

What happens after treatment and  
your PSA rises? Assessing  
Prostate Cancer Progression.

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CLS 449 (617-735-2062)

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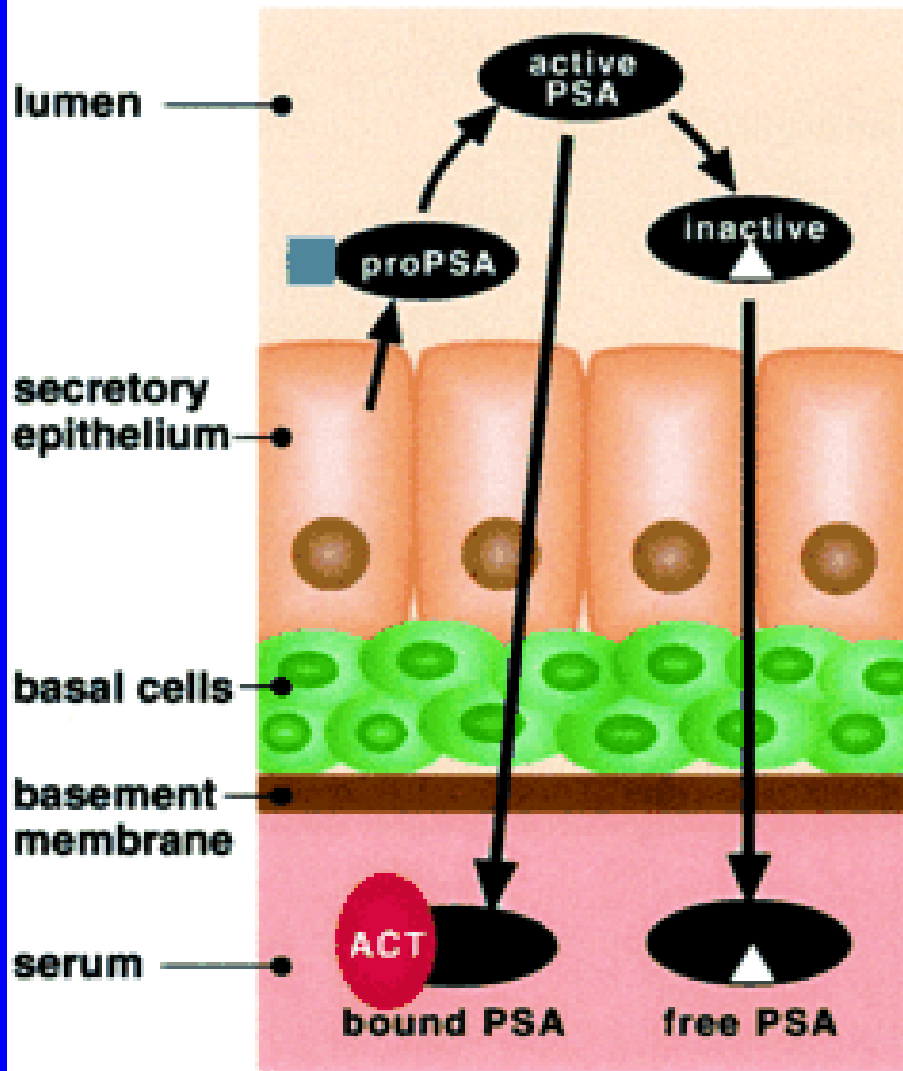
# Today's agenda

- What is PSA and where is it made?
- How is it measured?
- PSA for screening compared to follow up after the cancer is treated
- What does it mean when it becomes detectable after radical prostatectomy?
- What does it mean when it rises after radiation therapy or brachytherapy?
- What can be done?
- Are there any experimental options?

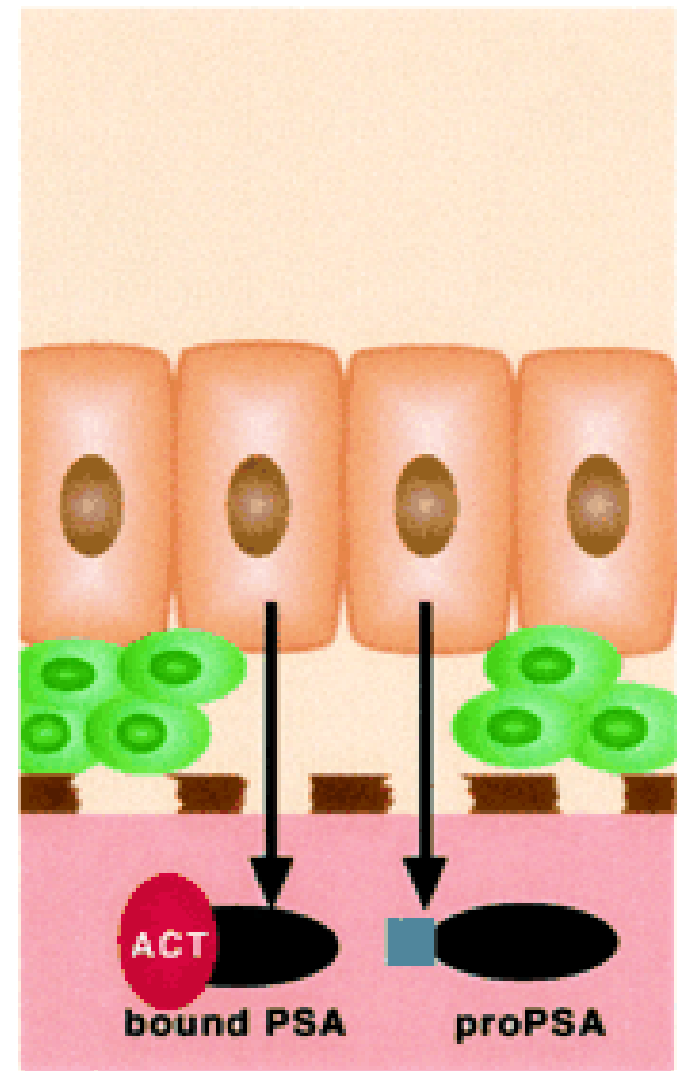
# What is PSA?

- A serum protein
- Produced by both normal prostate cells and prostate cancer cells
- Other sources (usually not significant)
  - Periurethral/perianal glands
  - Salivary glands

## Normal



## Cancer



# How is PSA measured?

- Serum levels are measured using an immunological assay (antibody to PSA)
- Total PSA usually measured
- Several different assays with different sensitivities including different lower ranges

# Natural history of prostate cancer

- Most men present with localized disease and are likely to be cured
- Approximately 50 000 men relapse each year
- Relapse heralded by detectable and rising PSA
  - Different for those treated with radiation therapy versus surgery

ORIGINAL ARTICLE

# Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,  
Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,  
Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D.,  
Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D.,  
Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S.,  
Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D.,  
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Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D.,  
for the PLCO Project Team\*

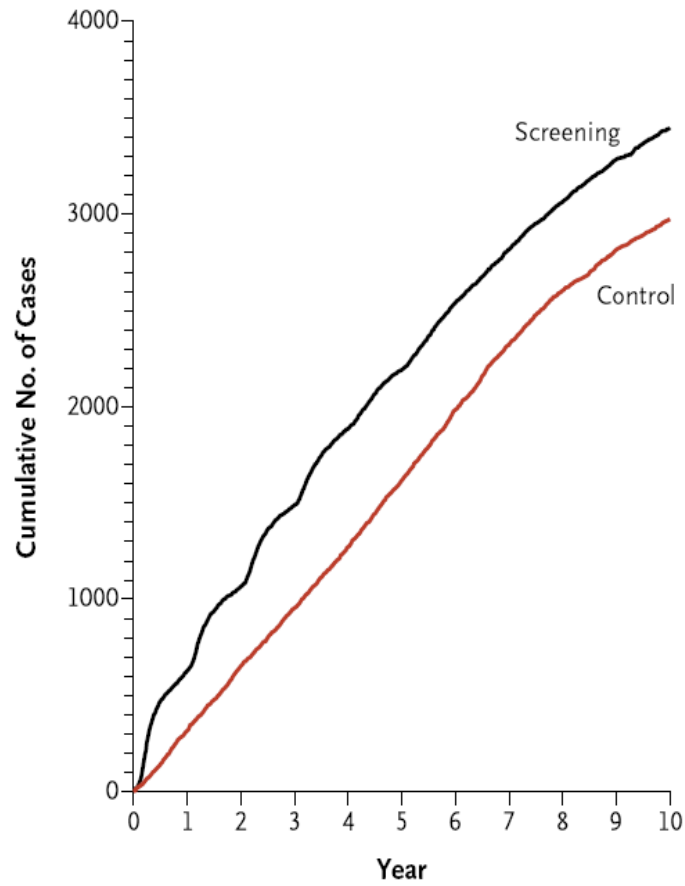
NATIONAL CANCER INSTITUTE

PLCO

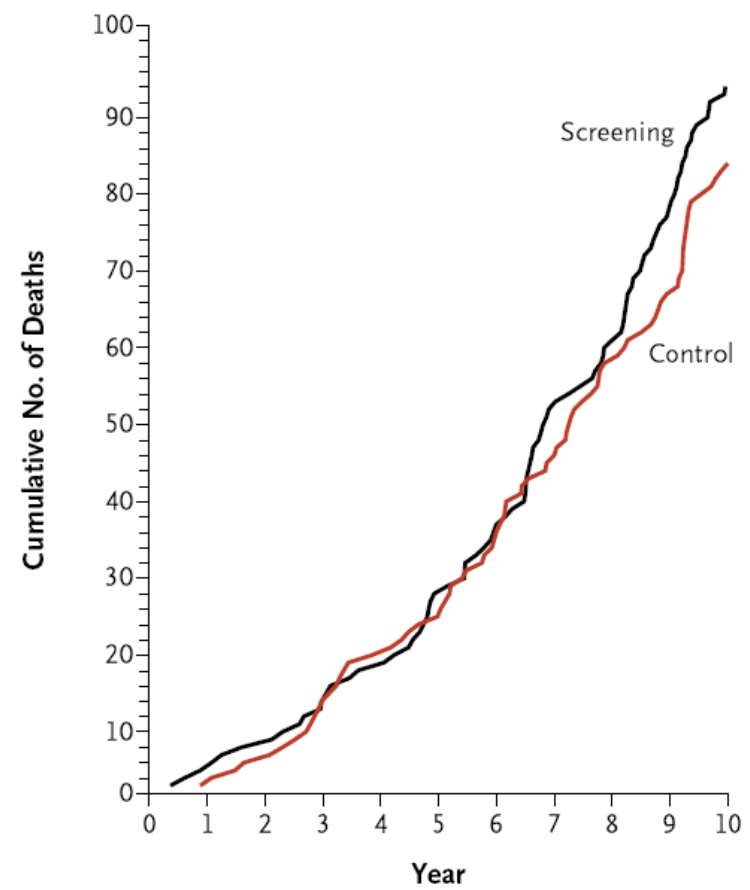
Prostate, Lung, Colorectal, & Ovarian  
CANCER SCREENING TRIAL

- From 1993 through 2001, men and women ages 55-74 were enrolled at 10 centers across the United States.
- The primary exclusion criteria were a history of a PLCO cancer, current cancer treatment, and having more than one PSA test in the previous 3 years.

**A Prostate Cancers**

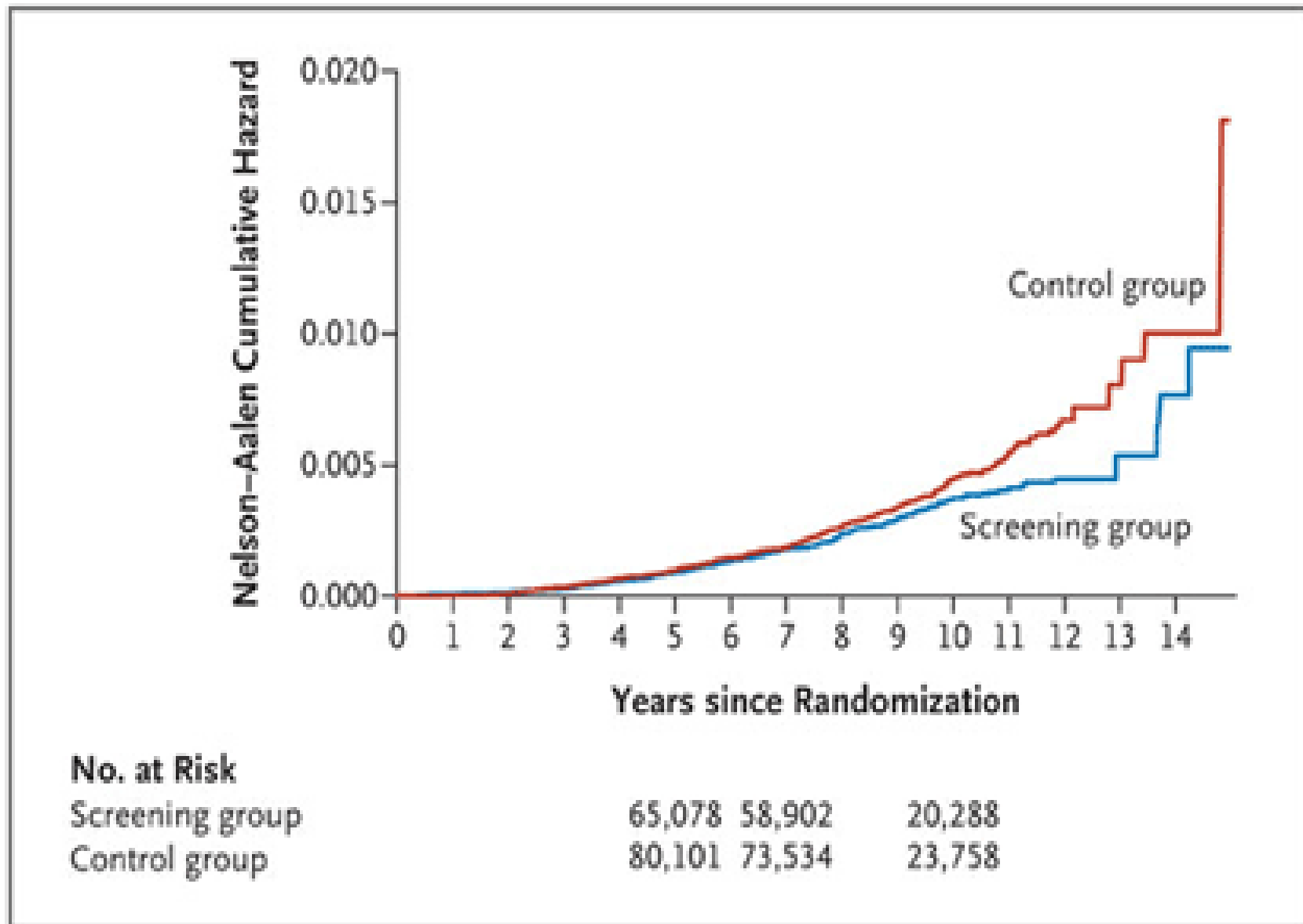


**B Prostate-Cancer Deaths**



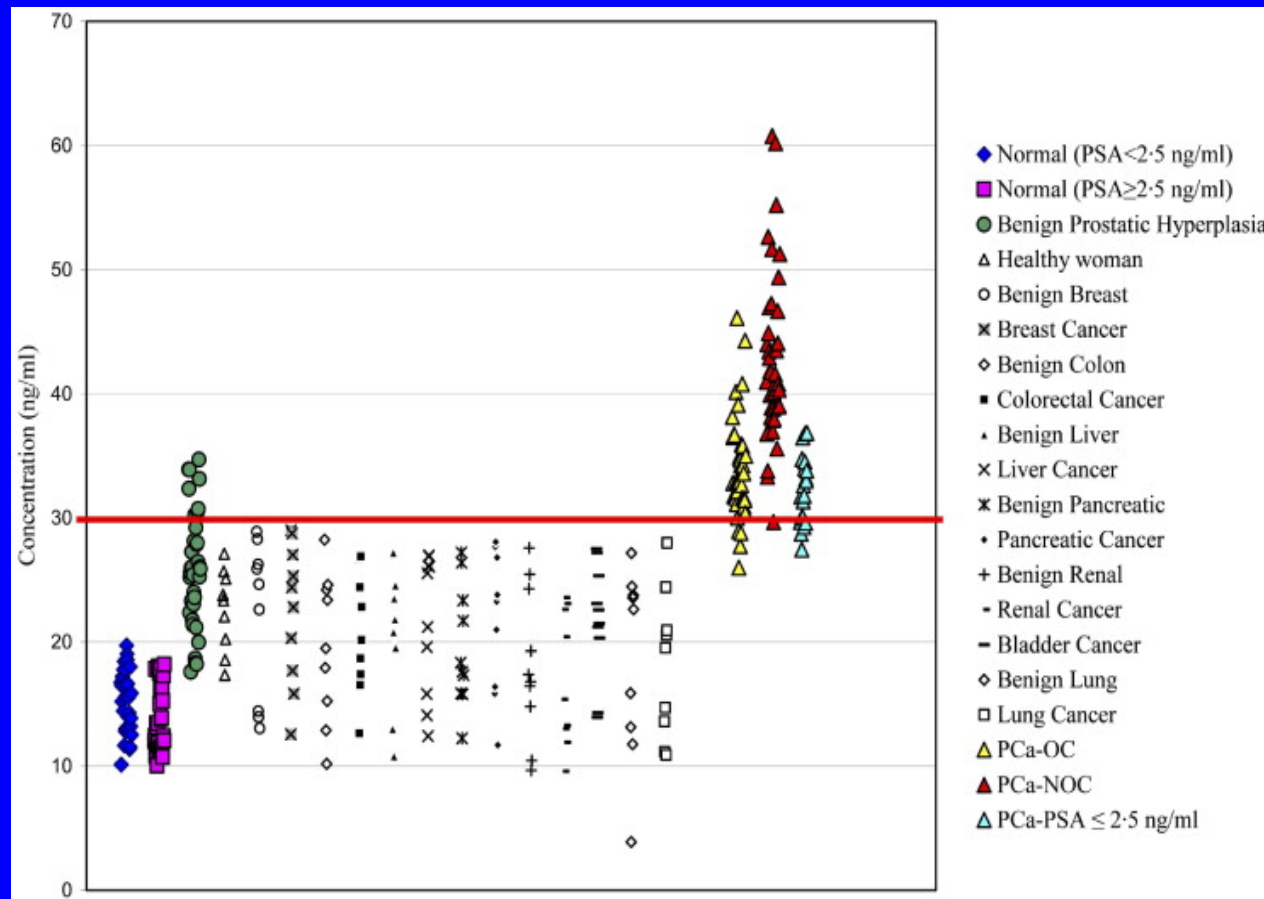
**Figure 1.** Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).





method was used for the calculation of

# EPCA-2 as a potential marker for prostate cancer



# Post prostatectomy

- Should be undetectable in most men after radical prostatectomy
- Usually not rechecked until  $>1$  month
- Low levels MAY be detected in a minority and may NOT be associated with relapse

# Post prostatectomy: lessons from the Johns Hopkins Cohort

- Studied the outcome of 1997 patients operated on by a single surgeon
- Only 15% recurred after 5.3 years



# Lessons from Surgery

Metastatic disease was seen in those with

- Short PSA doubling time <10 months
- High gleason score 8-10
- Short time to PSA recurrence.

# Post radiation therapy

- Usually takes 12-24 months after external beam radiation therapy to reach lowest PSA
- Those who have a nadir PSA of  $<1$  ng/ml are more likely to have a durable response
- 3 consecutive rises in PSA is considered to be a relapse

# Post radiation therapy

- PSA doubling time also very important
- Biopsy Gleason score important
- Complicated by the “PSA bounce”

# “PSA Bounce”

- A transient increase in PSA after either brachytherapy or radiation therapy not associated with disease recurrence
- Causes
  - Unknown
  - Precipitated by ejaculation, rectal inflammation, bike riding?
- Can occur in upto 1/3 of patients
- Usually at 18-36 months after treatment
- No absolute value of PSA

# PSA doubling time standards

- PSAdT of <6 months suggests metastatic disease within a few years, and usually patients are started on treatment (hormonal or trials)
- PSAdT >6 months and <10-12 months: gray area
- PSA>12 months: usually observation

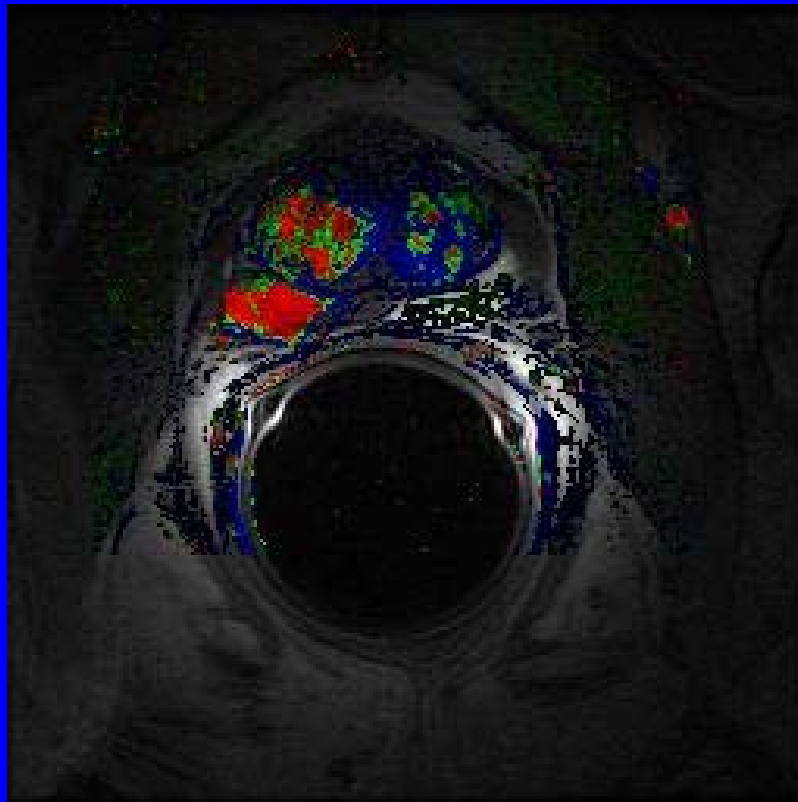
# What tests should be done if my PSA rises after treatment?

- repeat the PSA test
- Digital rectal examination
- Ultrasound guided biopsy
  - For those who received radiation/brachtherapy
- ProstaScint scan
- Bone scan
- CT scan
- PET scan

# What is the purpose of these tests?

- To determine if relapse has occurred
- To determine if relapse is local versus distant

**Innovative and Individualized Diagnosis/ Treatment:**  
*Contrast-enhanced 3T MRI to Facilitate Pre-operative plan for wide excision of neurovascular bundle and replacement nerve graft*



56 yrs, PSA = 14.8;  
DRE: Right nodularity

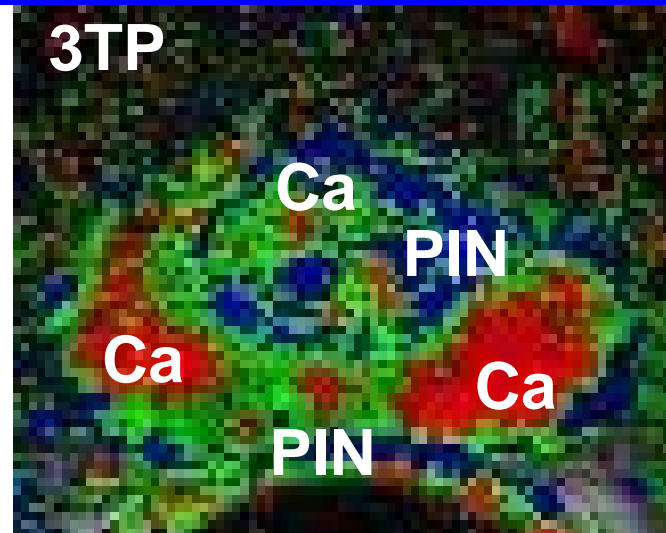
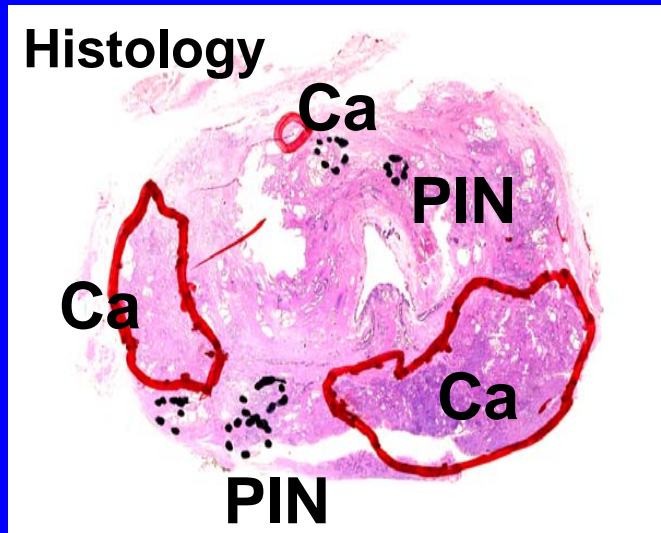
Biopsy: right 3/6 biopsy  
cores have cancer (50%  
of bx core) Gleason = 6

MRI: extra-capsular  
extension into nerves

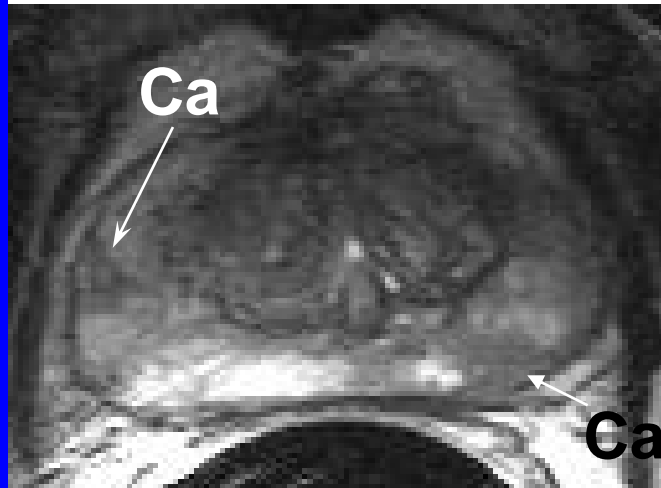
Surgery: wide excision on  
right including nerves  
and with Dr. Borud a  
sural nerve graft on that  
side

Pathology: Extracapsular  
extension confirmed;  
Negative Surgical  
Margins

# Rad-Path Correlation



DCE MRI T2b



T2-W MRI T2b

HistoT2b

# Local Therapy after Prostatectomy

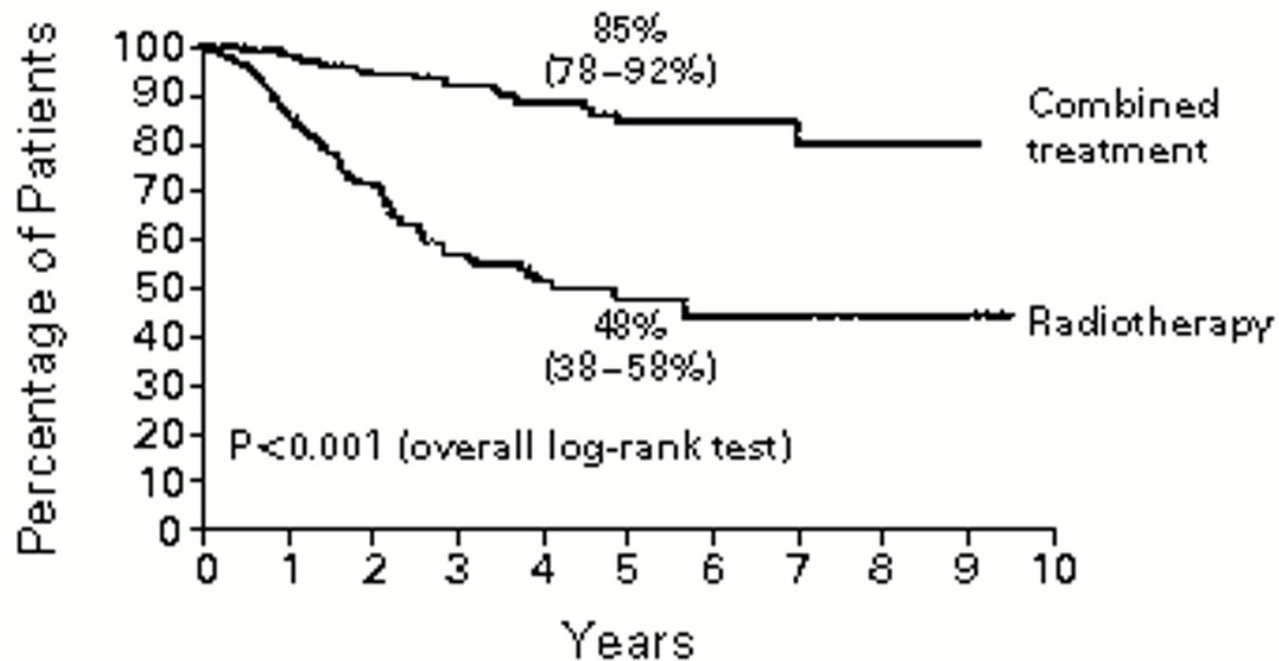
- External beam radiation therapy
- Most common
- Often used for those with positive margins
- Effectiveness measured by a decrease in PSA
- Toxicity is modest
- 1/3 may benefit???
- Perhaps even greater benefit if given in combination with hormonal therapy (ADT)

# Treatment of Post Prostatectomy Failure

- No controlled trial data
- Time of biochemical failure may differentiate between systemic vs local relapse
  - Prostate scan not helpful
  - Biopsy of prostate bed
- Radiation therapy to prostate bed
  - PSA decline in 30-83%
  - Better results if XRT initiated when PSA  $\leq$  2ng/mL
  - Possible improvement if men are also on androgen deprivation therapy

# Effect of XRT+/- Androgen Ablation Cancer Specific Survival

Bolla NEJM 1997; 337:1031



	No. of PATIENTS AT RISK										No. with DISEASE PROGRESSION	
	0	1	2	3	4	5	6	7	8	9	10	
Radiotherapy	208	163	107	59	38	19	11	5	3	1		78
Combined treatment	207	189	138	108	78	51	36	16	5	0		20

# Salvage XRT for Recurrence after Radical Prostatectomy

## Adverse Prognostic Factors:

- Gleason score 8-10
- PreXRT PSA > 2
- Negative Surgical Margins
- Seminal Vesicle Invasion
- PSA DT < 10 months

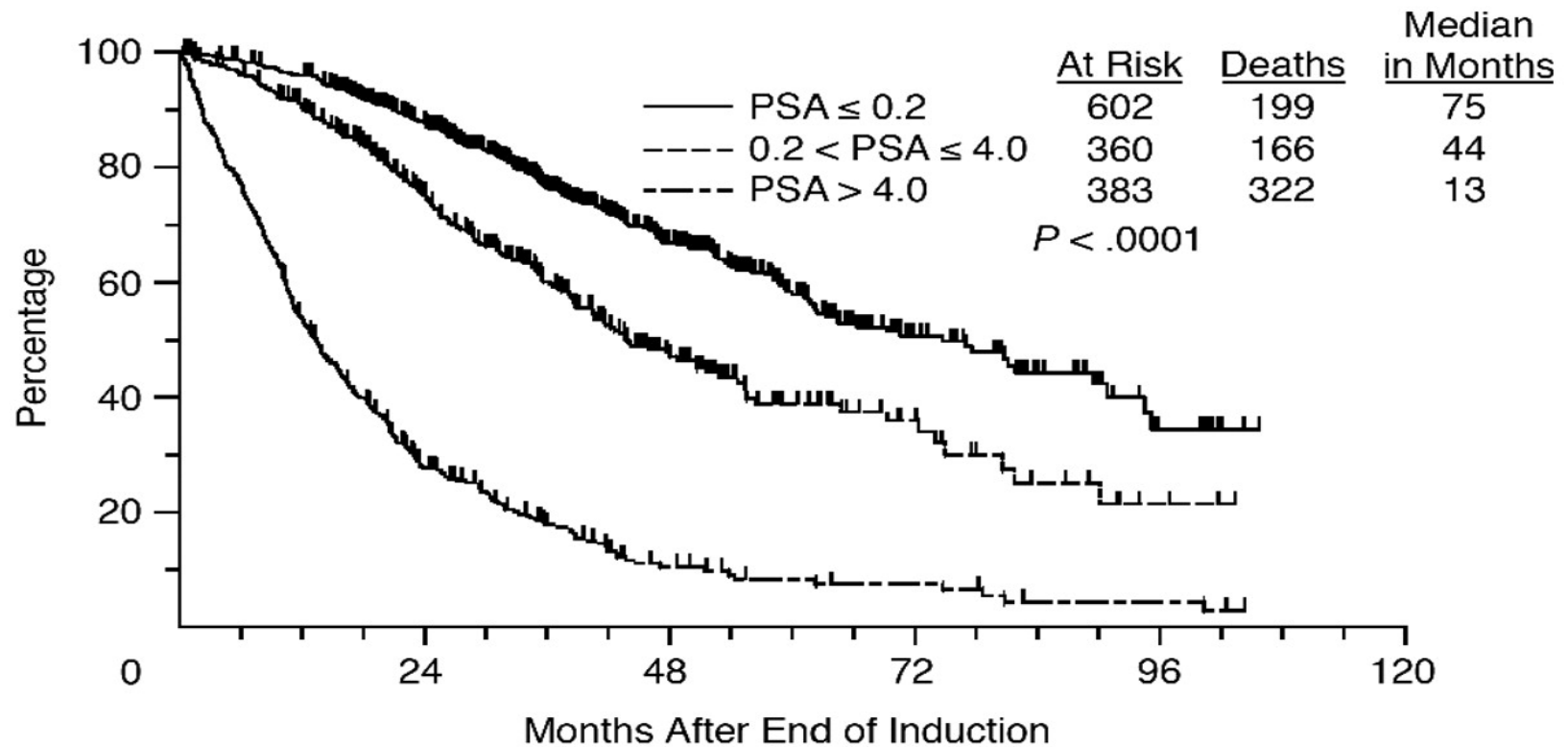
JAMA 2004; 291: 1325-332

# Local Therapy after Radiation

- After external beam radiation
  - Salvage prostatectomy
  - Brachytherapy (a few seeds in one or more location)
  - Cryotherapy
- After brachytherapy
  - Salvage prostatectomy
  - Cant give more external beam therapy as the dose to the prostate is too high

# Hormonal Therapy

- Intermittent androgen therapy
  - Experimental
  - May delay development of hormone independence
  - Possible fewer side effects



At risk:

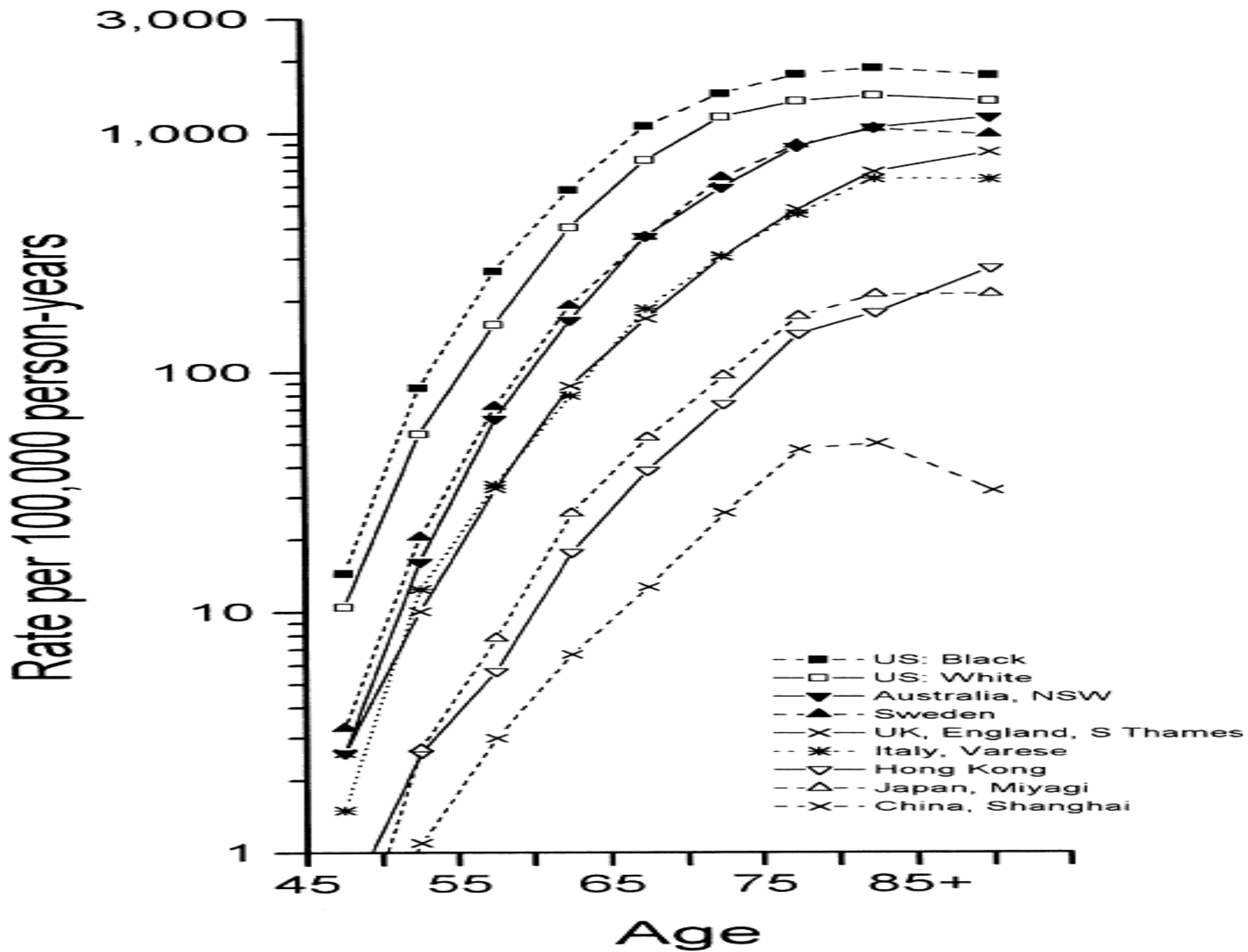
PSA $\leq 0.2$ ng/mL	453	210	63
0.2 < PSA $\leq 4.0$	219	77	20
PSA > 4.0	92	17	7

# Early versus Late

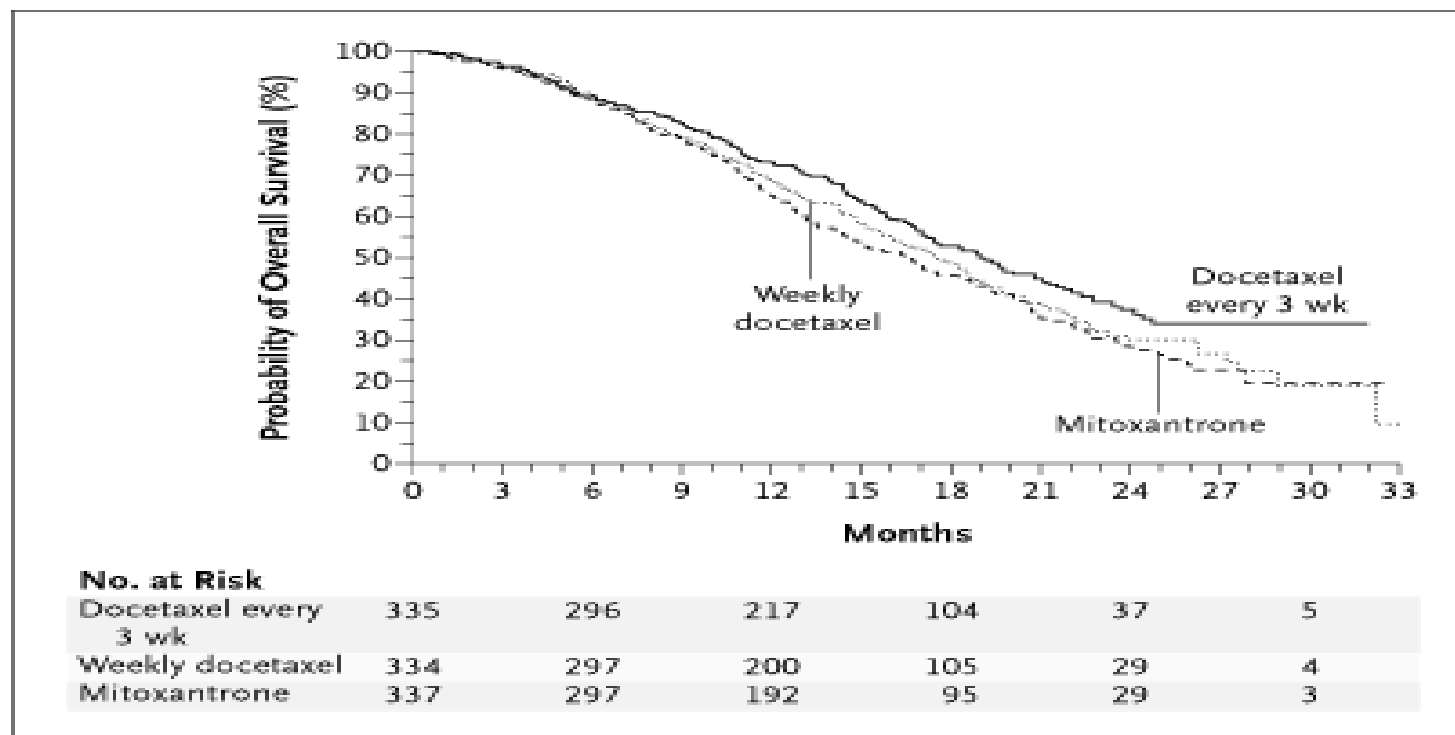
- Is the goal to improve survival?
- Suggestion of better survival and fewer metastasis with early therapy
- Trade off is side effects
- When to start therapy
  - PSA 10, 20, 30, 40??

# Experimental Approaches

- Early use of chemotherapy
  - Docetaxel/avastin and hormonal therapy combination: a possible knock-out blow
- Vaccines
  - PSA vaccine: been tested and looks promising, but not available
  - Provenge, it was tested in men who have castration resistant disease
- COX-2 inhibitors (Celebrex): modest
- Diet modification: modest effects



# Effect of docetaxel on prostate ca survival (NEJM, Oct 2004)



# Other approaches

- Statins: mixed data about statins and risk; many patients with rapid PSA<sub>dt</sub> already on lipitor et al
- Pomengranate juice: a trial is underway
- Coenzyme q 10
- Prostasol (Dr. Donsbach's product)

## Local trials for CRPC

- Taxotere/Avastin vs Taxotere awaiting data in 2010
- Abiraterone; a new lyase inhibitor ( better ketoconazole) (pre or post taxane)
- Provenge: approved
- Newer anti-androgens that are better than casodex (medivation 3100)
- Targeted therapy

# Abiraterone Acetate (CB7630)

- An irreversible inhibitor of CYP17 (P450c17, 17 $\alpha$  -hydroxylase/C<sub>17,20</sub>-lyase)
- A pro-drug of abiraterone (CB7598)
- Designed to reduce testosterone production by the testis, adrenal glands, and possibly prostate

# Clinical Trial Resources

- Centerwatch
  - <http://www.centerwatch.com/>
- NCI
  - <http://www.centerwatch.com/>

Our office is 617-735-2062 (G. Bublely)

# Summary

- PSA is used to monitor for relapse
- Detectable and rising PSA precede recurrent disease
- PSA doubling time
- Relapse may be distant or local
- Hormonal therapy effective but associated with side effects
- Expanding choice of experimental treatments