

# Prostate Intervention Versus Observation Trial (PIVOT)



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## Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D., William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D., Patricia Gilhooly, M.D., B. Mayer Grob, M.D., Imad Nsouli, M.D., Padmini Iyer, M.D., Ruben Cartagena, M.D., Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Roohollah Sharifi, M.D., William Blank, M.D., Parikshit Pandya, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., and Thomas Wheeler, M.D.,  
for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group

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ORIGINAL ARTICLE

# Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

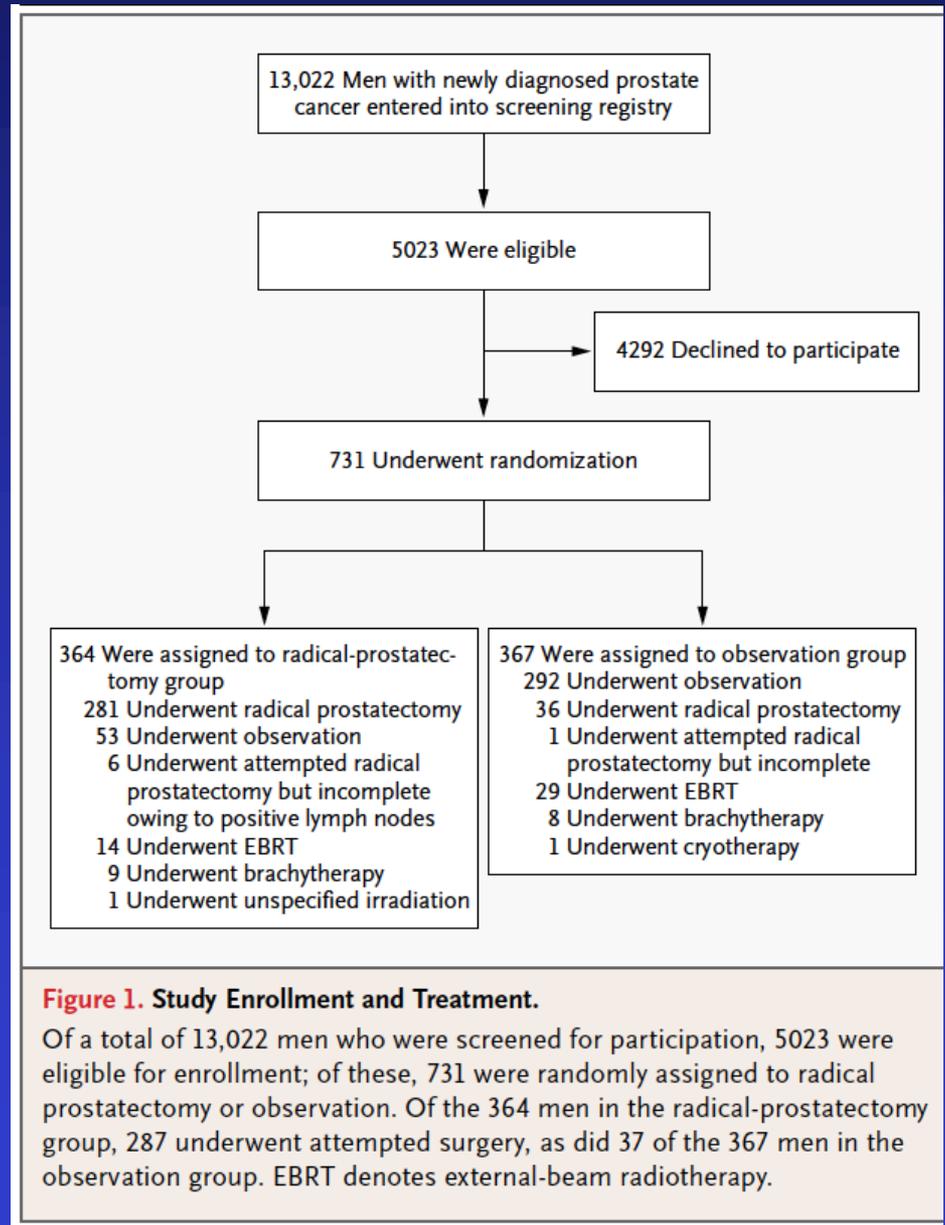
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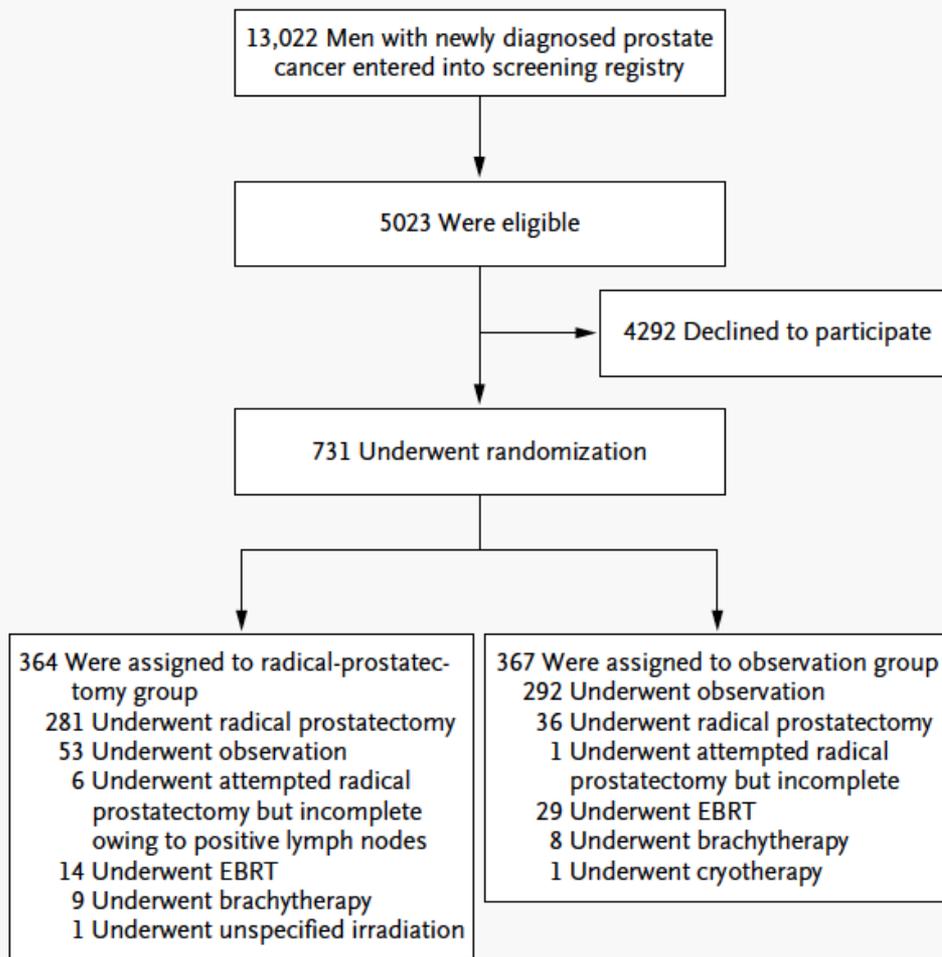
# PIVOT Objective

Among men with screen-detected, clinically localized prostate cancer during the “early” PSA era, **does the intent to treat** with radical prostatectomy reduce all-cause &/or prostate cancer mortality compared to observation?

## Compliance

281/364 (77%) had RP  
53/364 (15%) had observation





**Figure 1. Study Enrollment and Treatment.**

Of a total of 13,022 men who were screened for participation, 5,023 were eligible for enrollment; of these, 731 were randomly assigned to radical prostatectomy or observation. Of the 364 men in the radical-prostatectomy group, 287 underwent attempted surgery, as did 37 of the 367 men in the observation group. EBRT denotes external-beam radiotherapy.

## Contamination

10% RP: median time  
61 days (30-624)

8% had other Rx:  
median time  
652 days (61-1501)

# Inclusion Criteria

- **Age  $\leq$  75 years**
- **T1-2, NX, M0 (all histologic grades)**
- **PSA  $<$  50 ng/mL**
- **Diagnosed  $\leq$  12 months**
- **Radical Prostatectomy candidate**
  - **Predicted life expectancy  $>$  10 years**

# Endpoints

- **Primary endpoint**
  - All-cause mortality
- **Secondary endpoint**
  - CaP mortality

# Baseline Characteristics

<u>Characteristic (%)</u>	<u>Observation</u>	<u>RP</u>
Mean Age; years	66.8	67.0
Race; Black	33.0	30.5
Married	54.2	55.8
ADLs: Fully Active	84.5	85.7
Charlson comorbid = 0	59.9	61.5

# Tumor Characteristics

<u>Characteristic</u>	<u>Observation</u>	<u>RP</u>
• PSA Mean (median)	10.2 (7.8)	10.1 (7.8)
– < 4.0 (%)	10.9	11.5
– $\geq$ 20 (%)	10.1	10.4
• Stage: T1c (%)	49.9	50.8
• Gleason Score (%)		
$\leq$ 6	70.1	69.8
7	17.4	19.0
8-10	6.0	8.0
• D'Amico Tumor Risk		
Low	40.3	40.7
Intermediate	32.7	35.4
High	21.8	21.2

# Cause-of-death ascertainment

- 3-person blinded end-point committee
  - Andriole, Barry, Culkin
- Deaths categorized as:
  - Prostate cancer
    - Definitely or probably due to CaP or Tx
  - Not Prostate cancer
    - Definitely or probably NOT due to CaP or Tx

# Ascertaining cause of death among men in the Prostate Cancer Intervention Versus Observation Trial

Michael J Barry<sup>a</sup>, Gerald L Andriole<sup>b</sup>, Daniel J Culkin<sup>c</sup>, Steven H Fox<sup>d</sup>, Karen M Jones<sup>e</sup>, Maureen H Carlyle<sup>f</sup> and Timothy J Wilt<sup>f</sup>

	Initial agreement		Total
	Yes	No	
Collapsed Question 1: (primary) cause of death			
Definitely OR probably <i>not</i> due to prostate cancer	276	25	301 (85.0%)
Definitely OR probably due to prostate cancer	26	23	49 (13.8%)
Definitely OR probably due to prostate cancer treatment	3	0	3 (0.9%)
Unknown	1	0	1 (0.3%)
Total	306	48	354 (100%)

# Ascertaining cause of death among men in the Prostate Cancer Intervention Versus Observation Trial

Michael J Barry<sup>a</sup>, Gerald L Andriole<sup>b</sup>, Daniel J Culkin<sup>c</sup>, Steven H Fox<sup>d</sup>, Karen M Jones<sup>e</sup>, Maureen H Carlyle<sup>f</sup> and Timothy J Wilt<sup>f</sup>

Table 4. PIVOT Endpoints Committee final adjudicated cause of death results by the primary question, cross-tabulated with cause of death as determined by whether prostate cancer is listed as the cause in any position on Part 1 of the death certificate (n = 46 prostate cancer deaths)

Question 1: cause of death	Death certificate cause of death		
	Prostate cancer	Not prostate cancer	Total
Definitely not due to prostate cancer	9	159	168
Probably not due to prostate cancer	2	21	23
Probably due to prostate cancer	13	0	13
Definitely due to prostate cancer	21	0	21
Probably due to prostate cancer treatment	0	2	2
Definitely due to prostate cancer treatment	1	0	1
Unknown	0	0	0
Total	46	182	228

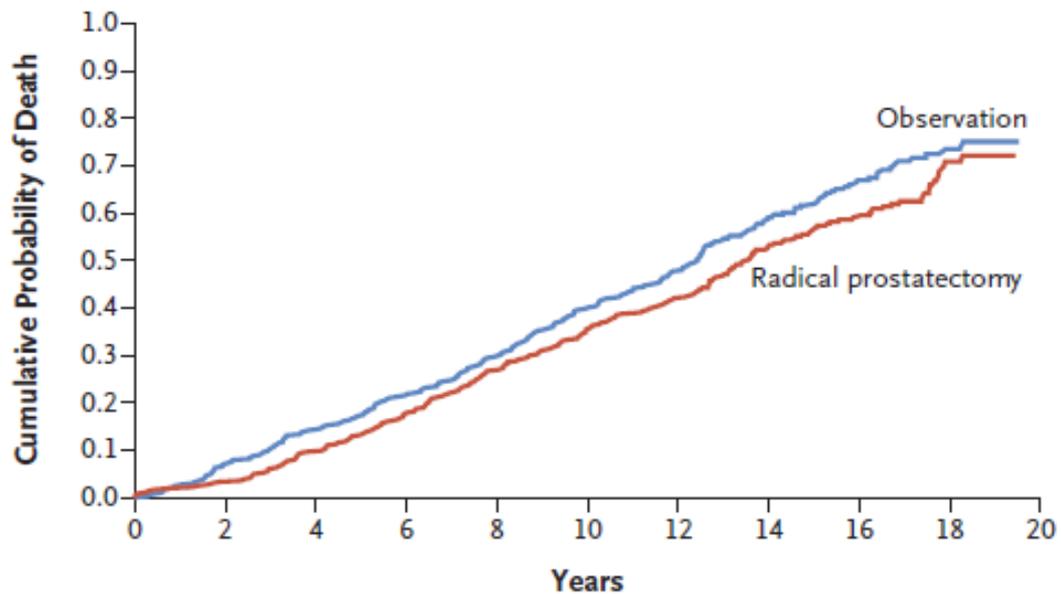
PIVOT: Prostate Cancer Intervention Versus Observation Trial.

*Clinical Trials* 2013; 10: 907–914

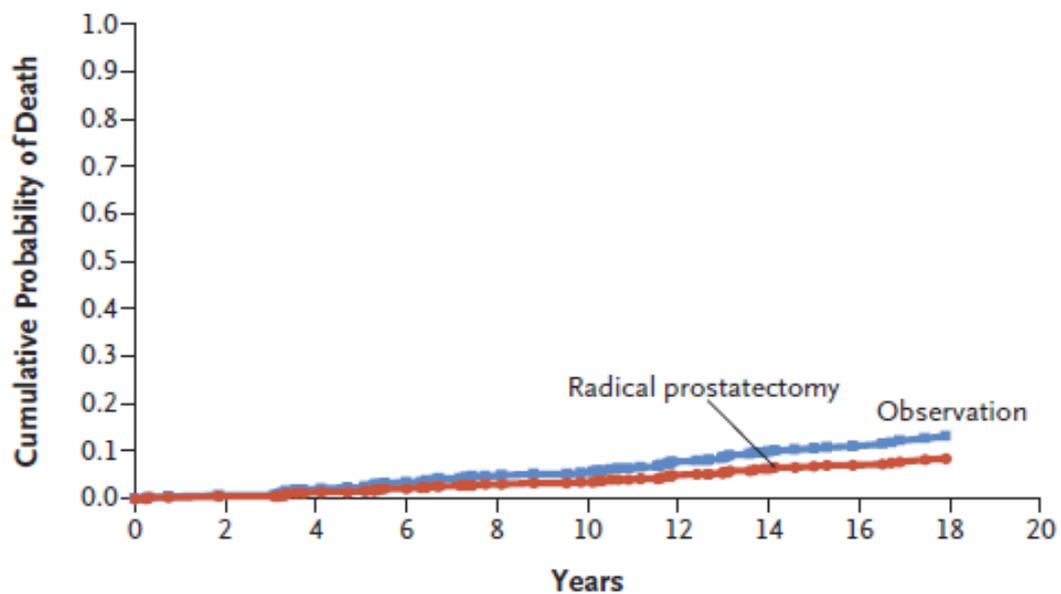
# Follow-up & Cumulative Events

- **Median follow-up**
  - 12.7 years (IQ range 12 to 19.5 years)
- **All-cause mortality**
  - 468/731 (64.1%)
  - Higher than expected
- **Prostate cancer mortality**
  - 69/731 (9.4%)

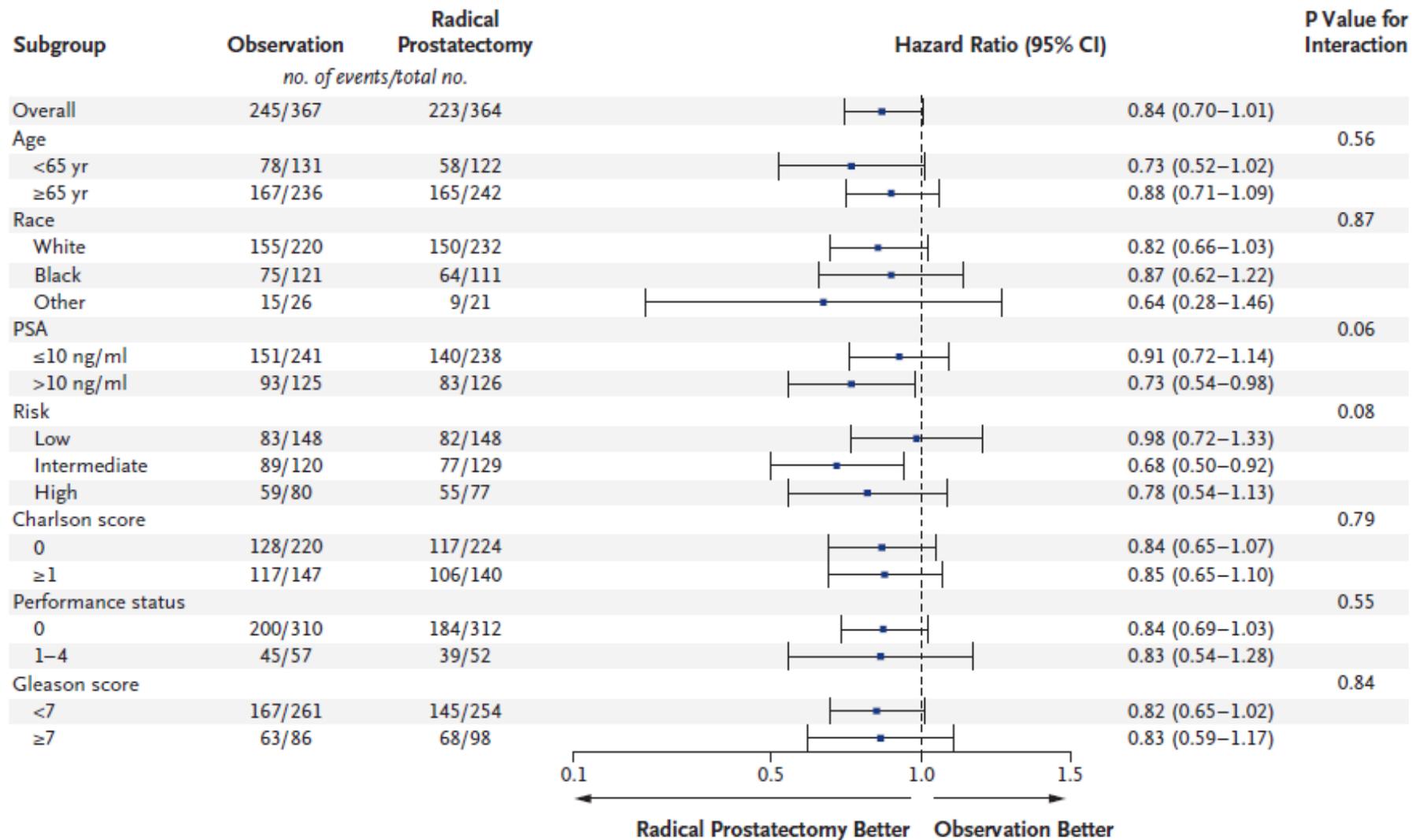
### A Death from Any Cause



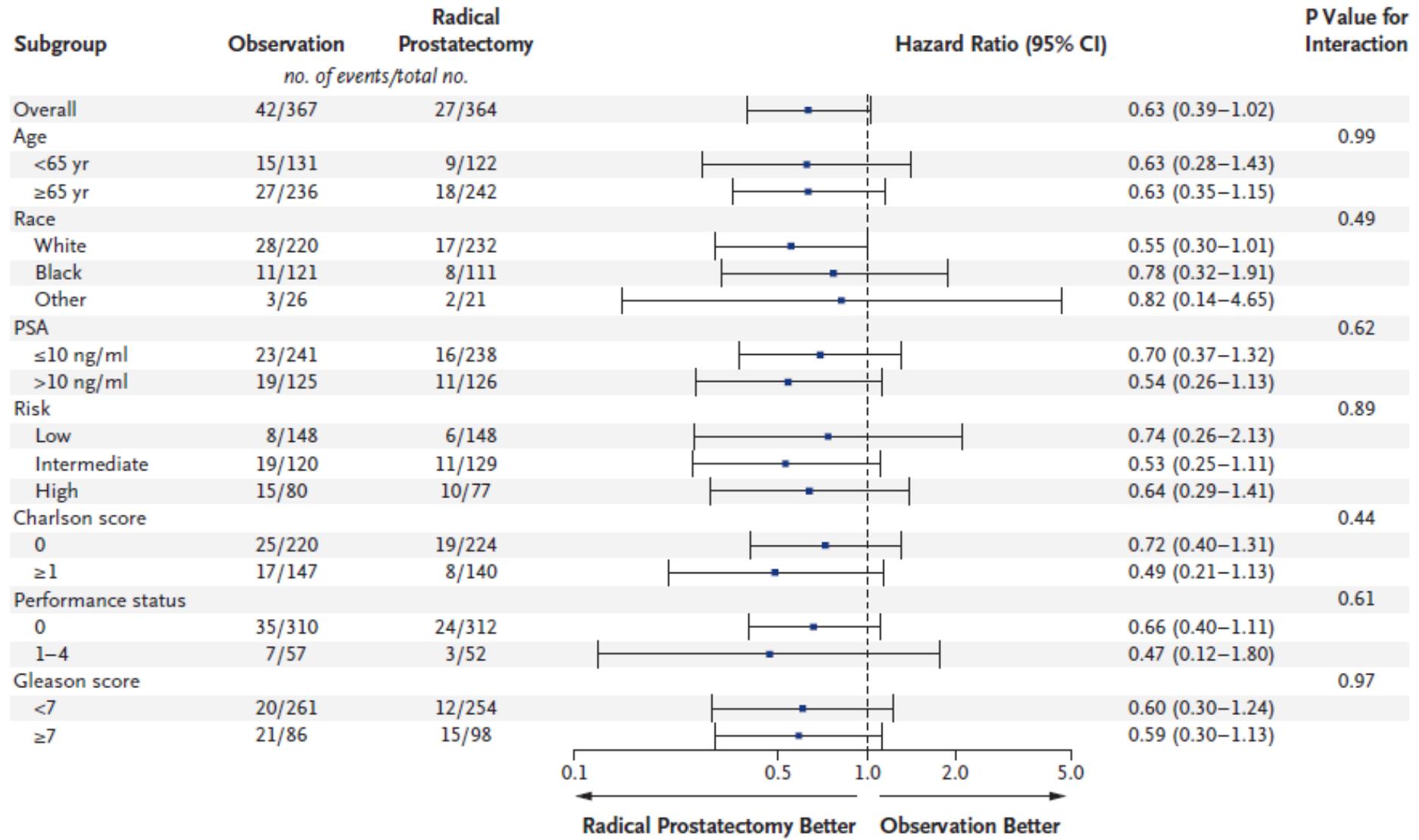
### B Death from Prostate Cancer



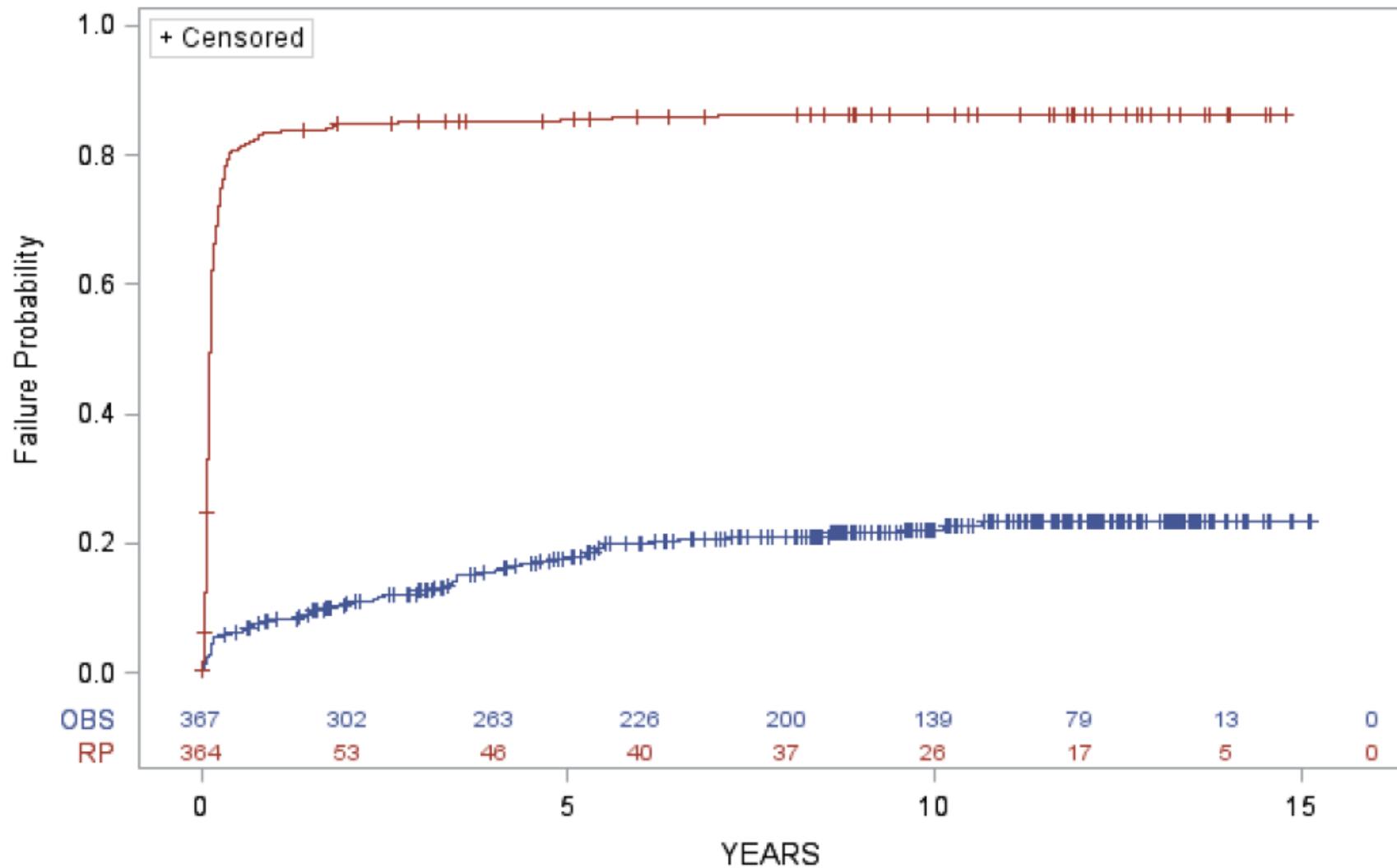
### A Death from Any Cause



**B Death from Prostate Cancer**

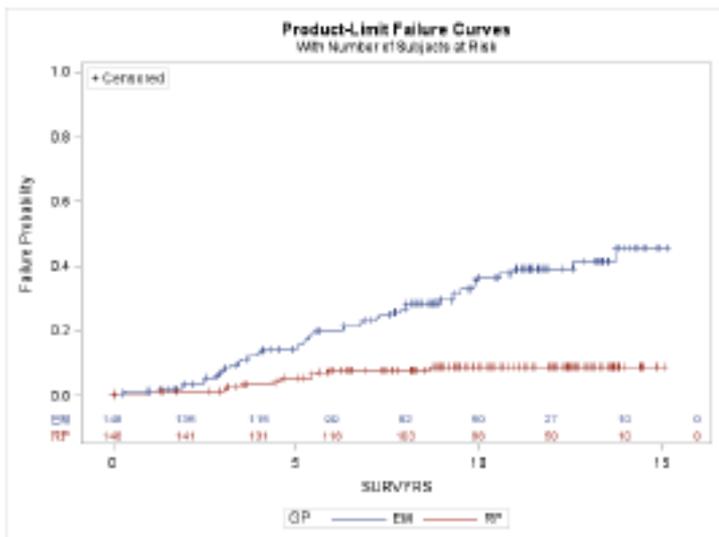


# Time to Definitive Intervention



GROUP — OBS — RP

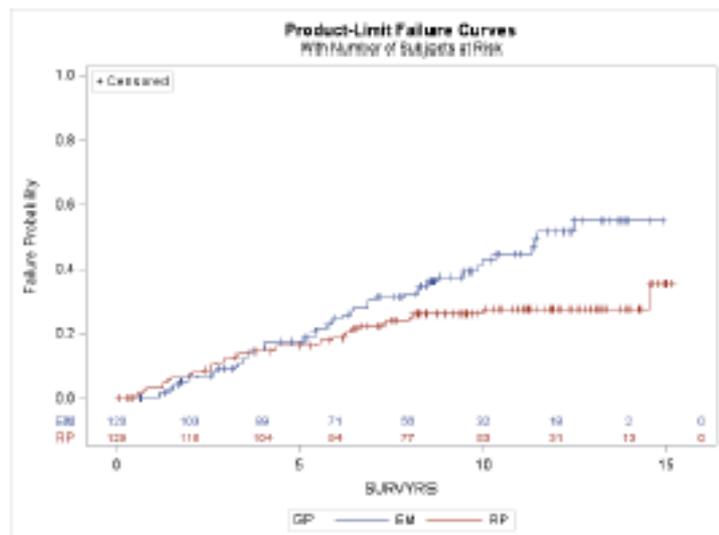
## Low Risk



**HR=0.22, 95%CI=0.11, 0.41;**

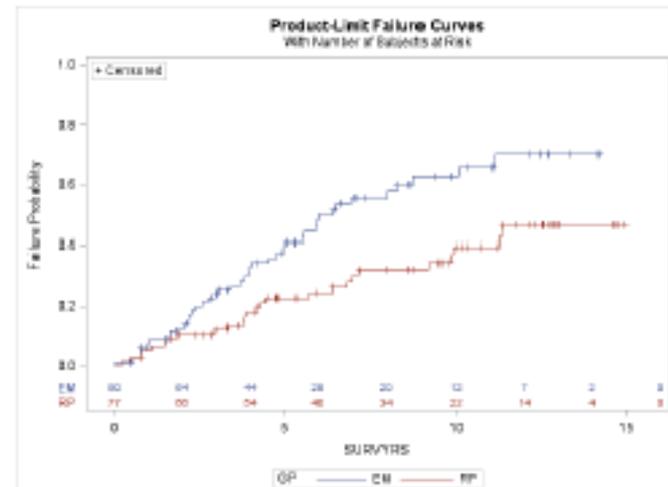
# Time to Treatment for Rising PSA

## Intermediate Risk



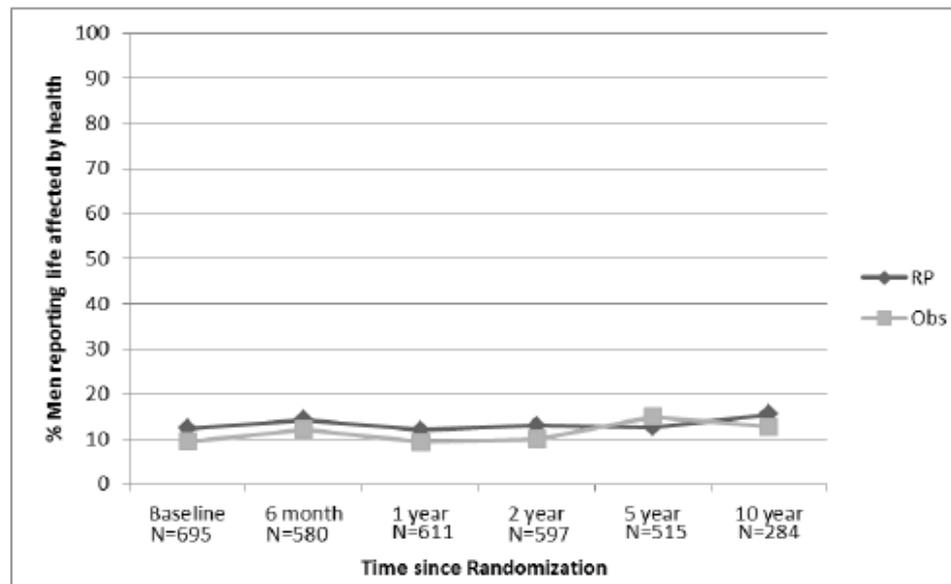
**HR=0.58, 95%CI=0.37, 0.91;**

## High Risk



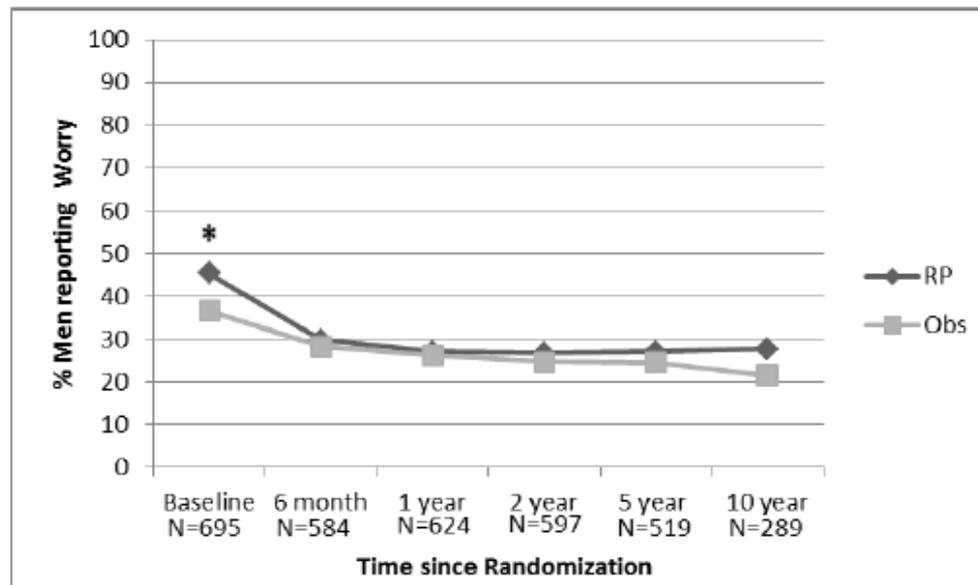
**HR=0.49, 95%CI=0.30, 0.80;**

## Overall Health (5a)



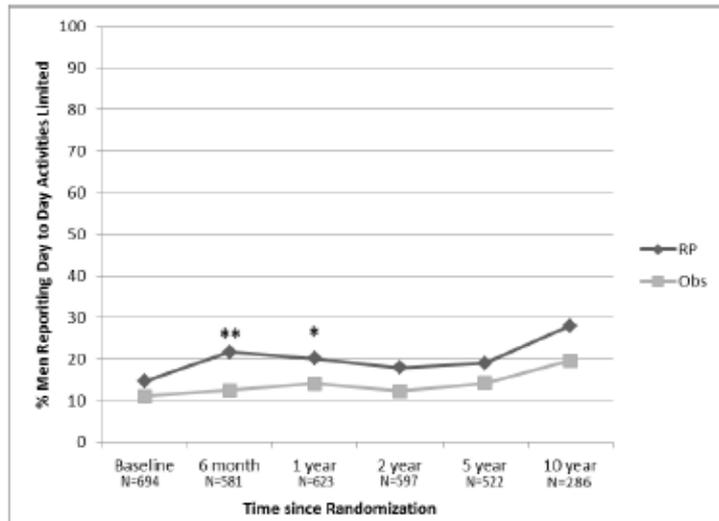
All P values > 0.20

## Worry about health (5b)



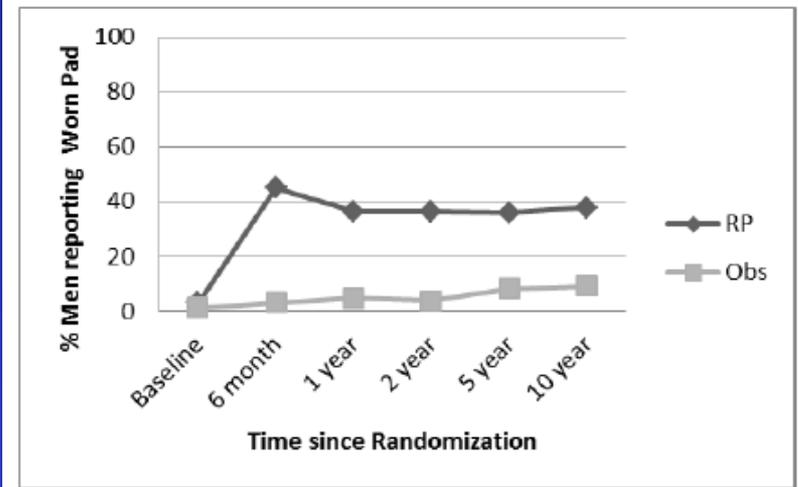
Baseline RP vs. Obs = 0.02 other comparison P values > 0.20.

### Limitations on Day-to Day Activities (5c)



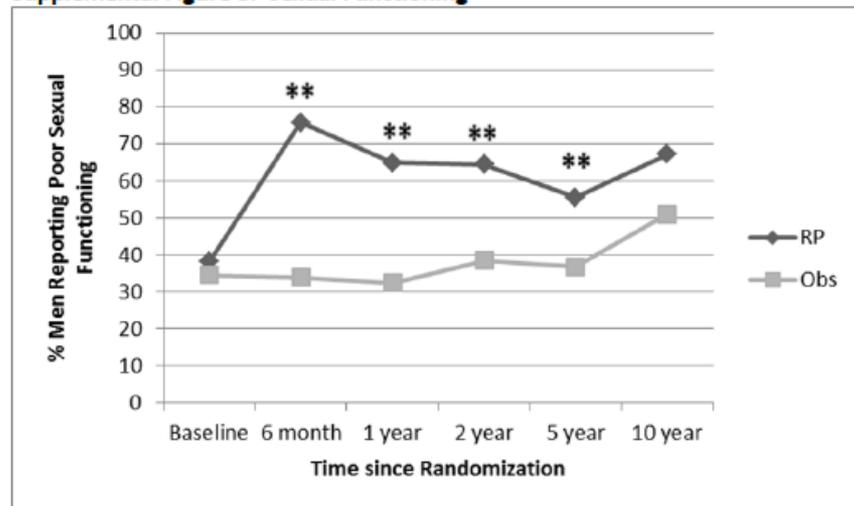
\*P<=0.05 ; \*\* P<=0.01

### a: Worn a pad per day



All P values < 0.001 except baseline

### Supplemental Figure 8: Sexual Functioning



\*\* P<=0.01

# Criticisms of PIVOT

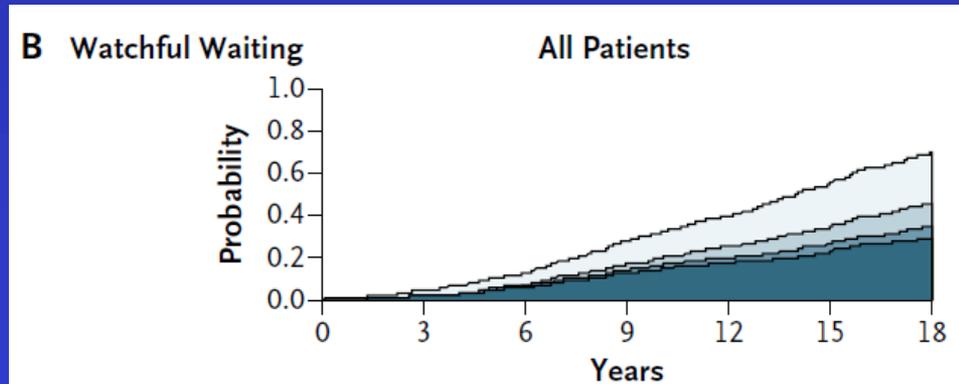
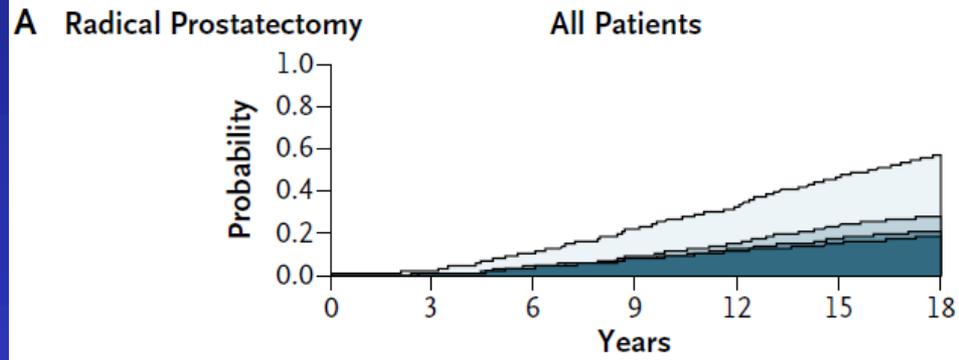
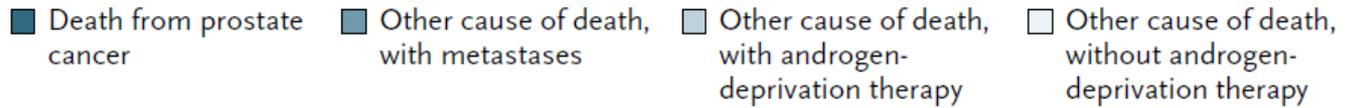
- Volunteers were sicker than most RP series
  - Higher death rate than anticipated
- Underpowered
  - Designed for 2000 patients
  - Need ~1500 pts. for 80% power
- Crossover/Non-compliance further dilutes power
  - ~20% in each arm

ORIGINAL ARTICLE

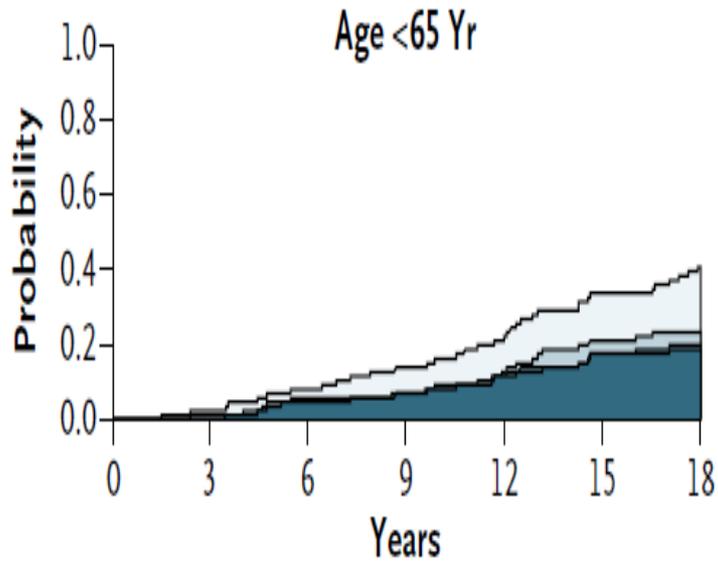
## Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D.,  
Jennifer R. Rider, Sc.D., Kimmo Taari, M.D., Ph.D., Christer Busch, M.D., Ph.D.,  
Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D.,  
Swen-Olof Andersson, M.D., Ph.D., Anders Spångberg, M.D., Ph.D.,  
Ove Andrén, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D.,  
Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.

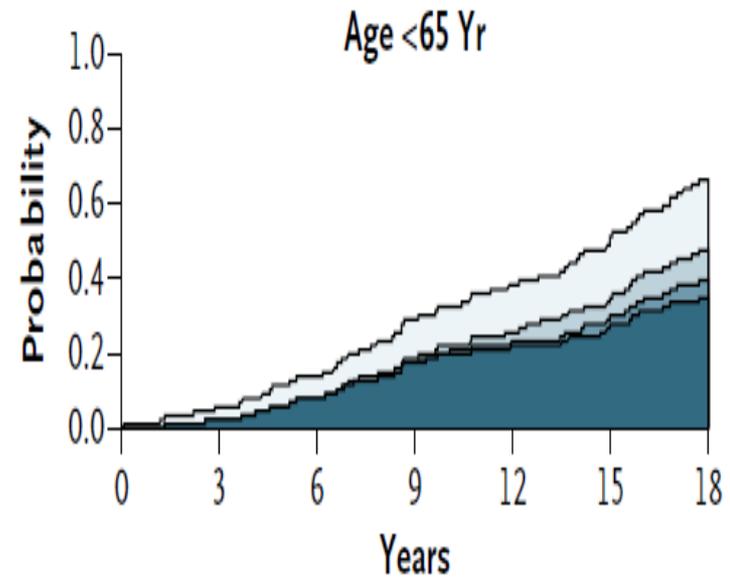
End Point	Cumulative Incidence				Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radical Prostatectomy (N=347)		Watchful Waiting (N=348)				
	no. of events	% (95% CI)	no. of events	% (95% CI)			
<b>Death from any cause</b>							
All	200	56.1 (50.9 to 62.0)	247	68.9 (63.8 to 74.3)	12.7 (5.1 to 20.3)	0.71 (0.59 to 0.86)	<0.001
<b>Age</b>							
<65 yr	69	40.0 (32.7 to 49.0)	112	65.6 (58.2 to 73.9)	25.5 (14.3 to 36.8)	0.50 (0.37 to 0.68)	<0.001
≥65 yr	131	69.8 (63.1 to 77.4)	135	71.7 (64.9 to 79.3)	1.9 (-8.2 to 12.0)	0.92 (0.73 to 1.18)	0.52
<b>Tumor risk</b>							
Low	51	43.4 (34.8 to 54.1)	85	59.1 (50.7 to 68.8)	15.6 (2.5 to 28.8)	0.57 (0.40 to 0.81)	0.002
Intermediate	87	57.1 (49.0 to 66.4)	95	72.5 (64.5 to 81.6)	15.5 (3.3 to 27.6)	0.71 (0.53 to 0.95)	0.02
High	62	73.3 (63.8 to 84.2)	67	78.8 (69.7 to 89.2)	5.6 (-8.5 to 19.6)	0.84 (0.60 to 1.19)	0.34
<b>Death from prostate cancer</b>							
All	63	17.7 (14.0 to 22.4)	99	28.7 (24.2 to 34.2)	11.0 (4.5 to 17.5)	0.56 (0.41 to 0.77)	0.001
<b>Age</b>							
<65 yr	31	18.3 (13.1 to 25.7)	58	34.1 (27.3 to 42.5)	15.8 (6.0 to 25.5)	0.45 (0.29 to 0.69)	0.002
≥65 yr	32	17.3 (12.5 to 24.0)	41	23.9 (18.2 to 31.5)	6.6 (-2.1 to 15.2)	0.75 (0.47 to 1.19)	0.19
<b>Tumor risk</b>							
Low	11	10.2 (5.8 to 18.0)	20	14.0 (9.1 to 21.5)	3.8 (-4.6 to 12.2)	0.54 (0.26 to 1.13)	0.17
Intermediate	24	15.1 (10.2 to 22.2)	50	39.3 (31.3 to 49.3)	24.2 (13.6 to 34.9)	0.38 (0.23 to 0.62)	<0.001
High	28	33.1 (24.0 to 45.7)	29	35.7 (26.3 to 48.5)	2.6 (-12.7 to 17.8)	0.87 (0.52 to 1.46)	0.84
<b>Distant metastases</b>							
All	89	26.1 (21.7 to 31.4)	138	38.3 (33.4 to 44.0)	12.2 (5.1 to 19.3)	0.57 (0.44 to 0.75)	<0.001
<b>Age</b>							
<65 yr	45	28.7 (22.2 to 37.1)	76	44.5 (37.3 to 53.0)	15.8 (5.1 to 26.6)	0.49 (0.34 to 0.71)	<0.001
≥65 yr	44	23.8 (18.4 to 30.9)	62	32.7 (26.4 to 40.5)	8.9 (-0.5 to 18.3)	0.68 (0.46 to 1.00)	0.04
<b>Tumor risk</b>							
Low	15	13.6 (8.4 to 21.9)	35	24.2 (17.8 to 33.0)	10.6 (0.7 to 20.6)	0.40 (0.21 to 0.73)	0.006
Intermediate	37	25.0 (18.8 to 33.3)	59	44.9 (36.9 to 54.7)	19.9 (8.5 to 31.3)	0.49 (0.32 to 0.74)	<0.001
High	37	45.9 (35.8 to 58.8)	44	50.8 (40.6 to 63.5)	4.9 (-11.2 to 21.0)	0.81 (0.52 to 1.26)	0.39
<b>Androgen-deprivation therapy</b>							
All	145	42.5 (37.5 to 48.1)	235	67.4 (62.6 to 72.6)	25.0 (17.7 to 32.3)	0.49 (0.39 to 0.60)	<0.001
<b>Age</b>							
<65 yr	68	44.2 (36.9 to 53.0)	122	72.6 (66.0 to 79.8)	28.4 (17.8 to 38.9)	0.39 (0.29 to 0.52)	<0.001
≥65 yr	77	40.9 (34.4 to 48.7)	113	62.8 (56.0 to 70.4)	21.8 (11.7 to 32.0)	0.60 (0.45 to 0.80)	<0.001
<b>Tumor risk</b>							
Low	32	27.9 (20.7 to 37.6)	63	47.9 (39.9 to 57.5)	20.1 (8.0 to 32.1)	0.45 (0.29 to 0.69)	0.001
Intermediate	65	44.9 (37.4 to 54.0)	98	73.6 (66.3 to 81.7)	28.6 (17.3 to 40.0)	0.45 (0.33 to 0.62)	<0.001
High	48	59.3 (49.3 to 71.2)	74	88.1 (81.2 to 95.6)	28.8 (15.8 to 41.9)	0.45 (0.31 to 0.65)	<0.001



- Death from prostate cancer
- Other cause of death, with metastases
- Other cause of death, with androgen-deprivation therapy
- Other cause of death, without androgen-deprivation therapy

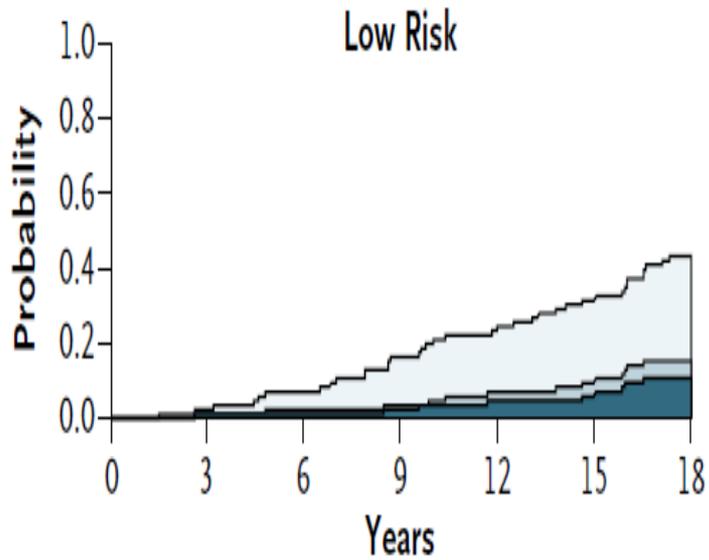


**No. at Risk**    157    154    145    136    124    96    60

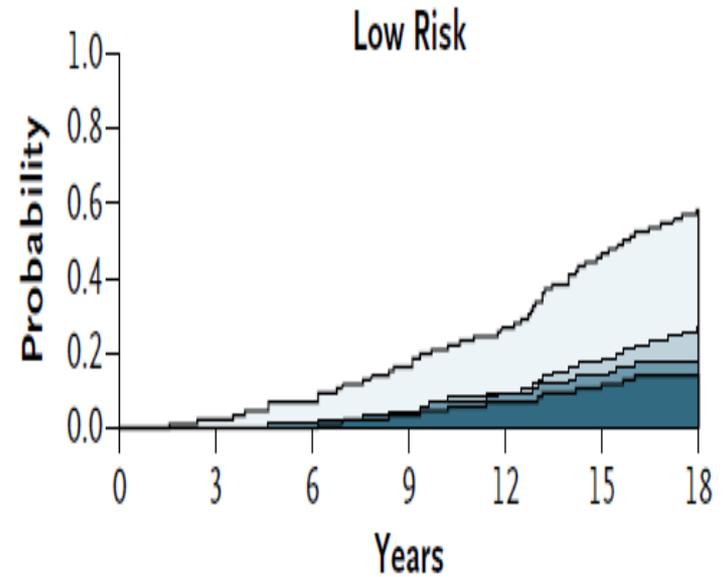


**No. at Risk**    166    157    144    118    102    75    34

- Death from prostate cancer
- Other cause of death, with metastases
- Other cause of death, with androgen-deprivation therapy
- Other cause of death, without androgen-deprivation therapy

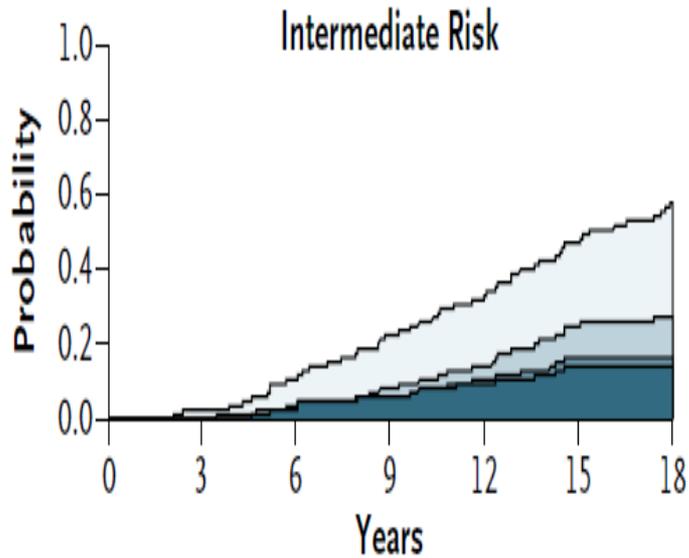


No. at Risk	118	115	110	99	89	72	40
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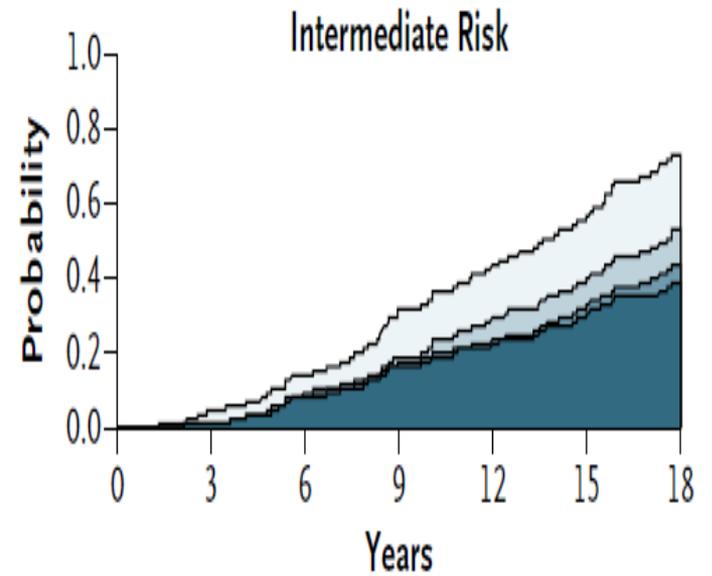


No. at Risk	131	128	122	109	95	66	31
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- Death from prostate cancer
- Other cause of death, with metastases
- Other cause of death, with androgen-deprivation therapy
- Other cause of death, without androgen-deprivation therapy

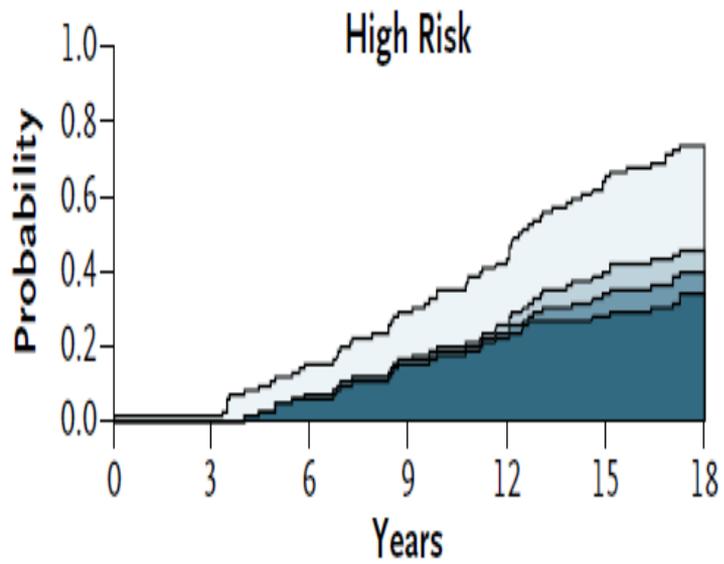


No. at Risk    148    144    132    114    100    68    33

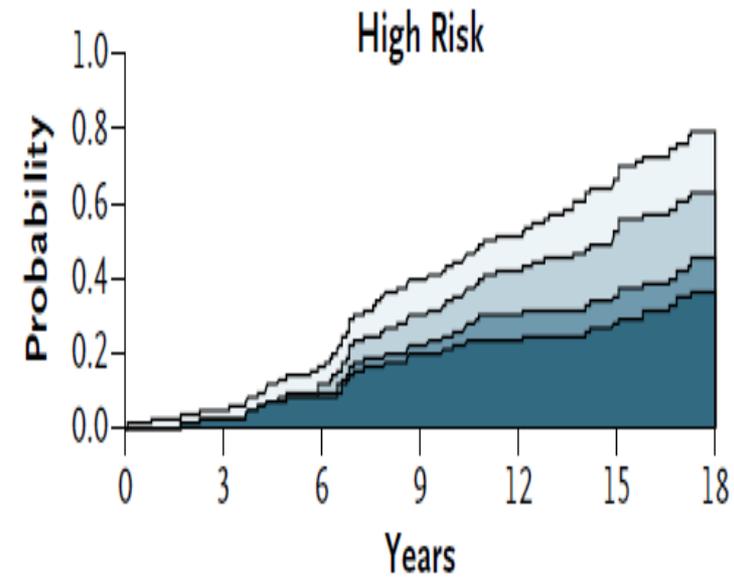


No. at Risk    133    126    113    91    75    55    18

- Death from prostate cancer
- Other cause of death, with metastases
- Other cause of death, with androgen-deprivation therapy
- Other cause of death, without androgen-deprivation therapy



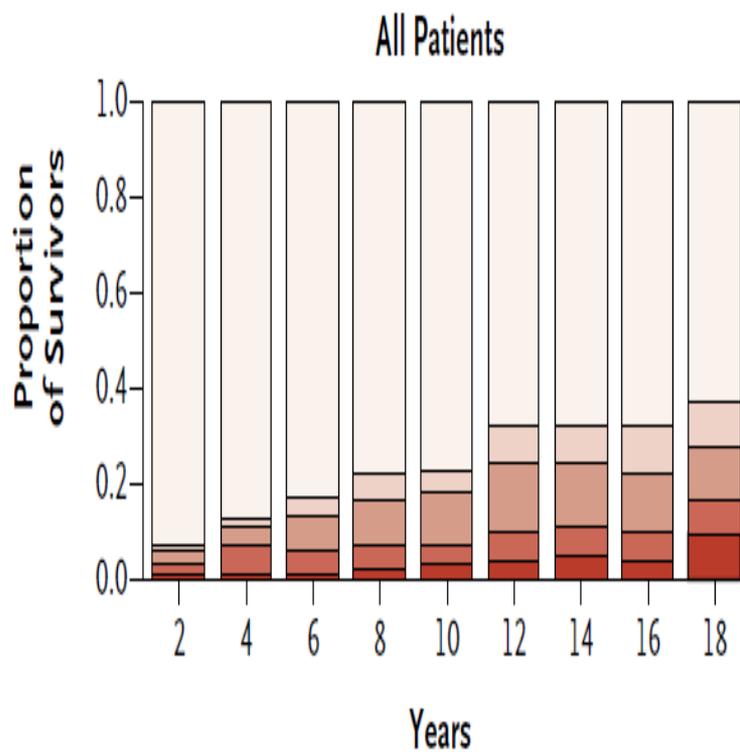
No. at Risk    81    80    69    58    47    28    14



No. at Risk    84    80    71    51    41    22    12

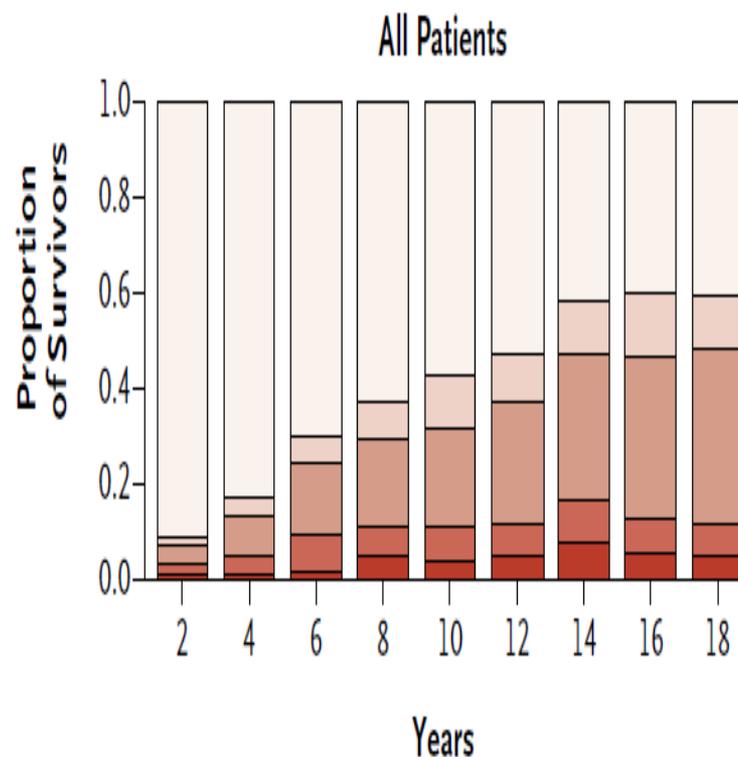
- No androgen-deprivation therapy or metastases
- Androgen-deprivation therapy with antiandrogen therapy, no metastases
- Androgen-deprivation therapy with GnRH or orchiectomy, no metastases
- Androgen-deprivation therapy with confirmed metastases
- Androgen-deprivation therapy and other palliative treatments (cytotoxic drugs or laminectomy) with confirmed metastases

### A Radical Prostatectomy



No. at Risk 343 332 311 285 257 236 201 145 87

### B Watchful Waiting



No. at Risk 341 326 306 270 238 211 173 111 61

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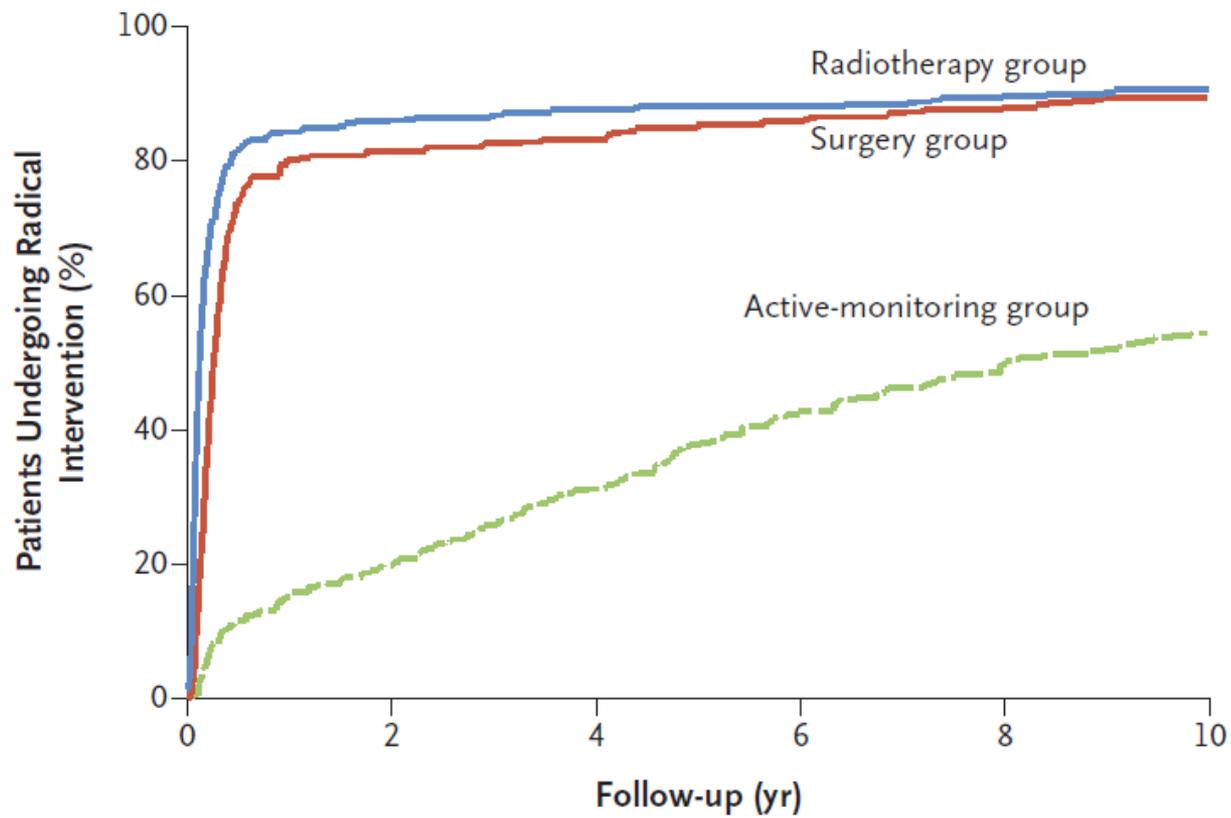
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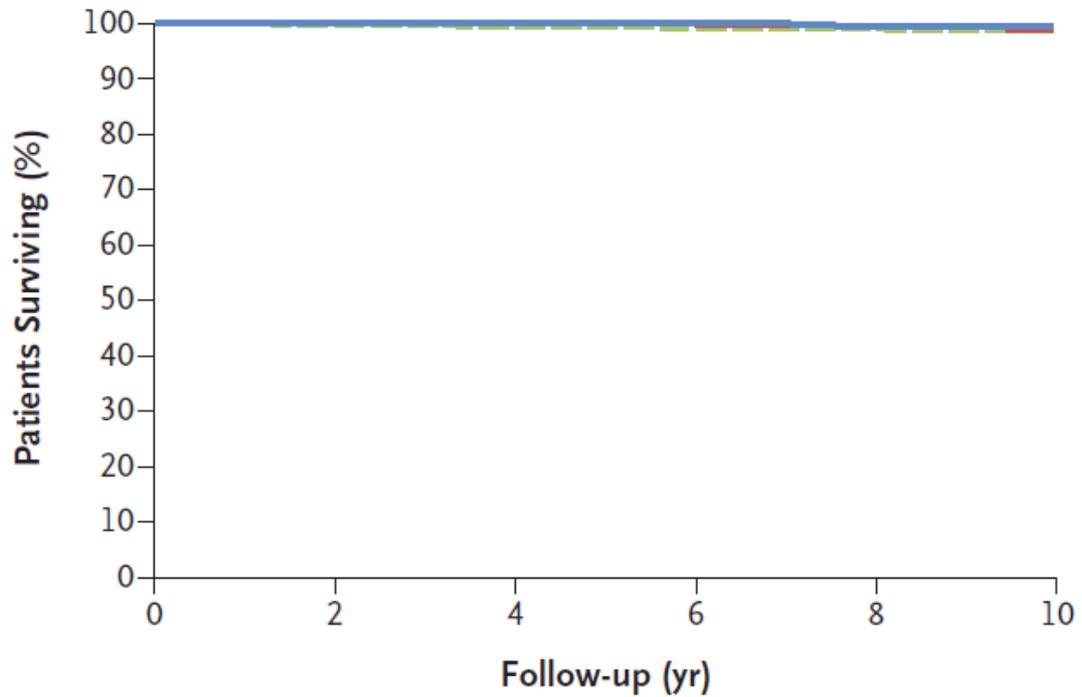
10-Year Outcomes after Monitoring, Surgery, or Radiotherapy  
for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal,  
for the ProtecT Study Group\*



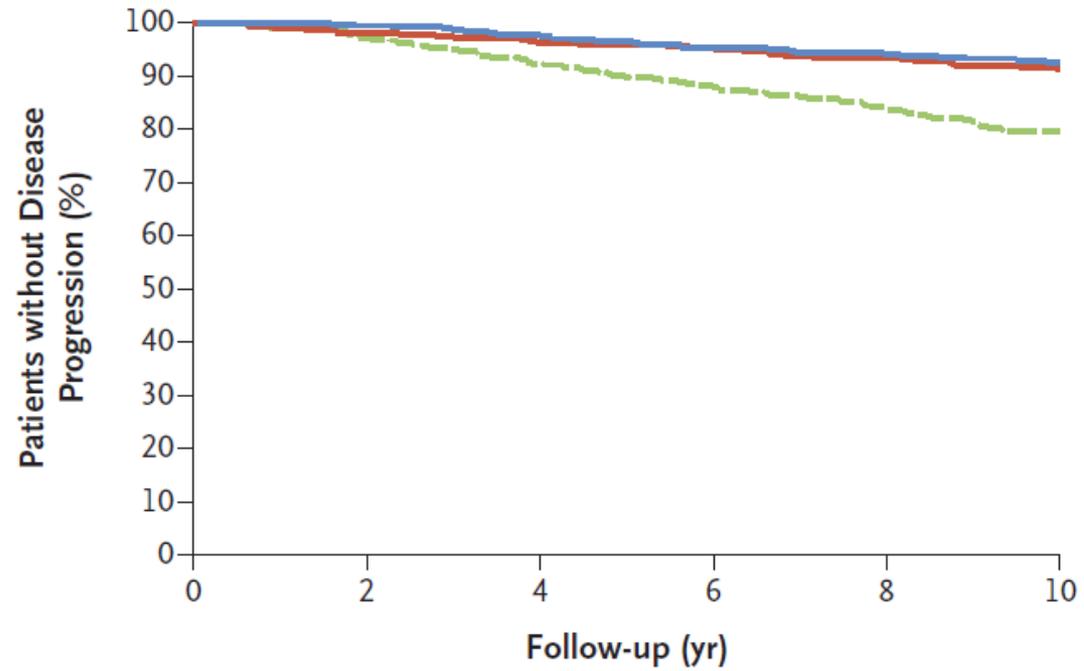
— Surgery — Radiotherapy - - - Active monitoring

### A Prostate-Cancer-Specific Survival



No. at Risk	0	2	4	6	8	10
1643	1643	1628	1605	1575	1286	746

### B Freedom from Disease Progression



No. at Risk	1643	1601	1533	1467	1175	666
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**Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.**

Variable	Active Monitoring (N = 545)	Surgery (N = 553)	Radiotherapy (N = 545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer–specific survival — % (95% CI)‡				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)‡	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004

	SPG-4	PIVOT	Klotz	PROTECT
Years	1989-1999	1994-2002	1995-	1999-2009
Intervention	RP v WW	RP v Obs	AS	RP or XRT v AS
# Biopsy cores	?????	6	????	10
# Randomized	695 (Unk)	731 (15%)	????	1643 (62%)
Age (mean)	<75 (65)	<75 (67)	<90 (68)	50-69 (61)
% White	????	62	????	99
Mean PSA	13	10	5.2	5.8
Clin T1c	11	50	78	76
Gleason <7	60	74	84	77

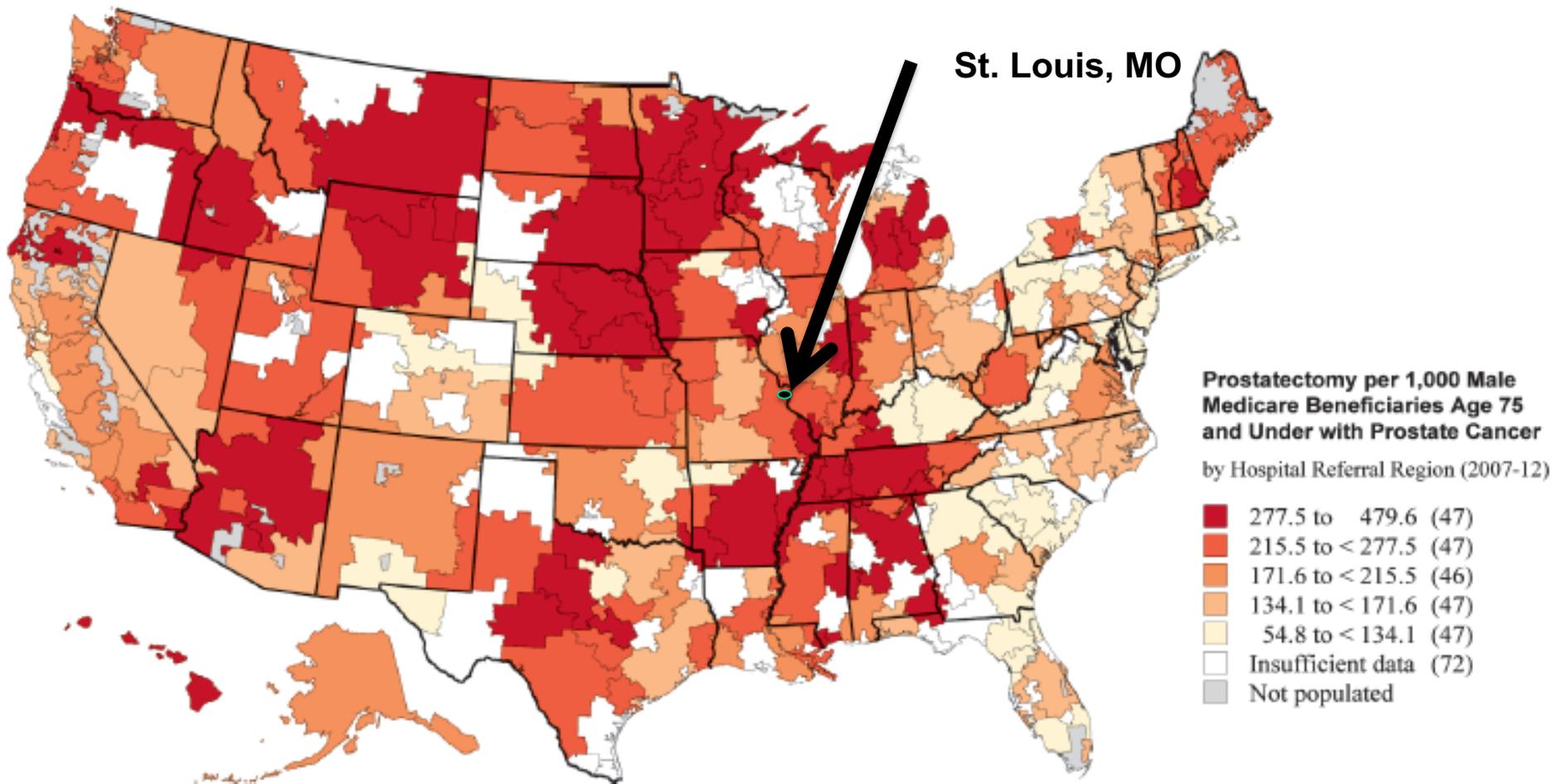
	<b>PIVOT</b>	<b>SPG-4</b>	<b>Klotz</b>	<b>Protect</b>
F-up (yr)	10	10.8	6.4	10
Death (%)	48	45	15	11
CaP Death (%)	7	19	3	1.5

	PIVOT	SPG-4
F-up (yr)	19.5	23.2
Death (%)	64	64
CaP Death (%)	9.4	29

## Variation in the Care of Surgical Conditions: Prostate Cancer

*A Dartmouth Atlas of Health Care Series*

# Variation in Rates of RP in USA



## Variation in the Care of Surgical Conditions: Prostate Cancer

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# Variation in Rates of RP in USA

**Table 5. Prostatectomy per 1,000 male Medicare beneficiaries age 75 and under with prostate cancer among hospital referral regions by comorbidity status (2007-12)**

Fewer than 2 chronic illnesses			2 or more chronic illnesses		
10 highest HRRs			10 highest HRRs		
Munster	IN	505.5	Munster	IN	403.1
Memphis	TN	409.8	Little Rock	AR	242.2
Nashville	TN	337.6	Memphis	TN	228.0
Phoenix	AZ	326.7	Orange County	CA	207.1
Little Rock	AR	315.9	Nashville	TN	191.1
Birmingham	AL	311.0	Milwaukee	WI	184.7
Milwaukee	WI	271.7	Birmingham	AL	180.1
Orange County	CA	263.7	Los Angeles	CA	159.4
St. Louis	MO	248.8	Phoenix	AZ	154.6
Los Angeles	CA	220.9	Springfield	IL	151.6

# PIVOT Summary

- Surgery did not reduce mortality in men with low PSA or low risk prostate cancer.
  - In conjunction with other trials, this observation has increased Urologists' and patients' awareness and acceptance of surveillance

# PIVOT Summary

- The low prostate cancer mortality in these low risk men was observed despite:
  - Majority diagnosed on sextant biopsy
  - Repeat and extended (saturation) or even MRI-targeted biopsies were NOT performed
  - Thus, some low risk men likely harbored Gleason pattern 4 elements that were undiagnosed
  - Notwithstanding the likely presence of some Gleason pattern 4 in some of these men, there was low prostate cancer mortality
  - Does this call into question early rebiopsy ( $\pm$  MRI) of men who are AS candidates?

# PIVOT Summary

- Surgery likely beneficial for men with higher PSA and/or intermediate risk disease.