hui Chen, PhD<sup>2</sup>; Judd W. Moul, MD<sup>3,4</sup>; W. Robert Lee, MD<sup>5</sup>; Bridget F. Koontz, MD<sup>5</sup>; Mitchell S. Anscher, MD<sup>6</sup>; Cary N. Robertson, MD<sup>3,4</sup>; Philip J. Walther, MD, PhD<sup>3,4</sup>; Thomas J. Polascik, MD<sup>3,4</sup>; and Anthony V. D'Amico, MD, PhD<sup>7</sup>

- Retrospective review, 4036 pts from Duke s/p RP
  - 519 Salvage RT

**Table 2.** Adjusted and Unadjusted Risk of All Cause Mortality After Postoperative Prostate-Specific Antigen Failure for Clinical, Pathologic, and Treatment Factors

Clinical Factor	No. of Deaths	No. of Men	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P	AHR (95% CI)	P
<b>Salvage RT Use</b>						
DT <6 mo, no salvage RT	46	88	1.00		1.00	
DT <6 mo, plus salvage RT	34	70	0.81 (0.52 to 1.26)	.34	0.53 (0.31 to 0.90)	.02
DT ≥6 mo, no salvage RT	65	212	0.69 (0.47 to 1.00)	.05	0.66 (0.44 to 0.99)	.04
DT ≥6 mo, plus salvage RT	50	149	0.44 (0.29 to 0.66)	<.001	0.34 (0.21 to 0.57)	<.001
DT ≥6 mo, no salvage RT <sup>a</sup>	65	212	1.00		1.00	
DT ≥6 mo, plus salvage RT	50	149	0.64 (0.44 to 0.93)	.02	0.52 (0.34 to 0.80)	.003

- Salvage RT decreased mortality for PSA DTS's <6mos or >6mos

# Summary: Salvage RT

- Salvage RT can:
  - Improve
    - biochemical control, distant mets, OS, PCa-specific OS
  - Early Usage (ie: low PSA) appears most beneficial



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# Adjuvant RT

- Adjuvant RT
  - “high risk” features → immediate RT
- non-randomized studies
  - Results: ART → significant improvement in bNED and disease-free survival rate
  - Criticism: retrospective series



# RP with or without Adjuvant RT

	Met-free survival (%)		DFS (%)	
	RP	RP + RT	RP	RP + RT
Anscher *	60	82	32	52
Cheng	84	100	90	92
Schild	83	100	90	90
Gibbons	70	95	39	39
Jacobson	83	100	92	89
Meier*	59	88	38	68
Shevlin*	72	100	80	80
Stein	88	100	67	92

\* Endpoint 10 year actuarial (all others 5 year)

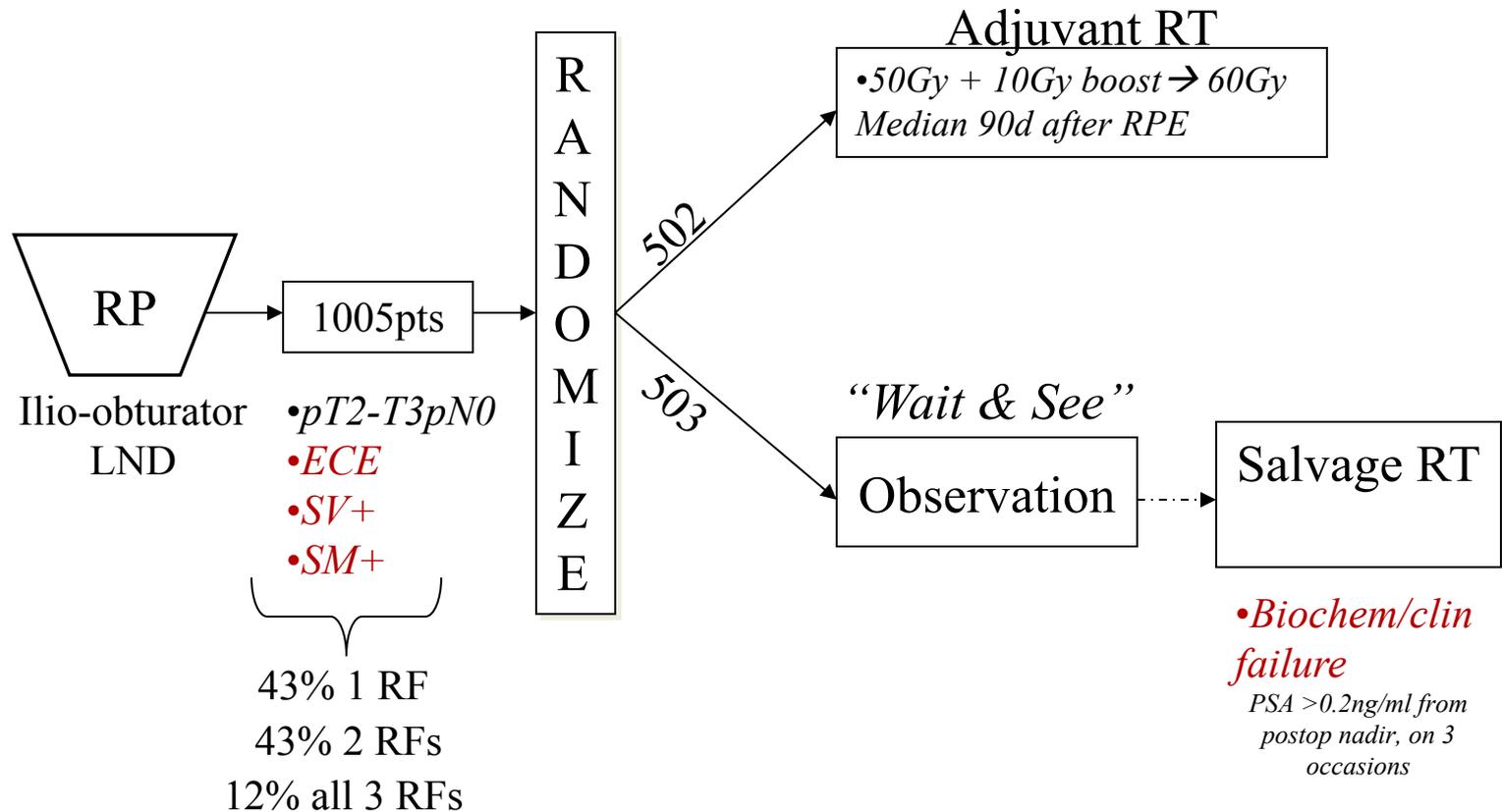
# Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911)

*Michel Bolla, Hein van Poppel, Laurence Collette, Paul van Cangh, Kris Vekemans, Luigi Da Pozzo, Theo M de Reijke, Antony Verbaeys, Jean-François Bosset, Roland van Velthoven, Jean-Marie Maréchal, Pierre Scalliet, Karin Haustemans, Marianne Piérart, for the European Organization for Research and Treatment of Cancer*

**Methods** After undergoing radical retropubic prostatectomy, 503 patients were randomly assigned to a wait-and-see policy, and 502 to immediate postoperative radiotherapy (60 Gy conventional irradiation delivered over 6 weeks). Eligible patients had pN0M0 tumours and one or more pathological risk factors: capsule perforation, positive surgical margins, invasion of seminal vesicles. Our revised primary endpoint was biochemical progression-free survival. Analysis was by intention to treat.

## EORTC 22911

# EORTC 22911



# Median f/u 5y

## Biochemical PFS

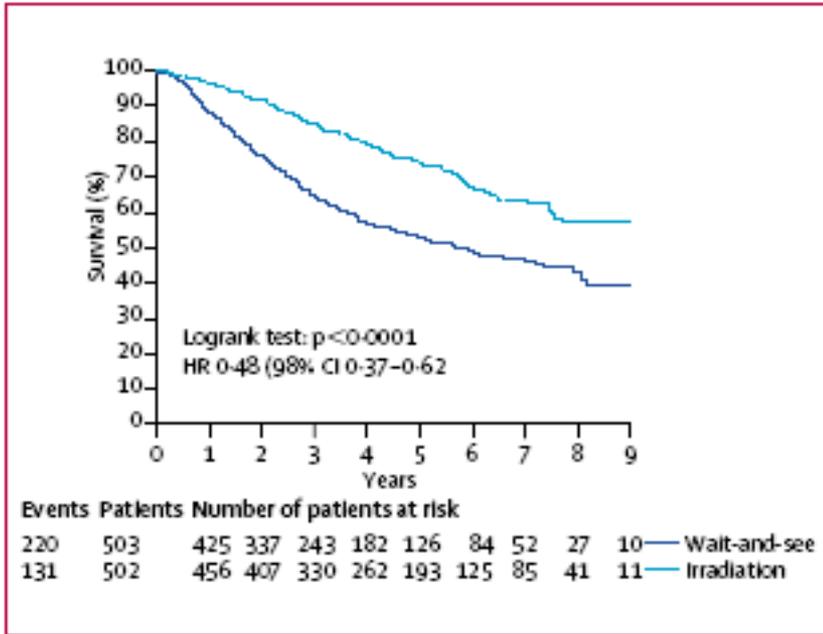


Figure 2: Biochemical progression-free survival

## Clinical PFS

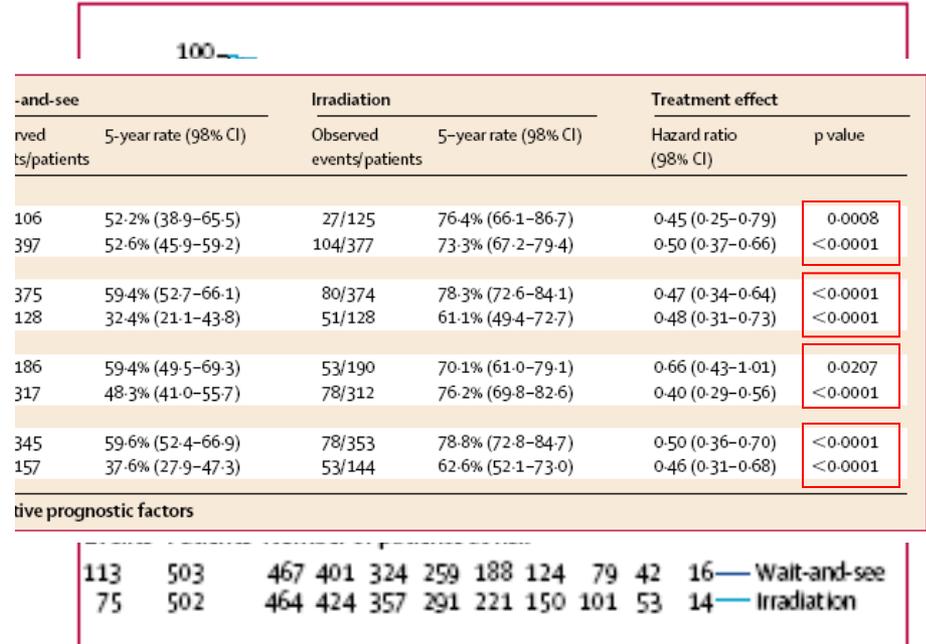


Figure 3: Clinical progression-free survival

5yr bPFS	74.0%	■	Adjuvant RT	■	85%	5yr clinical PFS
	52.6%	■	Observation	■	78%	

Most failures loco-regional

Median f/u 5y

Toxicity

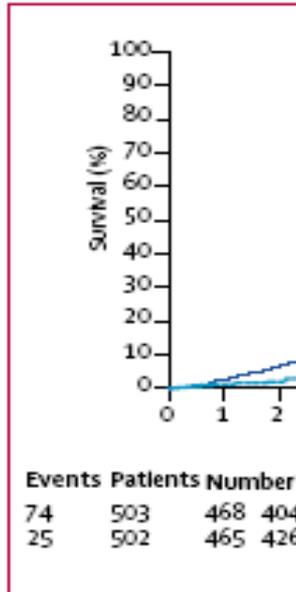


Figure 4: Cumulative incid

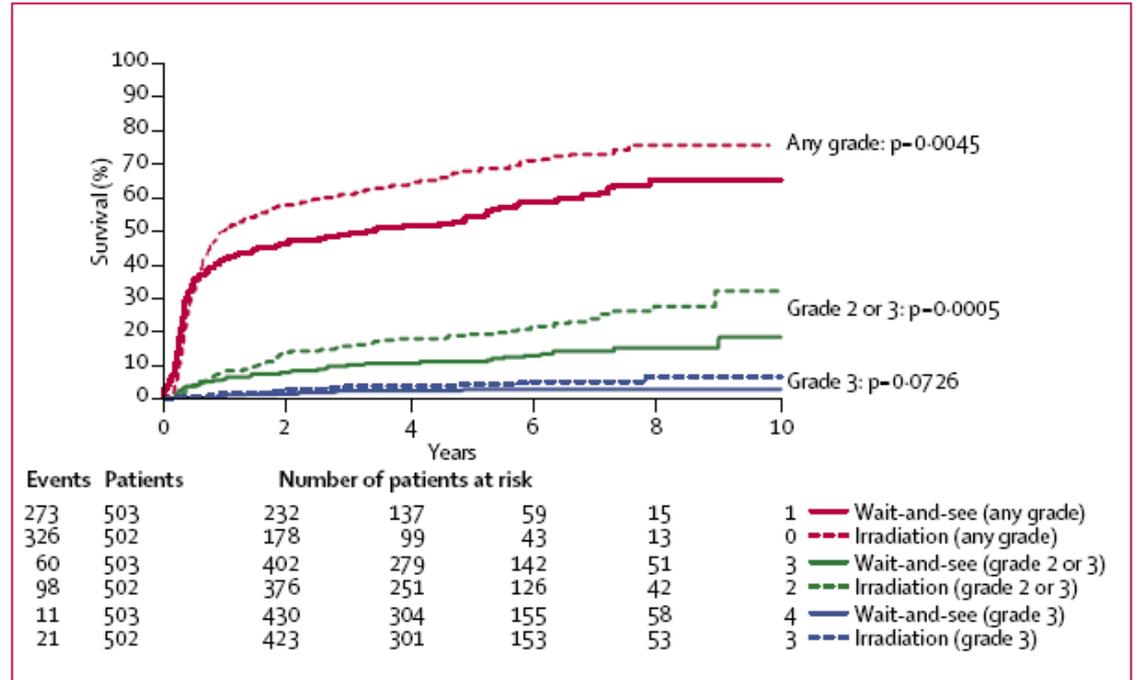


Figure 5: Cumulative incidence of late complications

p values indicate comparison of wait-and-see with irradiation groups.

5yr LRF's	5.4%	■	Adjuvant RT	■	4.2%
	15.4%	■	Observation	■	2.6%

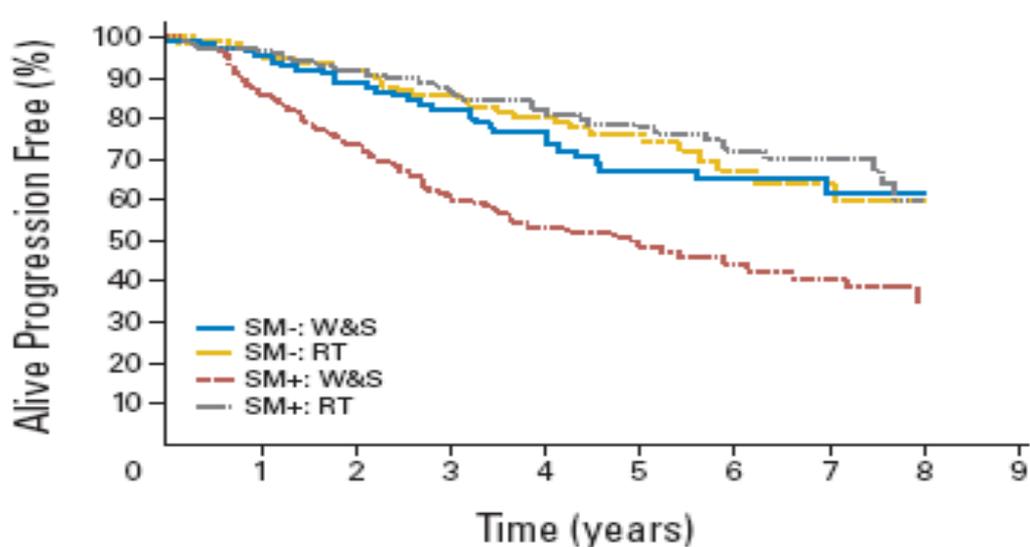
NS

Grade 3 toxicity

2D RT techniques  
No grade 4 tox

## Identification of Patients With Prostate Cancer Who Benefit From Immediate Postoperative Radiotherapy: EORTC 22911

Theodorus H. Van der Kwast, Michel Bolla, Hein Van Poppel, Paul Van Cangh, Kris Vekemans, Luigi Da Pozzo, Jean-Francois Bosset, Karl H. Kurth, Fritz H. Schröder, and Laurence Collette



	0	N	No. of patients at risk							
SM-: W&S	33	116	109	95	72	53	38	25	19	11
SM-: RT	29	114	105	94	81	62	45	25	16	10
SM+: W&S	79	152	129	107	81	58	40	27	18	8
SM+: RT	35	142	135	125	103	83	62	45	34	12

**Fig 3.** Biochemical progression-free survival by surgical margin status and allocated treatment. N, number of patients; O, number of events; SM-/+ , surgical margin negative/positive; W&S, wait-and-see group (control); RT, irradiation.

post hoc analysis  
 • improvement in bRFS  
 most pronounced in pts  
 with SM+

## Median F/U 10.6 years update

- adjuvant RT improved 10 yr bPFS 61% vs. 41% (SS).  
10 yr LRR 7.3% (RT) vs 16.6% (obs) (SS).
  - *No difference in DM, OS or CSS.*
- Conclusion: Postop RT improves bPFS and local control vs. observation, consistent with 5-yr results. However, improvements in clinical PFS were not maintained.

## Phase III Postoperative Adjuvant Radiotherapy After Radical Prostatectomy Compared With Radical Prostatectomy Alone in pT3 Prostate Cancer With Postoperative Undetectable Prostate-Specific Antigen: ARO 96-02/AUO AP 09/95

From the Department of Radiation Oncology, University Hospital Ulm, Ulm; Departments of Urology and Radiation Oncology, Charité Universitätsmedizin, Campus Benjamin-Franklin, Berlin; Department of Pathology, Helios-Clinic Wuppertal, Wuppertal; Departments of Radiation Oncology and Urology, University Hospital Münster, Münster; Department of Radiation Oncology, General Hospital Hagen, Hagen; Departments of Urology and Radiation Oncology, University Hospital Homburg/Saar, Homburg/Saar; Department of Urology, Euro-Med-Clinic Fürth, Fürth; Department of Urology, General Hospital Berlin-Herzberge, Berlin-Herzberge; Department of Urology, Diakonissen-Krankenhaus Dessau,

*Thomas Wiegel, Dirk Bottke, Ursula Steiner, Alessandra Siegmann, Reinhard Golz, Stephan Störkel, Norman Willich, Axel Semjonow, Rainer Souchon, Michael Stöckle, Christian Rübe, Lothar Weißbach, Peter Althaus, Udo Rebmann, Tilman Kälble, Horst Jürgen Feldmann, Manfred Wirth, Axel Hinke, Wolfgang Hinkelbein, and Kurt Miller*

### A B S T R A C T

#### **Purpose**

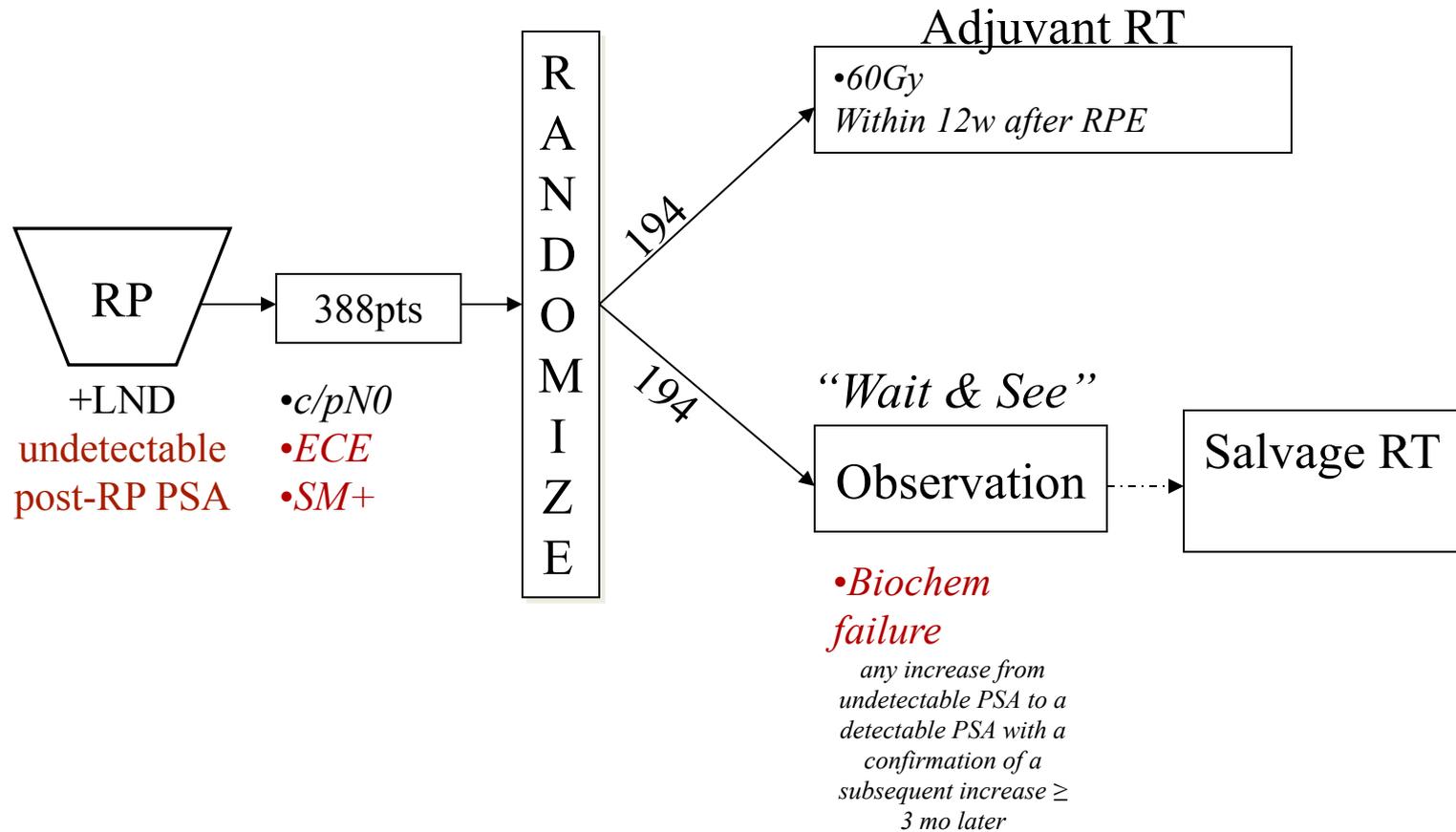
Local failure after radical prostatectomy (RP) is common in patients with cancer extending beyond the capsule. Two randomized trials demonstrated an advantage for adjuvant radiotherapy (RT) compared with a wait-and-see policy. We conducted a randomized, controlled clinical trial to compare RP followed by immediate RT with RP alone for patients with pT3 prostate cancer and an undetectable prostate-specific antigen (PSA) level after RP.

#### **Methods**

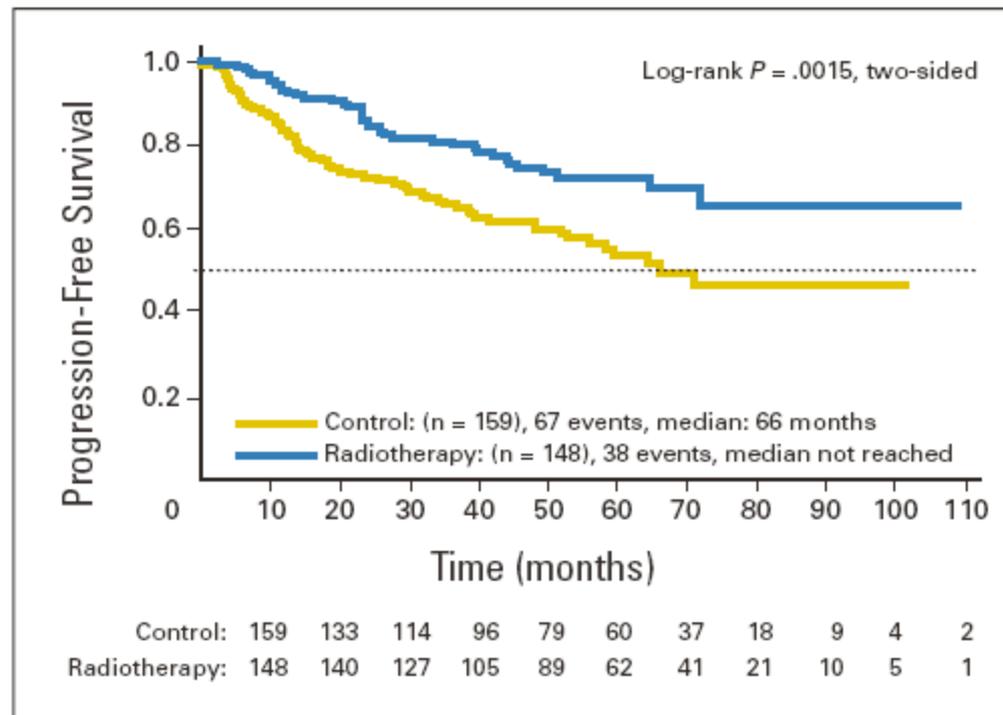
After RP, 192 men were randomly assigned to a wait-and-see policy, and 193 men were assigned

# German Intergroup ARO/AUO 96-02

# ARO/AUO 96-02



Median f/u 4.5yrs



**Fig 3.** Biochemical progression-free survival of all patients with undetectable prostate-specific antigen after radical prostatectomy

- 5yr bNED 72% vs. 54%,  $p=.002$
- 1 grade 3 urinary toxicity
- DM 3% vs. 2% (NS)
- Conclusion → pts w pT3, w undetectable PSA s/p RPE benefit from adjuvant RT

- bNED at 10-yrs: 35% (no RT) vs 56% (RT); HR=0.51 (SS). No sig difference

- Toxic Grad

- Conc was

- A st

## *Pound et al, JAMA*

- at mean f/u 5.3 years, 15% of patients (304) developed biochemical failure (PSA  $\geq$  0.2 ng/ml)

– 103/304 developed mets

- Median time from first PSA elevation to development of mets  $\rightarrow$  8 years
- Median time to **death** after mets  $\rightarrow$  5 years

ART

%. The

# Agenda

- Clinical Case: CR
- Clinical Significance of biochemical failure
  - *Pound et al, JAMA*
  - Prediction Tools/Nomograms
- Salvage Radiation
  - Retrospective series
  - GETUG-AFU 16
  - RTOG 96-01
- Adjuvant Radiation
  - Retrospective series
  - EORTC 2291, *Lancet*
  - ARO/AUO 96-02, *JCO*
  - **SWOG 8794, *JAMA***
- Consensus Guidelines

# Adjuvant Radiotherapy for Pathologically Advanced Prostate Cancer

## A Randomized Clinical Trial

Ian M. Thompson, Jr, MD

Catherine M. Tangen, DrPH

Jorge Paradelo, MD

M. Scott Lucia, MD

Gary Miller, MD, PhD†

Dean Troyer, MD

Edward Messing, MD

Jeffrey Forman, MD

Joseph Chin, MD

Gregory Swanson, MD

Edith Canby-Hagino, MD

E. David Crawford, MD

**R**ADICAL PROSTATECTOMY IS SELECTED for treatment of localized prostate cancer by approximately one third of the 230 000 patients newly diagnosed each

**Context** Despite a stage-shift to earlier cancer stages and lower tumor volumes for prostate cancer, pathologically advanced disease is detected at radical prostatectomy in 38% to 52% of patients. However, the optimal management of these patients after radical prostatectomy is unknown.

**Objective** To determine whether adjuvant radiotherapy improves metastasis-free survival in patients with stage pT3 N0 M0 prostate cancer.

**Design, Setting, and Patients** Randomized, prospective, multi-institutional, US clinical trial with enrollment between August 15, 1988, and January 1, 1997 (with database frozen for statistical analysis on September 21, 2005). Patients were 425 men with pathologically advanced prostate cancer who had undergone radical prostatectomy.

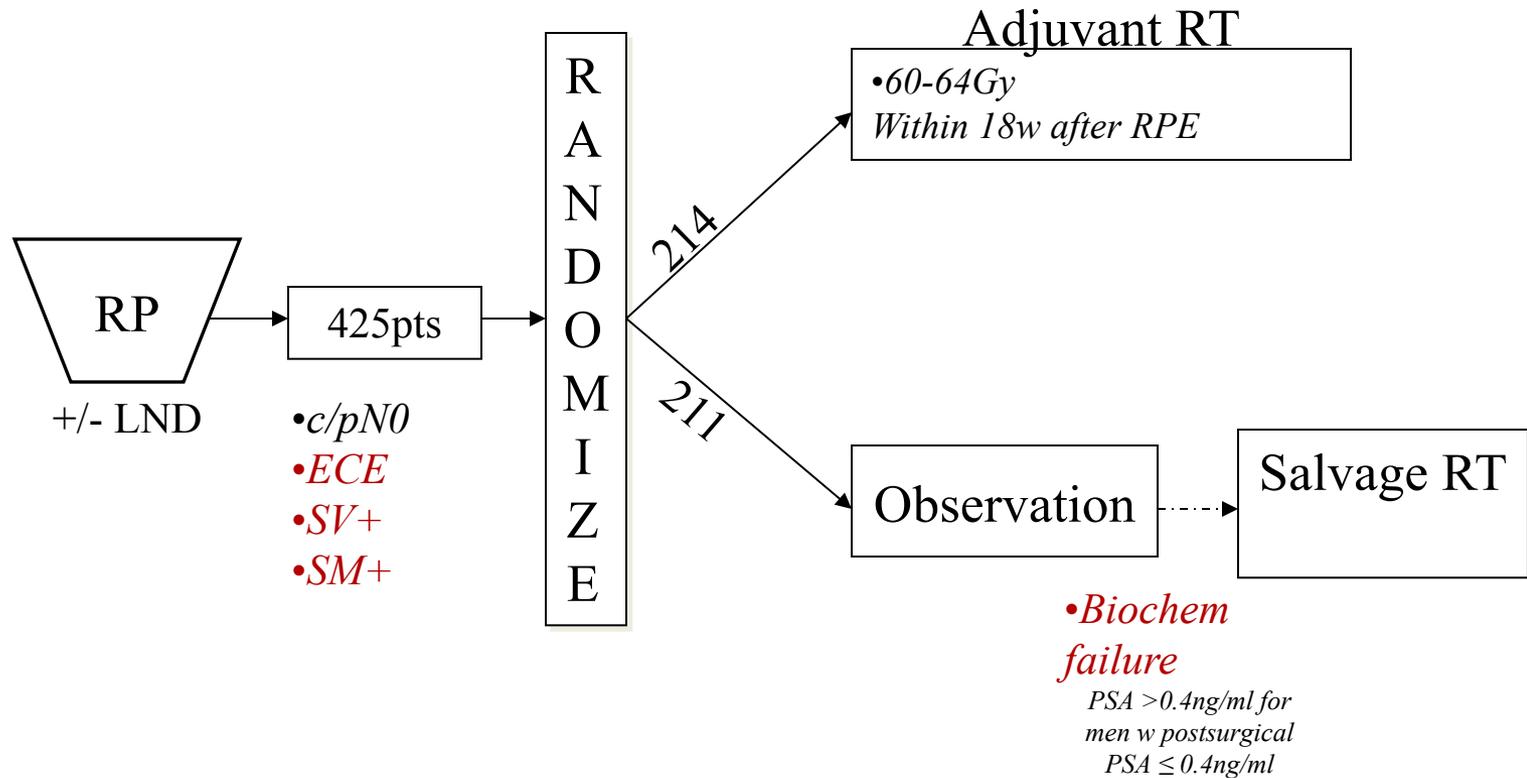
**Intervention** Men were randomly assigned to receive 60 to 64 Gy of external beam radiotherapy delivered to the prostatic fossa (n=214) or usual care plus observation (n=211).

**Main Outcome Measures** Primary outcome was metastasis-free survival, defined as time to first occurrence of metastatic disease or death due to any cause. Secondary outcomes included prostate-specific antigen (PSA) relapse, recurrence-free survival, overall survival, freedom from hormonal therapy, and postoperative complications.

**Results** Among the 425 men, median follow-up was 10.6 years (interquartile range, 9.2-12.7 years). For metastasis-free survival, 76 (35.5%) of 214 men in the adjuvant radiotherapy group were diagnosed with metastatic disease or died (median metastasis-free estimate, 14.7 years), compared with 91 (43.1%) of 211 (median metastasis-free estimate, 13.2 years) of those in the observation group (hazard ratio [HR], 0.75;

# SWOG 8794

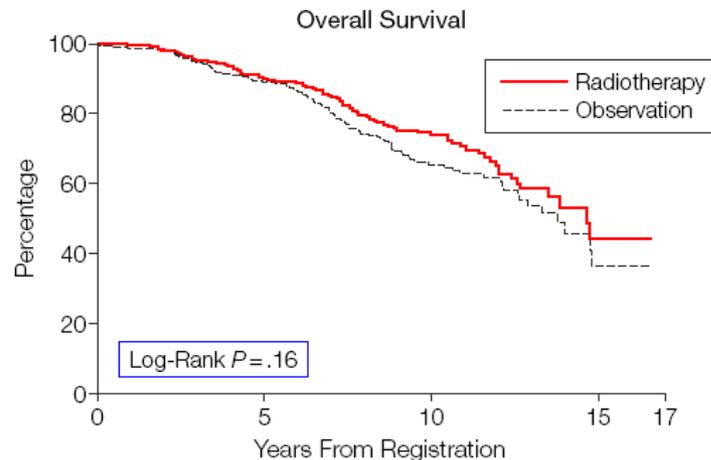
# SWOG 8794



Median f/u 10.6y

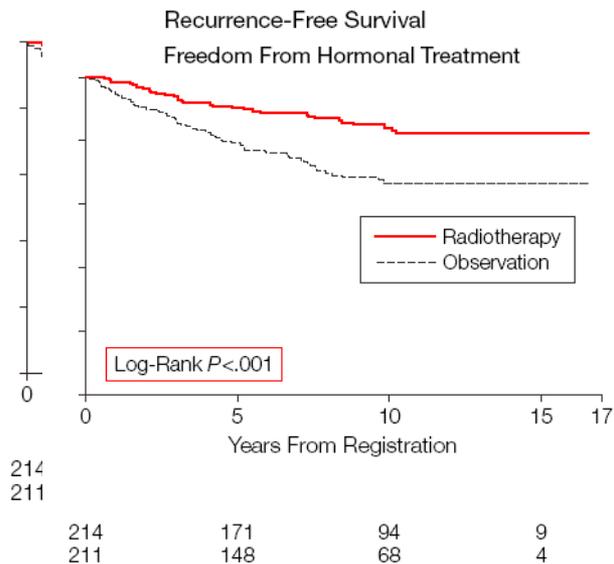
# SWOG 8794

	Arm 1	Arm 2	
	Adjuvant RT	Observation	P
PSA relapse	34.9%	64.0%	<.001
Median RFS	13.8 years	9.9 years	.001



No. at Risk	0	5	10	15
Radiotherapy	214	188	109	10
Observation	211	183	91	5

RFS= Recurrence Free Survival  
 OS= Overall Survival  
 FFHT= Freedom from Hormonal Therapy



# SWOG 8794

- Conclusion: Adjuvant RT decreases PSA and clinical recurrence by ~50%

## Predominant Treatment Failure in Postprostatectomy Patients Is Local: Analysis of Patterns of Treatment Failure in SWOG 8794

*Gregory P. Swanson, Michael A. Hussey, Catherine M. Tangen, Joseph Chin, Edward Messing, Edith Canby-Hagino, Jeffrey D. Forman, Ian M. Thompson, and E. David Crawford*

From the University of Texas Health Science Center, San Antonio, TX; Southwest Oncology Group Statistical Center, Seattle, WA; University of Western Ontario, James P. Wilmot Cancer Center, University of Rochester School of Medicine, Rochester, NY; Wayne State University School of Medicine, Detroit, MI; University of Colorado Health Science Center, Denver, CO; and the Department of Surgical Oncology, London, Ontario, Canada.

Submitted October 23, 2006; accepted March 12, 2007.

### A B S T R A C T

#### **Purpose**

Southwest Oncology Group (SWOG) trial 8794 demonstrated that adjuvant radiation reduces the risk of biochemical (prostate-specific antigen [PSA]) treatment failure by 50% over radical prostatectomy alone. In this analysis, we stratified patients as to their preradiation PSA levels and correlated it with outcomes such as PSA treatment failure, local recurrence, and distant failure, to serve as guidelines for future research.

#### **Patients and Methods**

Four hundred thirty-one subjects with pathologically advanced prostate cancer (extraprostatic extension, positive surgical margins, or seminal vesicle invasion) were randomly assigned to adjuvant radiotherapy or observation.

# SWOG 8794: Patterns of Failure

Median f/u 10.6y

# SWOG 8794

	LF		DM	
	Adjuvant RT	Observation	Adjuvant RT	Observation
Post RP PSA				
≤ 0.2ng/ml	7%	20%	4%	12%
0.2-1ng/ml	9%	25%	12%	16%
>1.0ng/ml	9%	28%	18%	44%
<b>OVERALL</b>	8%	22%	7%	16%

## Conclusion

The pattern of treatment failure in high-risk patients is predominantly local with a surprisingly low incidence of metastatic failure. Adjuvant radiation to the prostate bed reduces the risk of metastatic disease and biochemical failure at all postsurgical PSA levels. Further improvement in reducing local treatment failure is likely to have the greatest impact on outcome in high-risk patients after prostatectomy.

Median f/u 10.6y

# SWOG 8794

- 70/211 in observation arm received Salvage RT

**Table 2.** PSA Failure-Free Rates by Post-RP PSA Subgroup Among Patients Who Received Immediate or Delayed Radiation

Post-RP PSA (ng/mL)		5-Year PSA Failure-Free Rate (%)
≤ 0.2		
Immediate XRT	adjuvant	77*
XRT at failure	salvage	38†
> 0.2 and ≤ 1.0		
Immediate XRT	adjuvant	34*
XRT at failure	salvage	18†

Abbreviations: RP, radical prostatectomy; PSA, prostate-specific antigen; XRT, radiation therapy.

\*Time to PSA failure = registration date to date of first PSA ≥ 0.4 ng/mL.

†Time to PSA failure = date of initiation of salvage RT to first subsequent date of PSA ≥ 0.4 ng/mL.

## Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial

Ian M. Thompson,\*,<sup>†</sup> Catherine M. Tangen, Jorge Paradelo, M. Scott Lucia, Gary Miller,<sup>‡</sup> Dean Troyer, Edward Messing, Jeffrey Forman, Joseph Chin, Gregory Swanson, Edith Canby-Hagino and E. David Crawford

*From the University of Texas Health Science Center at San Antonio (IMT, DT, GS) and Wilford Hall Medical Center (ECH), San Antonio, Texas, The Fred Hutchinson Cancer Research Center, Seattle, Washington (CMT), The Kansas City Community Clinical Oncology Program, Kansas City, Missouri (JP), The University of Colorado Health Science Center, Denver, Colorado (MSL, GM, EDC), The James P. Wilmot Cancer Center, University of Rochester School of Medicine, Rochester, New York (EM), Wayne State University School of Medicine, Detroit, Michigan (JF), and the University of Western Ontario, Department of Surgical Oncology, London, Ontario (JC)*

### Abbreviations and Acronyms

EORTC = European Organization for the Research and Treatment of Cancer

PSA = prostate specific antigen

RT = radiotherapy

SWOG = Southwest Oncology Group

S8794 = Southwest Oncology Group Study 8794

Submitted for publication September 15, 2008.

Study received approval from individual institutional review boards of the participating institutions.

Supported by Public Health Service Cooperative Agreement grants awarded by the National Cancer Institute, Department of Health and Human Services: CA38926, CA32102, CA14028, CA58416, CA56658, CA42777, CA27057, CA46136, CA35431, CA56882, CA12644, CA59861, CA35090, CA37981, CA76429, CA04919, CA76132, CA35119, CA56178, CA56179, CA46322, CA27076, CA46377

**Purpose:** Extraprostatic disease will be manifest in a third of men after radical prostatectomy. We present the long-term followup of a randomized clinical trial of radiotherapy to reduce the risk of subsequent metastatic disease and death.

**Materials and Methods:** A total of 431 men with pT3N0M0 prostate cancer were randomized to 60 to 64 Gy adjuvant radiotherapy or observation. The primary study end point was metastasis-free survival.

**Results:** Of 425 eligible men 211 were randomized to observation and 214 to adjuvant radiation. Of those men under observation 70 ultimately received radiotherapy. Metastasis-free survival was significantly greater with radiotherapy (93 of 214 events on the radiotherapy arm vs 114 of 211 events on observation; HR 0.71; 95% CI 0.54, 0.94;  $p = 0.016$ ). Survival improved significantly with adjuvant radiation (88 deaths of 214 on the radiotherapy arm vs 110 deaths of 211 on observation; HR 0.72; 95% CI 0.55, 0.96;  $p = 0.023$ ).

**Conclusions:** Adjuvant radiotherapy after radical prostatectomy for a man with pT3N0M0 prostate cancer significantly reduces the risk of metastasis and increases survival.

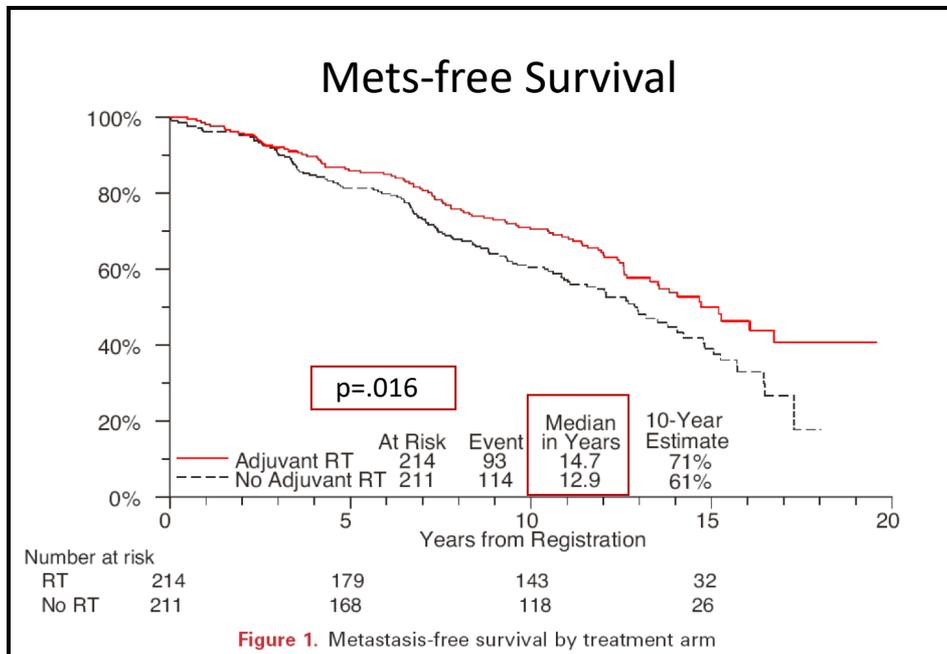
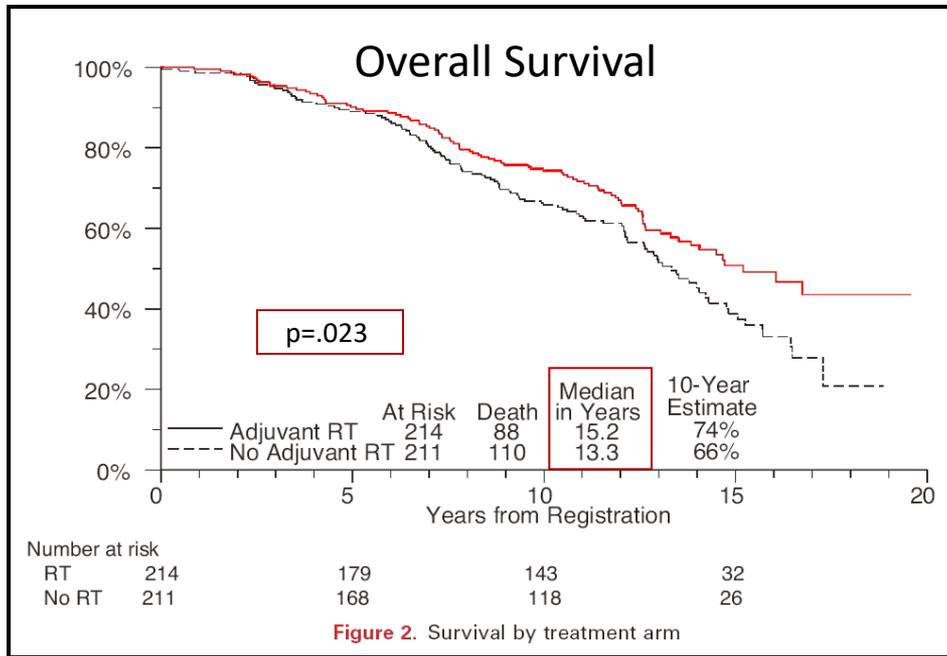
**Key Words:** prostatic neoplasms, radiotherapy, prostate-specific antigen, neoplasm metastasis

Of the 186,320 patients estimated to be diagnosed with prostate cancer in invasion.<sup>5</sup> Positive margins and seminal vesicle invasion are associated

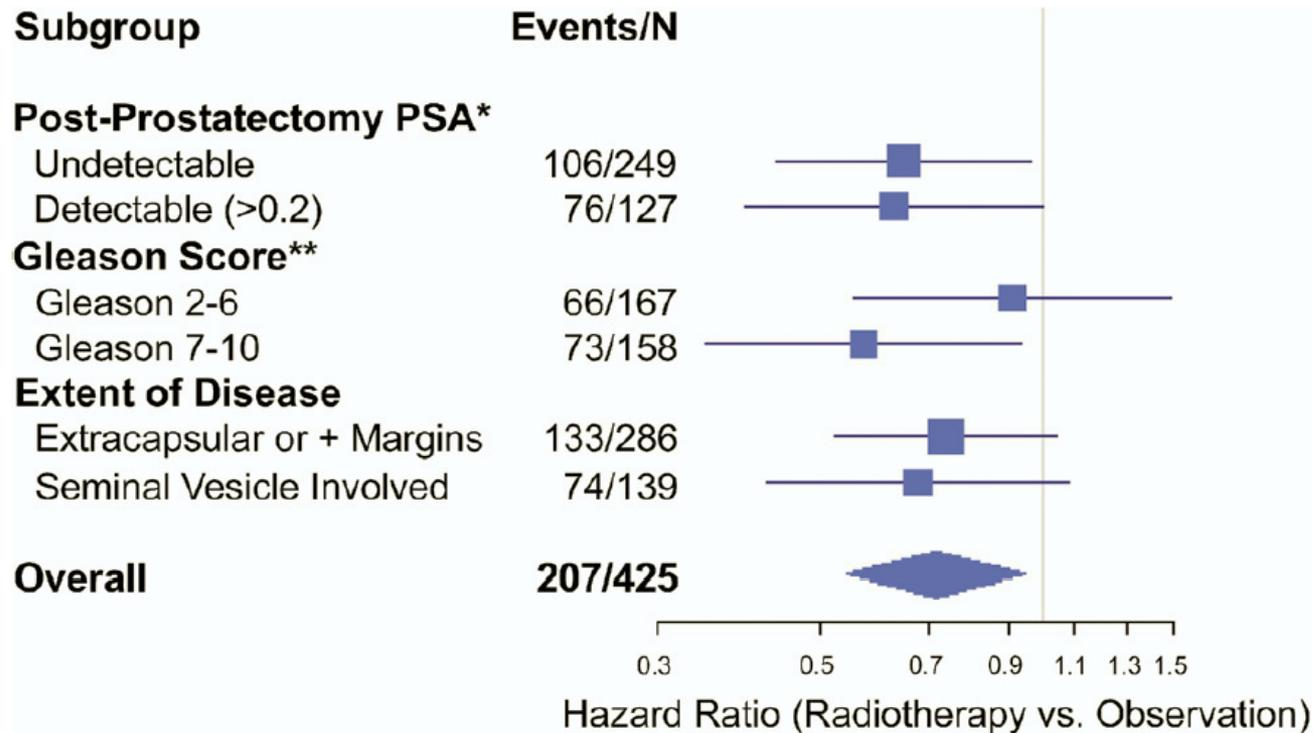
# SWOG 8794, 15 year update

# SWOG 8794, 15 year update

NNT, T3dz adjuvant RT to prevent 1 death, at f/u of 12.6 yrs → 9.1



NNT, T3dz adjuvant RT to prevent 1 case of met dz, at f/u of 12.6 yrs → 12.2



- In each pre-tx grouping, HR < 1, suggesting benefit of adjuvant RT
  - No particular subset should NOT receive adjuvant RT
- Adjuvant RT at relatively modest 1980's dosing sig reduces met dz and improves OS in pts with pT3, +MS, SVI, ECE, ≥GS7

# Agenda

- Clinical Significance of biochemical failure
  - *Pound et al, JAMA*
  - Prediction Tools/Nomograms
- Salvage Radiation
  - Retrospective series
- Adjuvant Radiation
  - Retrospective series
  - EORTC 2291, *Lancet*
  - ARO/AUO 96-02, *JCO*
  - SWOG 8794, *JAMA*
- Consensus Guidelines: “Do you Concur?”
- Meta Level Considerations

**CHOOSE YOUR OWN ADVENTURE™ · 1**

**YOU'RE THE STAR OF THE STORY!  
CHOOSE FROM 40 POSSIBLE ENDINGS**

NCCN National Comprehensive Cancer Network  
**NCCN Guidelines Version 3.2016  
 Prostate Cancer**

RISK GROUP	INITIAL THERAPY	ADJUVANT THERAPY
High: <sup>a</sup> • T3a or • Gleason score 8-10 or • PSA >20 ng/mL	EBRT <sup>b</sup> + ADT <sup>c</sup> (2-3 y) (category 1) or EBRT <sup>b</sup> + brachytherapy ± ADT <sup>c</sup> (2-3 y) or EBRT <sup>b</sup> + ADT <sup>c</sup> (2-3 y) + docetaxel <sup>d</sup> or RP <sup>e</sup> + PLND	Adverse features: <sup>f</sup> EBRT <sup>b</sup> or Observation <sup>g</sup>
	See Monitoring (PROS-6)	Lymph node metastasis: ADT <sup>c</sup> (category 1) ± EBRT <sup>b</sup> (category 2B) or Observation <sup>g</sup> (category 2B)

<sup>a</sup>Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

**PROSTATE CANCER +911**

by

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**Adjuvant or Salvage Therapy after Radical Prostatectomy**

Most patients who have undergone radical prostatectomy are cured of prostate cancer. However, some men will suffer pathologic or biochemical failure. **Selecting men appropriately for adjuvant or salvage radiation is difficult.**





Guidelines

International Journal of  
Radiation Oncology  
biology • physics

www.redjournal.org

## Adjuvant and Salvage Radiation Therapy After Prostatectomy: American Society for Radiation Oncology/American Urological Association Guidelines

Richard K. Valicenti, MD, MBA,\* Ian Thompson Jr., MD,† Peter Albertsen, MD, MS,‡ Brian J. Davis, MD, PhD,§ S. Larry Goldenberg, MD,|| J. Stuart Wolf, MD,¶ Oliver Sartor, MD,# Eric Klein, MD,\*\* Carol Hahn, MD,†† Jeff Michalski, MD, MBA,‡‡ Mack Roach III, MD,§§ and Martha M. Faraday, PhD|||

## Adjuvant and Salvage Radiotherapy After Prostatectomy: AUA/ASTRO Guideline

Ian M. Thompson,\* Richard K. Valicenti,\* Peter Albertsen, Brian J. Davis, S. Larry Goldenberg, Carol Hahn, Eric Klein, Jeff Michalski, Mack Roach, Oliver Sartor, J. Stuart Wolf, Jr. and Martha M. Faraday

From the American Urological Association Education and Research, Inc., Linthicum, Maryland, and the American Society for Radiation Oncology, Fairfax, Virginia

**Purpose:** The purpose of this guideline is to provide a clinical framework for the use of radiotherapy after radical prostatectomy as adjuvant or salvage therapy.  
**Materials and Methods:** A systematic literature review using the PubMed®, Embase, and Cochrane databases was conducted to identify peer-reviewed pub-



American  
Urological  
Association



### Guideline statement 3

Physicians should offer adjuvant RT to patients with adverse pathologic findings at prostatectomy, including SVI, positive surgical margins, or EPE because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression (Standard; Evidence Strength Grade A).

The Panel notes that the apparent benefits associated with ART are partially the result of a patient subset that was treated who never would have presented with recurrence. The Panel emphasizes that ART should be offered to all patients at high recurrence risk because of adverse pathology. By “offered,” the Panel means that the patient, his family, and the multidisciplinary treatment team should engage in a shared decision making process in which the patient is advised to consider the possibility of additional treatment (ie, RT). Whether ART should be administered is a decision best made by the multidisciplinary treatment team and the patient with consideration of the patient’s history, functional status, values, and preferences and his tolerance for the potential toxicities and QoL effects of RT.

### Guideline statement 7

Physicians should offer SRT to patients with PSA or local recurrence after RP in whom there is no evidence of distant metastatic disease (Recommendation; Evidence Strength Grade C).

# Adjuvant and Salvage Radiotherapy After Prostatectomy:



American Urological Association



Mendelson, Pinnacle Oncology Hemadale, AZ; Howard M. ...rs-Sinai Medical Center, CA.

and recommendations.

### Results

The panel determined that the guideline recommendations on adjuvant and salvage radiotherapy after prostatectomy, published in August 2013, are clear, thorough, and based on the most relevant scientific evidence. ASCO endorsed the guideline on adjuvant and salvage radiotherapy after prostatectomy, adding one qualifying statement that not all candidates for adjuvant or salvage radiotherapy have the same risk of recurrence or disease progression, and thus, risk-benefit ratios are not the same for all men. Those at the highest risk for recurrence after radical prostatectomy include men with seminal vesicle invasion, Gleason score 8 to 10, extensive positive margins, and detectable postoperative prostate-specific antigen (PSA).



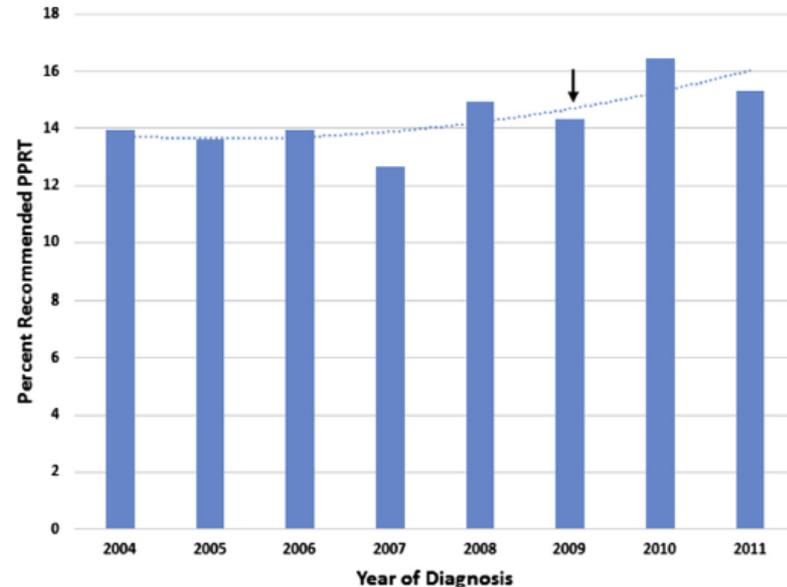


## National Trends in the Recommendation of Radiotherapy After Prostatectomy for Prostate Cancer Before and After the Reporting of a Survival Benefit in March 2009

Brandon A. Mahal,<sup>1</sup> Karen E. Hoffman,<sup>2</sup> Jason A. Efstathiou,<sup>3</sup> Paul L. Nguyen<sup>4</sup>

- SEER analysis, 2004-2011
- 35,361 men s/p RP w ECE, SVI, or SM+
- **14.4%** received recommendation for Adjuvant RT

**Figure 1** Percentage of Men Recommended Adjuvant Radiotherapy (Post-Prostatectomy Radiotherapy; PPRT) After Radical Prostatectomy With Adverse Pathological Features From 2004 to 2011, With Fitted Polynomial Regression Trend Line. Arrow Indicates "Join Point" Where a Significant Increase in the Rate of PPRT Recommendations Occurred



# Low Use of Immediate and Delayed Postoperative Radiation for Prostate Cancer with Adverse Pathological Features

Matthew J. Maurice, Hui Zhu and Robert Abouassaly\*

From the Urology Institute, University Hospitals Case Medical Center (MJM, RA), Louis Stokes Cleveland Veterans Affairs Medical Center (MJM, HZ) and Glickman Urologic and Kidney Institute, Cleveland Clinic (HZ), Cleveland, Ohio

## Abbreviations and Acronyms

APF = adverse pathological features  
CCI = Charlson comorbidity index  
dRT = delayed radiotherapy  
iRT = immediate radiotherapy  
NCDB = National Cancer Data Base  
PC = prostate cancer  
PSA = prostate specific antigen  
PSM = positive surgical margin  
RCT = randomized controlled trial  
RP = radical prostatectomy  
RT = radiotherapy

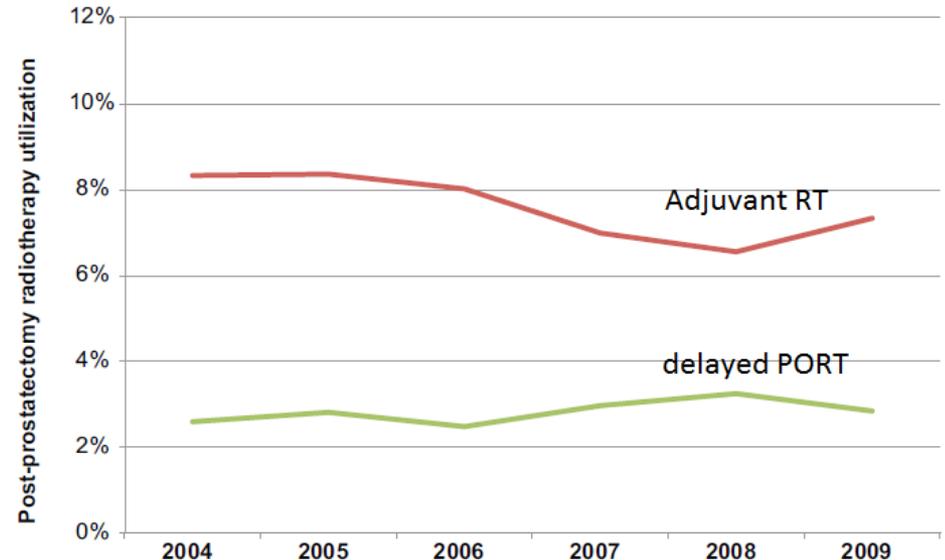
Accepted for publication March 27, 2015.  
Study received institutional review board approval.  
The American College of Surgeons and

**Purpose:** Level 1 evidence supports immediate radiation in post-prostatectomy patients with adverse pathological features while analogous evidence for delayed radiation is lacking. We evaluated immediate and delayed radiation practice patterns and identified factors affecting their use.

**Materials and Methods:** Using the National Cancer Data Base we identified 57,448 men diagnosed with pT3 disease and/or positive margins from 2004 to 2009. Postoperative radiation use through 2011 was analyzed by time trends and multivariate analysis.

**Results:** A total of 4,316 men (7.5%) received immediate radiation, 1,637 (2.8%) received delayed radiation and 51,495 (90%) were observed. Immediate and delayed radiation use remained relatively stable except for a small but significant decrease in immediate radiation in 2008. This decrease was associated with a relative increase in delayed radiotherapy. Compared to 2004 men diagnosed in 2007 to 2009 had 1.3-fold to 1.5-fold higher odds of delayed radiation than of immediate radiation ( $p < 0.01$ ). The strongest predictor were margin status, T stage, N stage, Gleason score or positive margins, seminal vesicle invasion, nodal disease greater and younger men had 2.3-fold to sixfold greater odds of immediate radiation than observation ( $p < 0.01$ ). Metastases were all immediate rather than delayed radiation ( $p < 0.01$ ).

- NCDB data, 2004-2009
  - 57,448 patients w PCa
  - Adverse path features
  - <10% ART



Post-RP immediate (red curve) and delayed (green curve) radiation therapy use from 2004 to 2009 with 2 years of followup.

**Platinum Priority – Prostate Cancer**

Editorial by Alberto Bossi, Thomas Wiegel and Mack Roach on pp. 775–776 of this issue

**Declining Use of Radiotherapy for Adverse Features After Radical Prostatectomy: Results From the National Cancer Data Base**

Helmneh M. Sineshaw<sup>a,†,\*</sup>, Phillip J. Gray<sup>b,†</sup>, Jason A. Efstathiou<sup>b,‡</sup>, Ahmedin Jamal<sup>a,‡</sup>

<sup>a</sup>American Cancer Society, 250 Williams Street NW, Atlanta, GA, USA; <sup>b</sup>Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

**Article info**

**Article history:**

Accepted April 1, 2015

**Keywords:**

Androgen deprivation therapy  
Postoperative radiotherapy  
Prostate cancer  
Radical prostatectomy

**Abstract**

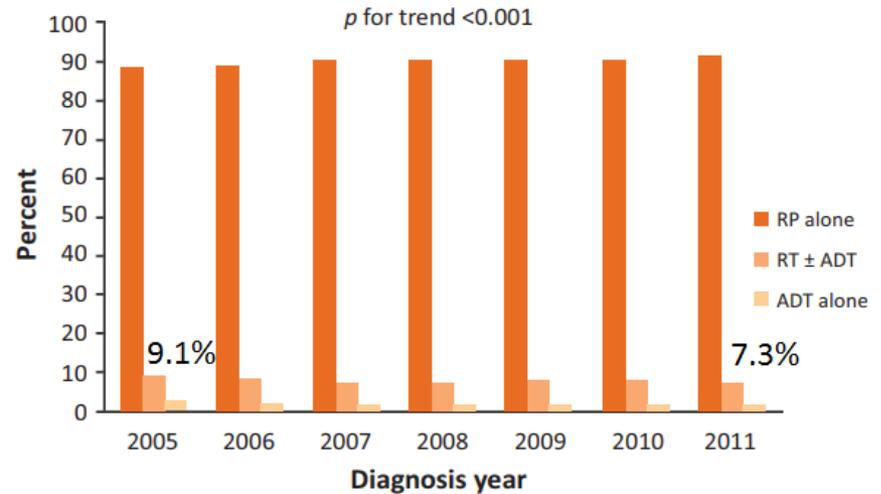
**Background:** Patterns of postoperative radiotherapy (RT) use in prostate cancer (PCa) after the publication of major randomized trials have not been well characterized.

**Objective:** To describe patterns of postoperative RT use after radical prostatectomy (RP) in patients with adverse pathologic features in the United States.

**Design, setting, and participants:** Retrospective analysis of 97 270 patients with PCa diagnosed between 2005 and 2011 whose present: the National Cancer Data Base.

**Outcome measurements and statistical analysis:** postoperative RT and factors associated with r  
**Results and limitations:** Between 2005 and 2011, r

- NCDB data, 2005-2011
  - 97,270 patients w PCa
  - Adverse path features



**Fig. 1 – Unadjusted patterns of practice within 6 mo of radical prostatectomy for patients with prostate cancer with adverse pathologic features, by year.**  
ADT = androgen deprivation therapy; RP = radical prostatectomy; RT = radiotherapy.

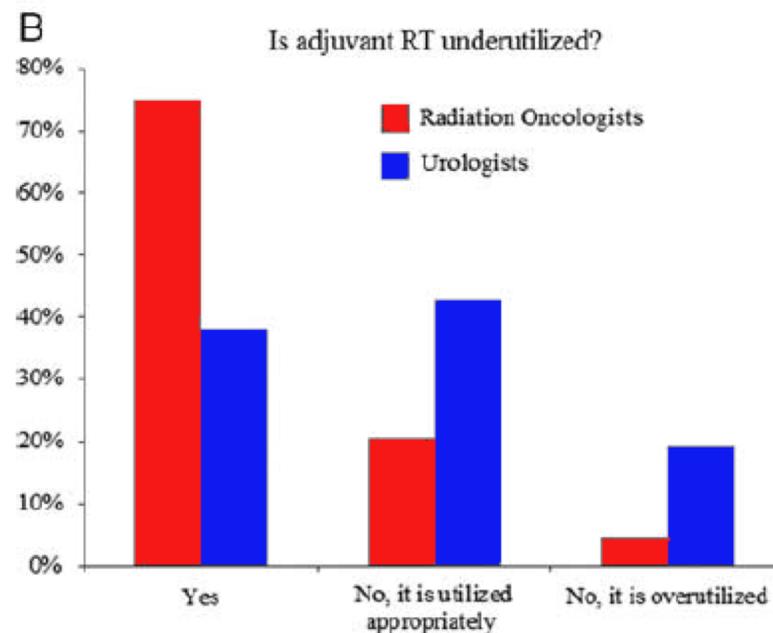
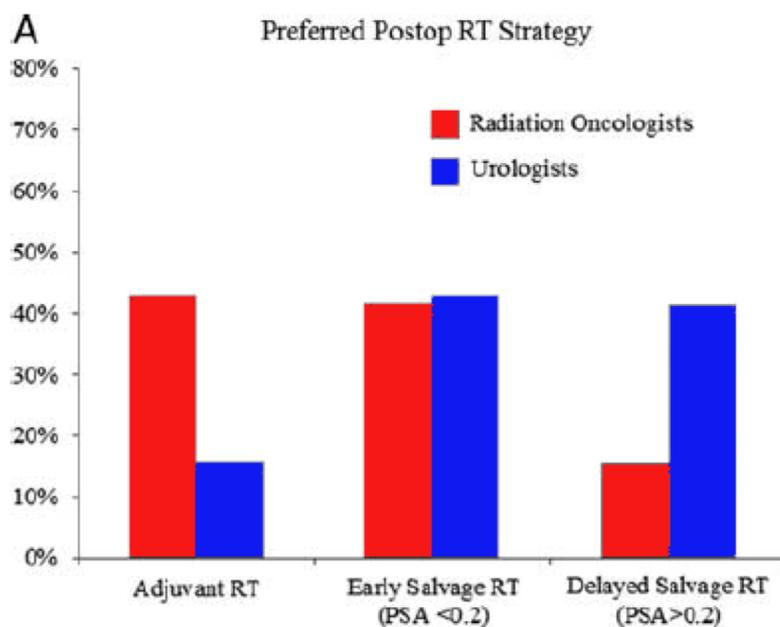
## Discord Among Radiation Oncologists and Urologists in the Postoperative Management of High-Risk Prostate Cancer

Amar U. Kishan, MD,\* Gillian Duchesne, MD,† Pin-Chieh Wang, PhD,\*  
 Jean-Claude M. Rwigyema, MD,\* Arun U. Kishan, MS,\* Christopher Saigal, MD,‡  
 Matthew Rettig, MD,§|| Michael L. Steinberg, MD,\*  
 and Christopher R. King, MD, PhD\*

- 846RO's, 407 Urologists Surveyed
- High Risk Prostate Cancer

American Journal of Clinical Oncology • Volume 00, Number 00, ■ ■ 2017

Discord in Postoperative Radiation

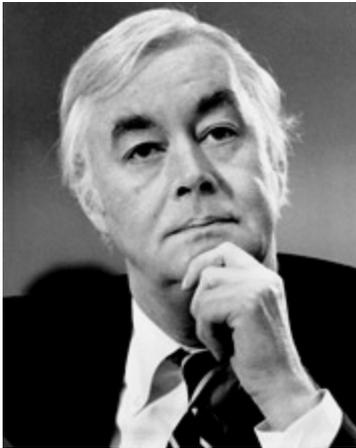


# Agenda

- Clinical Significance of biochemical failure
  - *Pound et al, JAMA*
  - Prediction Tools/Nomograms
- Salvage Radiation
  - Retrospective series
- Adjuvant Radiation
  - Retrospective series
  - EORTC 2291, *Lancet*
  - ARO/AUO 96-02, *JCO*
  - SWOG 8794, *JAMA*
- Consensus Guidelines: “Do you Concur?”
- **Meta Level Considerations**

# Meta level considerations: Bird's Eye View

- Is There Discordance Between Data/Guidelines and Clinical Practice?



- Data Exists to Support Both Arguments. So are you a *Believer*?

“Everyone is entitled to his own opinion, but not his own facts.”

-Daniel Patrick Moynihan (former US Senator)



# Meta level considerations

- The 3RCT's are between Adjuvant RT and observation
  - Not Adjuvant vs. early Salvage
- Differences in RT timing:
  - Only 56% of pts with recurrence in EORTC given Salvage RT
  - Clinical or Locoregional Progression already Present at time of Salvage RT
    - 40%, EORTC, 41% SWOG
- Await Two PH3 RCTs: Adjuvant RT vs. early Salvage
  - MRC RADICALS trial
    - Radiotherapy and Combined Androgen Deprivation after Local Surgery
  - TROG RAVES trial
    - Radiotherapy Adjuvant vs. Early Salvage following Radical Prostatectomy

# Retrospective Adjuvant vs. Early Salvage?



European Association of Urology

EUROPEAN UROLOGY 71 (2017) 886–893

## Platinum Priority – Prostate Cancer

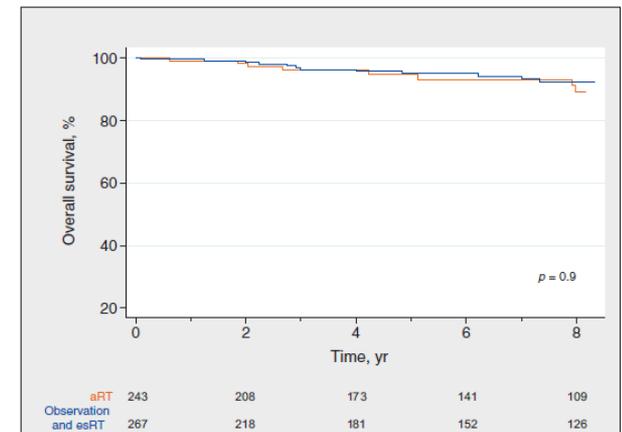
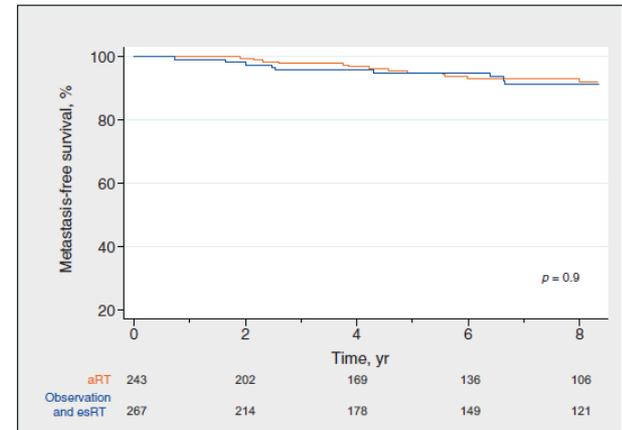
Editorial by Christopher J.D. Wallis, Raj Satkunasivam and Robert K. Nam on pp. 894–895 of this issue

### Long-term Impact of Adjuvant Versus Early Salvage Radiation Therapy in pT3N0 Prostate Cancer Patients Treated with Radical Prostatectomy: Results from a Multi-institutional Series

Nicola Fossati<sup>a,\*</sup>, R. Jeffrey Karnes<sup>b</sup>, Stephen A. Boorjian<sup>b</sup>, Marco Moschini<sup>b</sup>, Alessandro Morlacco<sup>b</sup>, Alberto Bossi<sup>c</sup>, Thomas Seisen<sup>c</sup>, Cesare Cozzarini<sup>d</sup>, Claudio Fiorino<sup>d</sup>, Barbara Noris Chiorda<sup>d</sup>, Giorgio Gandaglia<sup>a</sup>, Paolo Dell'Oglio<sup>a</sup>, Steven Joniau<sup>e</sup>, Lorenzo Tosco<sup>e</sup>, Shahrokh Shariat<sup>f</sup>, Gregor Goldner<sup>g</sup>, Wolfgang Hinkelbein<sup>h</sup>, Detlef Bartkowiak<sup>i</sup>, Karin Haustermans<sup>j</sup>, Bertrand Tombal<sup>k</sup>, Francesco Montorsi<sup>a</sup>, Hein Van Poppel<sup>e</sup>, Thomas Wiegel<sup>i</sup>, Alberto Briganti<sup>a</sup>

<sup>a</sup>Division of Oncology/Unit of Urology, URI; IRCCS Ospedale San Raffaele, Milan, Italy; <sup>b</sup>Department of Urology, Mayo Clinic, Rochester, MN, USA; <sup>c</sup>Department of Radiation Oncology, Gustave Roussy Institute, Villejuif, France; <sup>d</sup>Department of Radiotherapy, IRCCS Ospedale San Raffaele, Milan, Italy; <sup>e</sup>University Hospitals Leuven, Department of Urology, Leuven, Belgium; <sup>f</sup>Department of Urology, Comprehensive Cancer Centre, Medical University of Vienna, Vienna General Hospital, Vienna, Austria; <sup>g</sup>Department of Radiation Oncology, Medical University of Vienna, Vienna, Austria; <sup>h</sup>Department of Radiation Oncology, Charité Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany; <sup>i</sup>Department of Radiation Oncology, University Hospital Ulm, Ulm, Germany; <sup>j</sup>University Hospitals Leuven, Department of Radiotherapy, Leuven, Belgium; <sup>k</sup>Department of Urology, Université Catholique de Louvain, Brussels, Belgium

- Multi-institutional cohort, 7 tertiary referral centers
- 510 pT3 pts
- Adjuvant RT vs. early Salvage RT
  - 8yr Met Free survival (92% vs. 91%, NS)
  - 8yr OS (89% vs. 92%, NS)



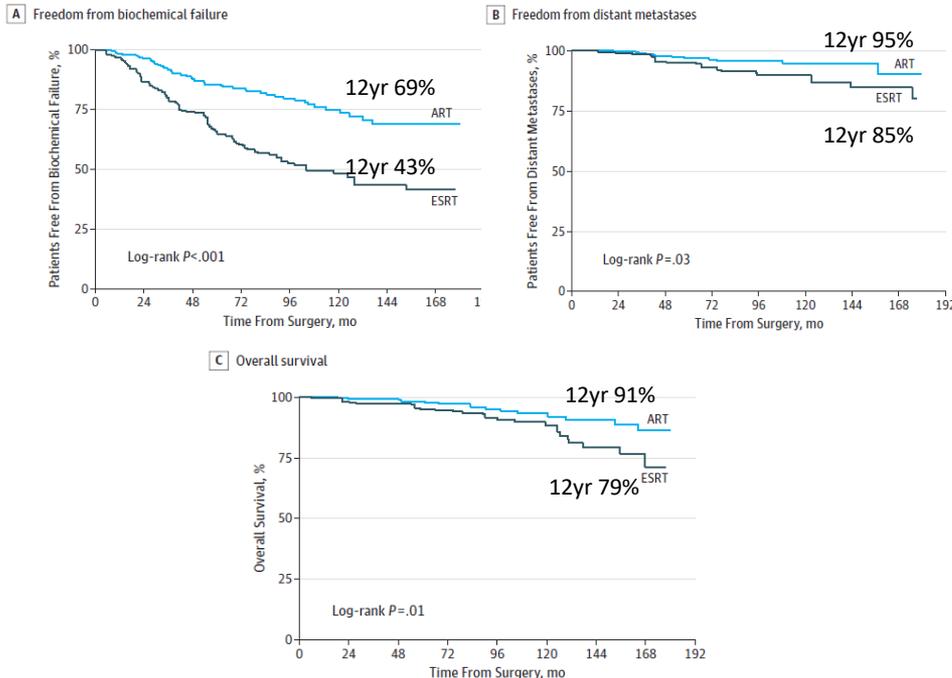
# Retrospective Adjuvant vs. Early Salvage?

JAMA Oncology | Original Investigation

## Comparison Between Adjuvant and Early-Salvage Postprostatectomy Radiotherapy for Prostate Cancer With Adverse Pathological Features

William L. Hwang, MD, PhD; Rahul D. Tendulkar, MD; Andrzej Niemierko, PhD; Shree Agrawal, BS; Kevin L. Stephens, MD; Daniel E. Spratt, MD; Jason W. Hearn, MD; Bridget F. Koontz, MD; W. Robert Lee, MD, ME, MS; Jeff M. Michalski, MD; Thomas M. Pisansky, MD; Stanley L. Liaw, MD; Matthew C. Abramowitz, MD; Alan Pollack, MD, PhD; Drew Moghanaki, MD, MPH; Mitchell S. Anscher, MD; Robert B. Den, MD; Anthony L. Zietman, MD; Andrew J. Stephenson, MD; Jason A. Efstathiou, MD, DPhil

**IMPORTANCE** Prostate cancer with adverse pathological features (ie, pT3 and/or positive margins) after prostatectomy may be managed with adjuvant radiotherapy (ART) or surveillance followed by early-salvage radiotherapy (ESRT) for biochemical recurrence. The optimal timing of postoperative radiotherapy is unclear.



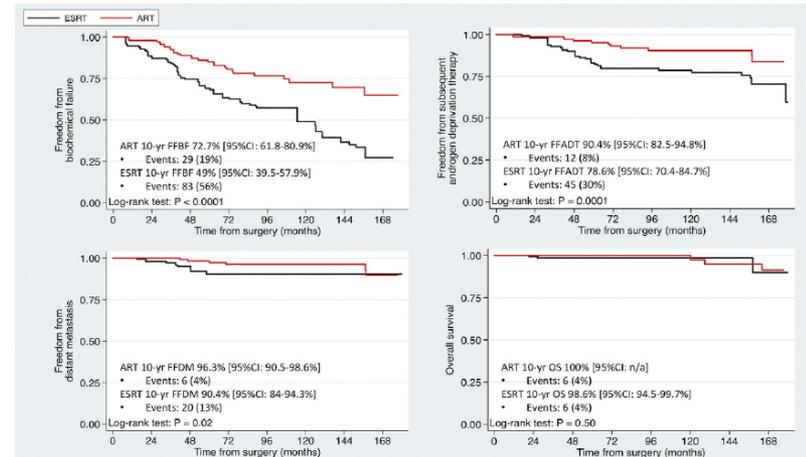
Original Report

Practical Radiation Oncology (2017) 7, e125-e133

## Long-term results of adjuvant versus early salvage postprostatectomy radiation: A large single-institutional experience



Daniela L. Buscariollo MD<sup>a</sup>, Michael Drumm BA<sup>b</sup>, Andrzej Niemierko PhD<sup>b</sup>, Rebecca H. Clayman BS<sup>c</sup>, Sigolene Galland-Girodet MD<sup>d</sup>, Danielle Rodin MD, MPH<sup>e</sup>, Adam S. Feldman MD, MPH<sup>f</sup>, Douglas M. Dahl MD<sup>f</sup>, Francis J. McGovern MD<sup>f</sup>, Aria F. Olumi MD<sup>f</sup>, Alec Eidelman BS<sup>g</sup>, William U. Shipley MD, FASTRO<sup>b</sup>, Anthony L. Zietman MD, FASTRO<sup>b</sup>, Jason A. Efstathiou MD, DPhil<sup>b,\*</sup>



# Meta level considerations

- Arguments for Delaying
  - Reduce Toxicity and Im

## Early Postoperative Radiotherapy is Associated with Worse Functional Outcomes in Patients with Prostate Cancer

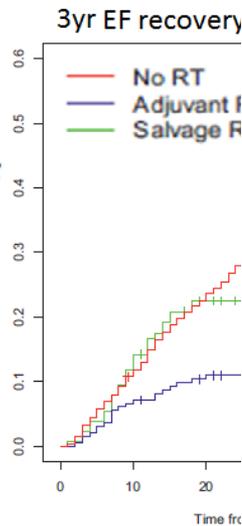
Emanuele Zaffuto, Giorgio Gandaglia, Nicola Fossati, Paolo Dell'Oglio, Marco Moschini, Vito Cucchiara, Nazareno Suardi, Vincenzo Mirone, Marco Bandini, Shahrokh F. Shariat, Pierre I. Karakiewicz, Francesco Montorsi and Alberto Briganti\*

From the Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan (EZ, GG, NF, PD'O, MM, VC, NS, MB, FM, AB), Urology Department, University of Naples Federico II, Naples (VM), Italy, Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada (EZ, PIK), and Department of Urology, Medical University of Vienna, Vienna, Austria (SFS)

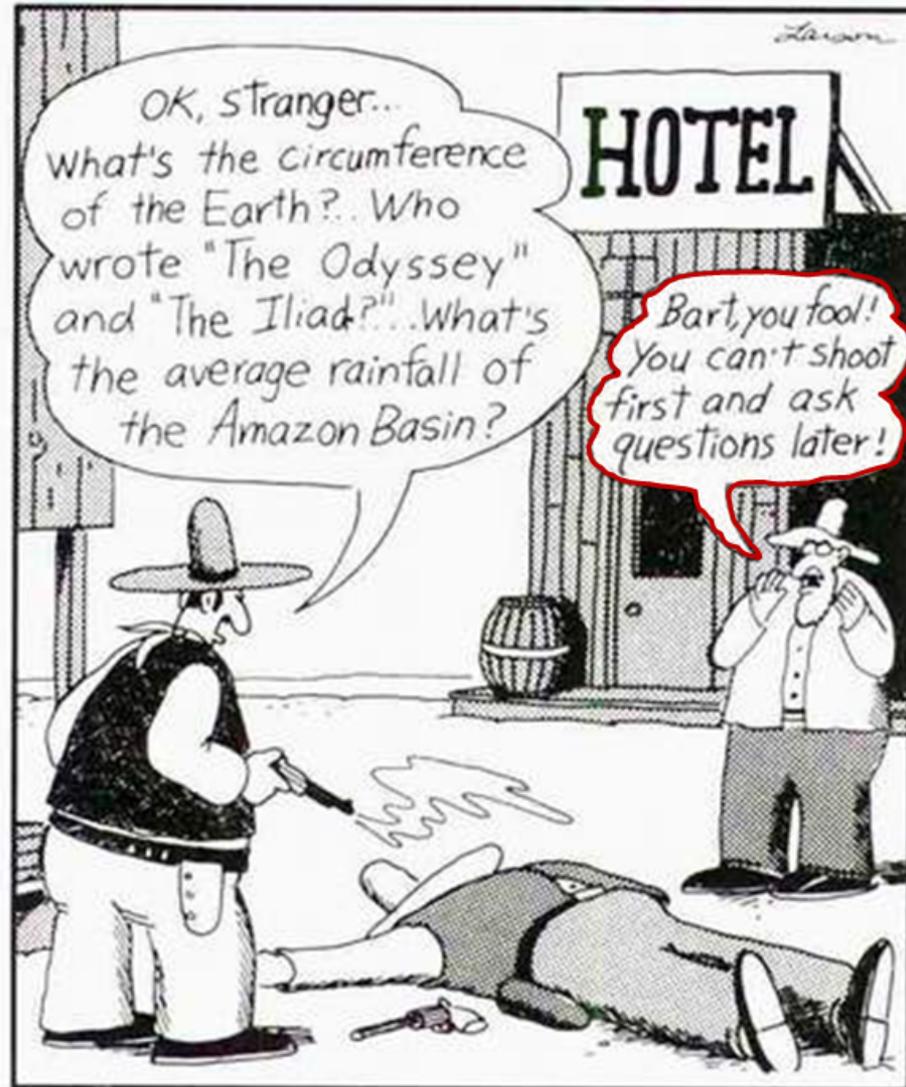
**Purpose:** The effect of time between radical prostatectomy and radiation therapy on postoperative functional outcomes is still unclear in patients with surgically managed prostate cancer. We hypothesized that a shorter time between radical prostatectomy and radiotherapy might be associated with worse functional recovery rates after radical prostatectomy.

**Materials and Methods:** We retrospectively evaluated 2,190 patients treated with radical prostatectomy and stratified according to radiotherapy schedule (adjuvant radiotherapy, salvage radiotherapy, no radiotherapy). We examined recovery rates for erectile function and urinary function according to adjuvant radiotherapy, salvage radiotherapy and no radiotherapy, and according to time from surgery to radiotherapy. Cox regression analyses were used to evaluate the impact of these predictors on functional outcomes.

**Results:** Median followup was 48 months. The 3-year erectile function recovery rates were 35.0%, 29.0% and 11.6% in patients who received no radiotherapy, salvage radiotherapy and adjuvant radiotherapy, respectively ( $p < 0.001$ ), and



- Retrospe
- RP +/- P





## Health-Related Quality of Life Results in Pathologic Stage C Prostate Cancer From a Southwest Oncology Group Trial Comparing Radical Prostatectomy Alone With Radical Prostatectomy Plus Radiation Therapy

*Carol M. Moinpour, Katherine A. Hayden, Joseph M. Unger, Ian M. Thompson Jr, Mary W. Redman, Edith D. Canby-Hagino, Betsy A. Higgins, Jerry W. Sullivan, Dianne Lemmon, Sheila Breslin, and E. David Crawford*

From the Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA.

Submitted December 27, 2006; accepted September 27, 2007.

Supported in part by the following Public Health Service Cooperative Agreement Grants awarded by the National Cancer Institute, Department of Health and Human Services: CA38926, CA32102, CA14028, CA58416, CA58658, CA42777, CA27057, CA46136, CA35431, CA58882, CA12644, CA58861, CA35090, CA37981, CA76429, CA04919, CA76132, CA35119.

### A B S T R A C T

#### **Purpose**

To compare short- and long-term effects of adjuvant treatment versus observation after surgery on health-related quality of life (HRQL) of prostate cancer patients.

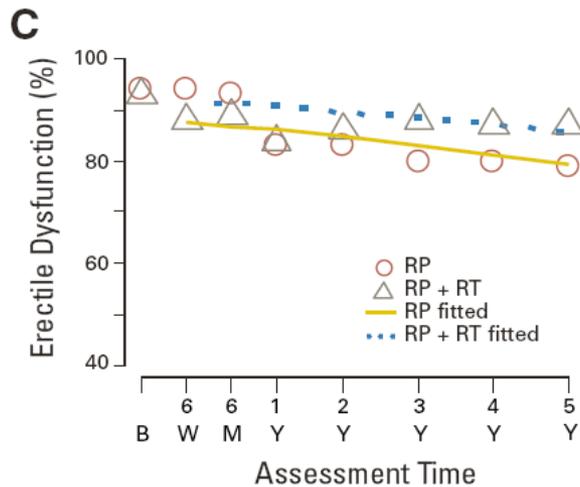
#### **Patients and Methods**

The Southwest Oncology Group (SWOG) intergroup trial compared radical prostatectomy (RP) plus observation versus RP plus adjuvant radiation therapy (RT). Two-hundred seventeen of 425 therapeutic trial patients were eligible and registered to the HRQL study. Patients completed the SWOG Quality of Life Questionnaire (emotional, physical, social, and role function; general symptom status; treatment/disease-specific symptoms; and global HRQL [GHRQL]) at baseline, 6 weeks, 6 months, and annually for 5 years. Prespecified outcomes were three genitourinary symptoms (bowel function tenderness, frequent urination, and erectile dysfunction [ED]) and measures of physical and emotional function. Adjustments were made for the baseline score.

# SWOG 8794

# Moinpour et al, SWOG 8794

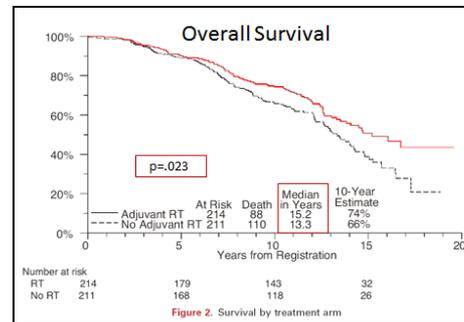
- 217 pts registered on HRQL study
  - Questionnaire for GI/GU sx's, and physical/emotional function
- 25% of pts on RPE-only arm received Salvage RT
- ADT
  - 22% pts in RPE-only arm
  - 13% pts in Adjuvant RT arm



- RP+RT worse bowel function through 2 years, and worse GU function.
  - No difference on ED
- Global QOL initially worse for RP+RT, but improved over time and eventually exceeded RP alone (SS).
- Conclusion: Adding RT to surgery resulted in more frequent urination, and early bowel dysfunction, but long-term QOL better

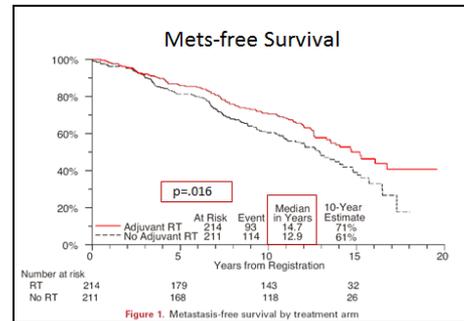
# Meta level considerations

- Arguments for Delaying RT after RP
  - Potential Overtreatment of patients who never would need RT → Prostate cancer has a long natural hx
  - What is the NNT?



SWOG 8794, 15 year update

NNT, T3dz adjuvant RT to prevent 1 death, at f/u of 12.6 yrs → 9.1



NNT, T3dz adjuvant RT to prevent 1 case of met dz, at f/u of 12.6 yrs → 12.2

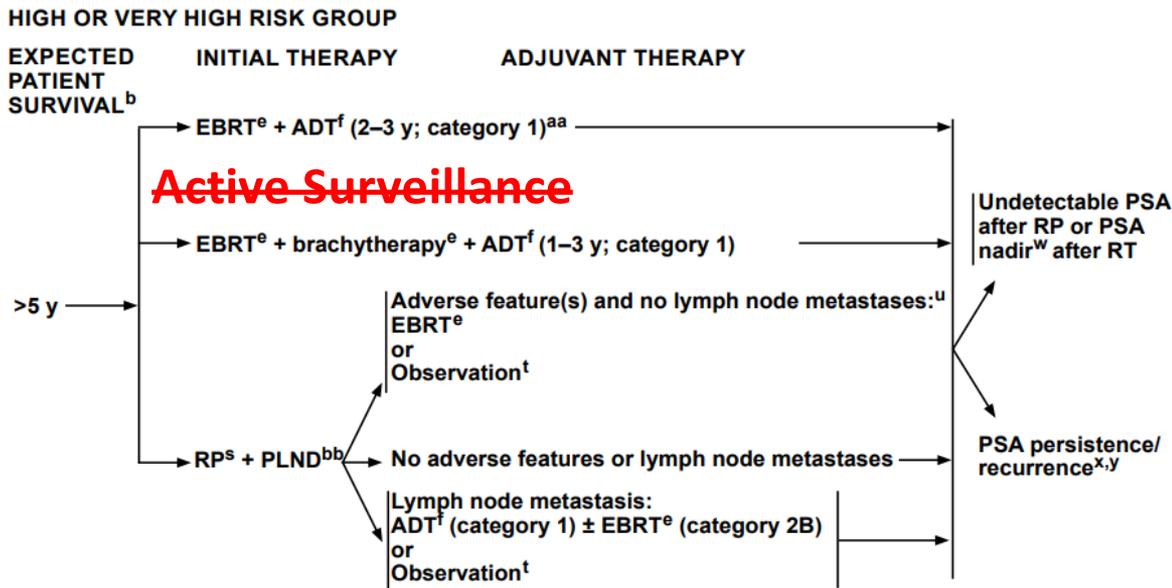


# NNT

	<u>NNT</u>	<u>Source</u>
Triple abx therapy to eradicate <i>H.pylori</i> <i>infxn</i>	1.1	Medscape
Acute otitis media, antibiotics for resolution of sx's in 1-2wks	7	J Pediatr. 1994 Mar;124(3):355-67.
<del>Adjunctive RT with pNOER on Br death pr BCS pr State prevention 2 flps BPE Fav ESC Subseq MMSctomy</del>	<del>29-22</del>	<del>J Natl Cancer Inst 2006 May 17;98(10):681-90.</del>
In pts with CAD, simvastatin for 5yrs to prevent 1 <b>death</b>	30	Eur Heart J 2001 Aug;22(15):1307-1
Flu vaccine to prevent 1 case of Influenza for people aged 65 and older	43	Vaccine. 2004 Jun 2;22(17-18):2192-8.
Vaccination to prevent 1 case of invasive pneumococcus	5206	Mooney et al. BMC Infect. Dis. 8: 53

# Meta level considerations

- For High Risk Patient post RP, why wait?



- Philosophical (In)consistency?
  - If would never rec AS for HR pt for 1-2 yrs, why, philosophically, ok after RP?

# How To Define **early** Salvage RT?

- Early Salvage RT:
  - ie: time from RP (allow functional improvement)
  - vs. pre-RT PSA (allow improvement in Ca control)
- Two ph3 RCTs: Adjuvant RT vs. early Salvage
  - MRC RADICALS trial
    - Radiotherapy and Combined Androgen Deprivation after Local Surgery
    - **Early Salvage= Tx at time of PSA failure after RP**
  - TROG RAVES trial
    - Radiotherapy Adjuvant vs. Early Salvage following Radical Prostatectomy
    - **Early Salvage= <4mos after PSA >0.2ng/ml**

# Before RADICALS and RAVES: A Middle Ground?



# Middle Ground(s)

- Delaying RT to allow for further recovery
  - One potential avenue: ADT prior to early Salvage
    - GETUG-AFU16
    - RTOG 96-01

# Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial

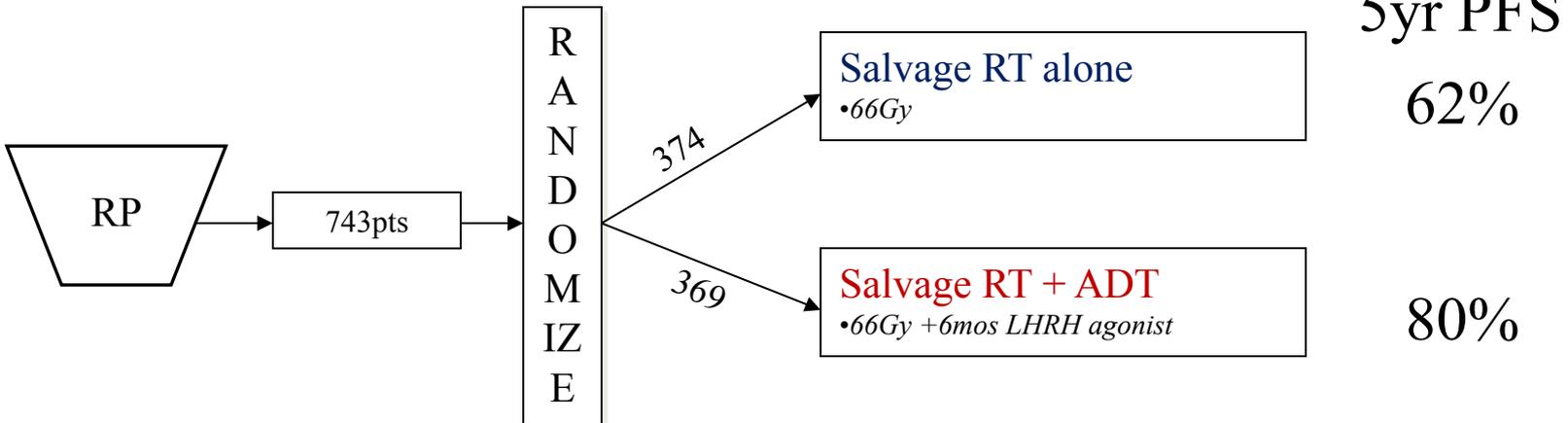


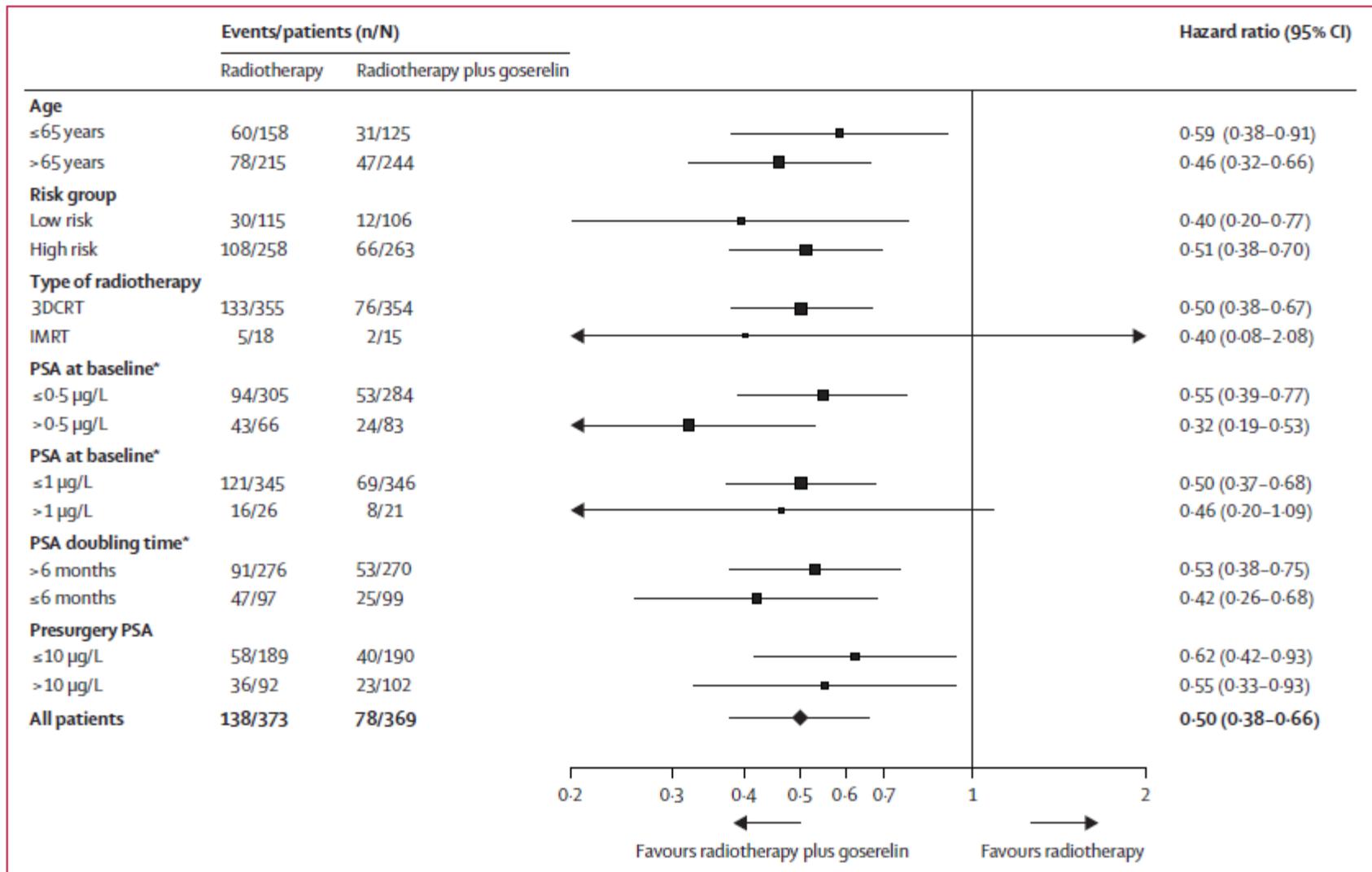
Christian Carrie, Ali Hasbini, Guy de Laroche, Pierre Richaud, Stéphane Guerif, Igor Latorzeff, Stéphane Supiot, Mathieu Bosset, Jean-Léon Lagrange, Véronique Beckendorf, François Lesaunier, Bernard Dubray, Jean-Philippe Wagner, Tan Dat N'Guyen, Jean-Philippe Suchaud, Gilles Créhange, Nicolas Barbier, Muriel Habibian, Céline Ferlay, Philippe Fournerey, Alain Ruffion, Sophie Dussart

**Summary**  
**Background** How best to treat rising prostate-specific antigen (PSA) concentration after radical prostatectomy is an urgent clinical question. Salvage radiotherapy delays the need for more aggressive treatment such as long-term androgen suppression, but fewer than half of patients benefit from it. We aimed to establish the effect of adding short-term androgen suppression at the time of salvage radiotherapy on biochemical outcome and overall survival in men with rising PSA following radical prostatectomy.

*Lancet Oncol 2016; 17: 747-56*  
Published Online  
May 6, 2016  
[http://dx.doi.org/10.1016/S1470-2045\(16\)00111-X](http://dx.doi.org/10.1016/S1470-2045(16)00111-X)

- Phase 3 RCT conducted in 43 French Centers
  - Lancet, June 2016





- Subgroup Analysis showed universal benefit

**NRG Oncology/RTOG 96-01**

Plenary Session of ASTRO, 2015  
San Antonio, TX



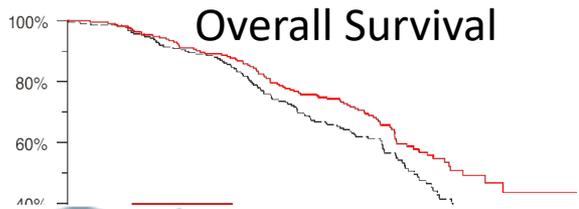
**A Phase III trial in patients following Radical Prostatectomy (RP) with pT2-3, pN0 prostate cancer and elevated PSA levels: Anti-Androgen Therapy (AAT) with Bicalutamide during and after *salvage* Radiation Therapy (RT) compared to Placebo + *salvage* RT.**

- Phase 3 double-blind RCT
- 761pts w Salvage RT +/-24mos bicalutamide

	Arm 1	Arm 2	P
	Anti-Androgen	Control	
10yr OS	82%	78%	.04
10yr mets	11%	19%	.005
Cardiac gr3+events	4%	2%	
gynecomastia	70%	11%	

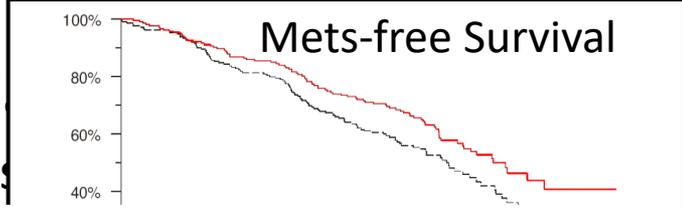
# Middle Ground(s)

- Improved Risk Adapted Approaches?
  - Integrating Molecular Imaging
    - $^{18}\text{F}$ -choline PET
    - $^{11}\text{C}$ -acetate PET
    - $^{68}\text{Ga}$ -Prostate Specific Membrane Antigen PET
  - Utilizing Genomic Biomarkers
    - ie: Decipher, Oncotype, Prolaris



# Conclusion

is a fantastic 1st



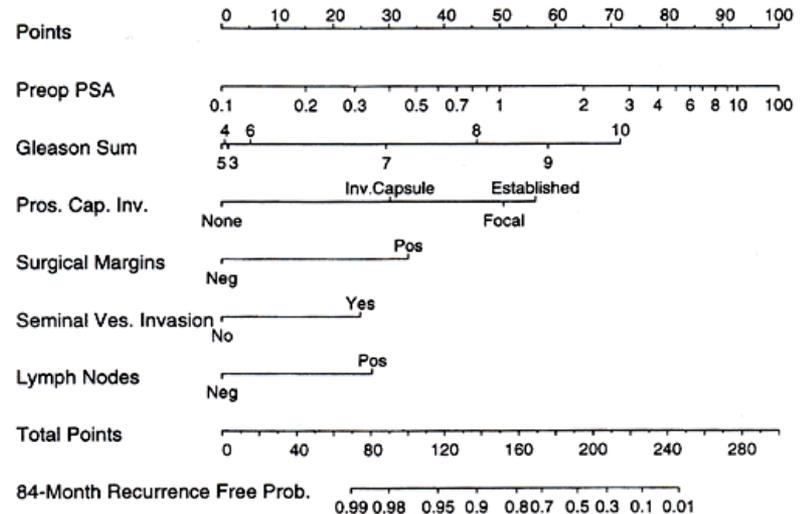
American Urological Association



- Level I evidence demonstrates that adjuvant

	Washington University <sup>1</sup>	Baylor <sup>2</sup>	Johns Hopkins <sup>3</sup>	Cleveland Clinic <sup>4</sup>
Follow-up, years	7	10	10	8
Biochemical RFS, all patients at last follow-up	81	73	68	76
<b>Pathologic Stage</b>				
OC (ECE-)	81	92	85	92
ECE+, MS-	76			77
ECE+, MS+	57			50
SV+	26	33	43	34
LN +	19	16*	0	0

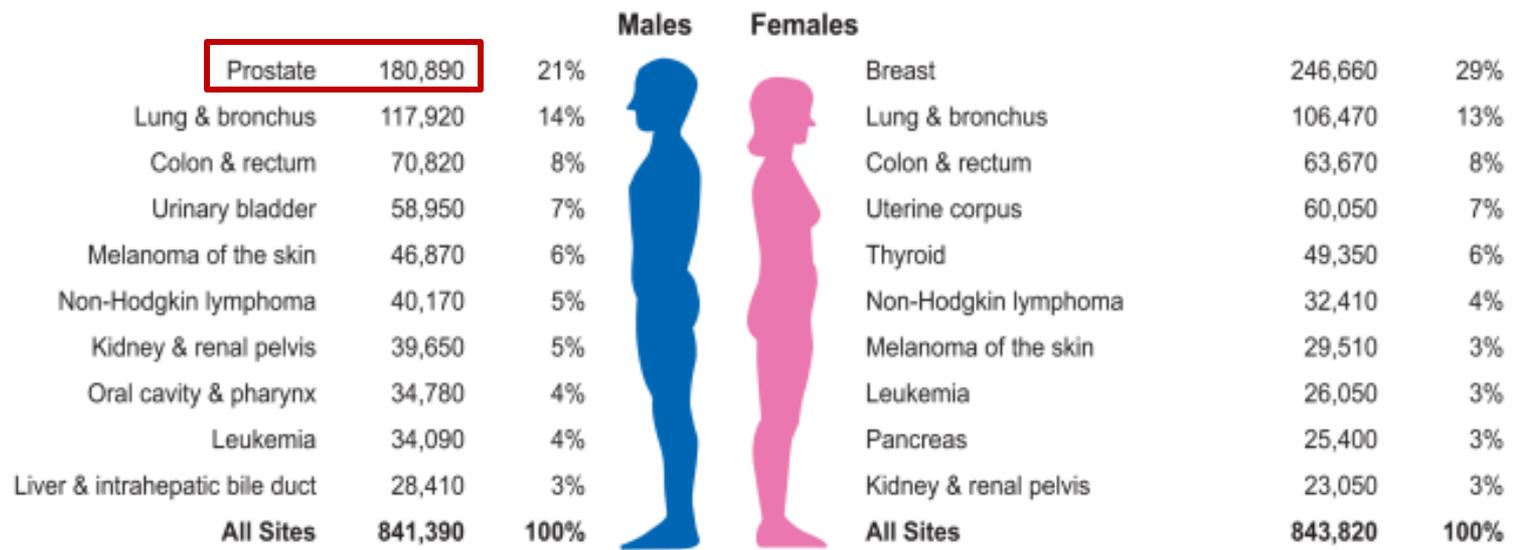
Postoperative Nomogram for Prostate Cancer Recurrence



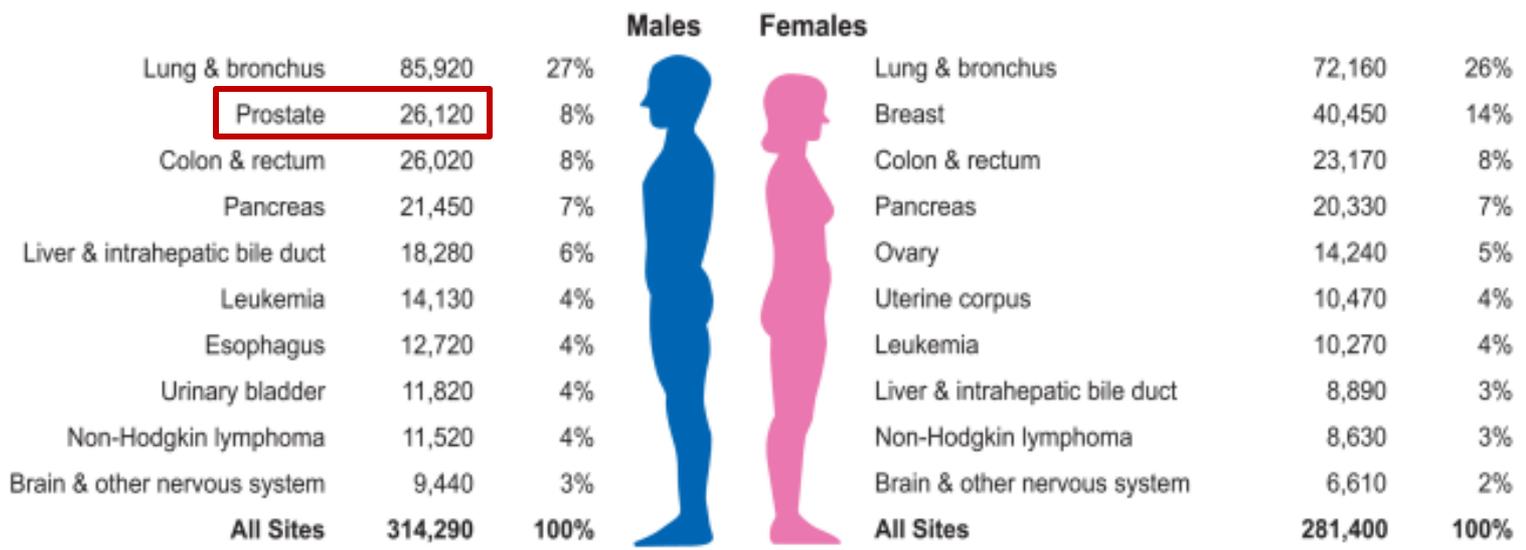
Thank You



Estimated New Cases



Estimated Deaths

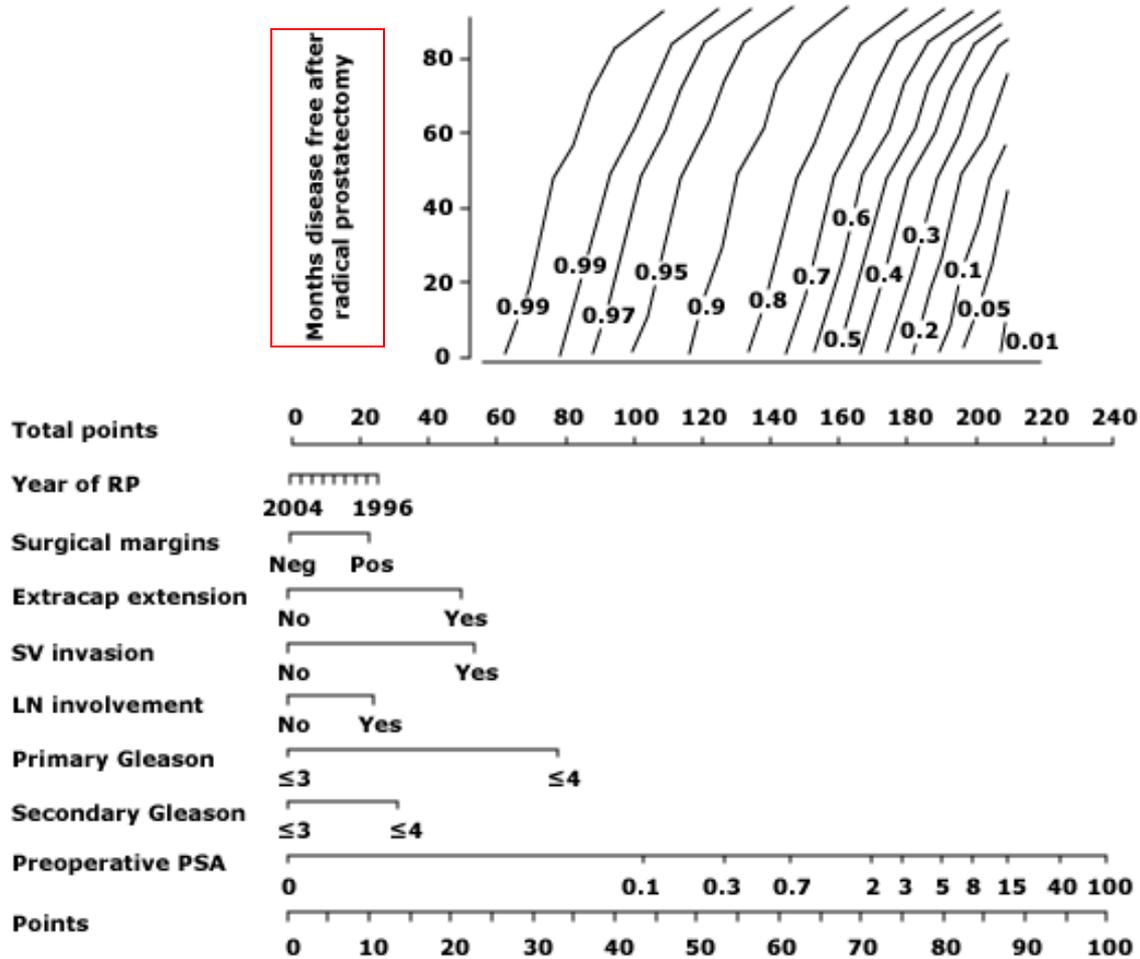


# Risk of Progression with(-) LN, (-) SV

<i><b>Findings at Prostatectomy</b></i>	<i><b>Progression-free risk at 4 years</b></i>	<i><b>Progression-free risk at 10 years</b></i>
Organ-confined	97.8%	84.7%
● Focal capsular penetration	91.2%	67.7%
Established capsular penetration	77.8%	58.4%
● Negative margins	94.6%	79.4%
Positive margins	74.0%	54.9%
● Gleason score 5-6	96.9%	81.9%
Gleason score 7	76.9%	51.5%
Gleason score 8-9	59.1%	34.9%

In MVA, Gleason score (P < 0.0001), surgical margins (P = 0.004), and capsular penetration (P = 0.007) were all INDEPENDENT predictors of progression

# Post-RPE Nomogram Predicting 10yr Progression-Free Probability



- So What?
  - Biochemical failure = clinical significant?
- Patient Selection
  - Key: selecting post prostatectomy patients who will/have failed
    - Locally → radiotherapy
    - Distantly → systemic therapy
  - Variety of factors used to help make determination