Memorial Sloan Kettering
Cancer Center

Prostate Cancer Recurrence

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Incidence and Mortality in 2018

- Incidence 2018-164,690
- Mortality 2018-29,430
  - Of those who die-
  - 1/3 of men present with advanced disease
  - 2/3 of men present with localized disease

Risk Factors

- Aging
- Race and Ethnic Background
- Dietary Factors
- Genetic Factors

Familial Prostate Cancer Genes

- Prostate cancer patients were prospectively enrolled in a study of tumor-normal sequencing for 76 genes associated with hereditary cancer predisposition.
- Pathogenic germline variants were detected in 71/362 (19.6%) of patients.
- Genetic testing based on current guidelines would not have identified 55.5% of those with actionable findings

Mandelkar et al JAMA 2018

Chemoprevention

The SELECT Trial

- Selenium and Vitamin E Cancer Prevention Trial
- 32,400 men
- 2 x 2 factorial design
  - Vitamin E vs placebo
  - Selenium vs placebo
- Endpoint: prostate cancer incidence

Chemoprevention: The SELECT Trial

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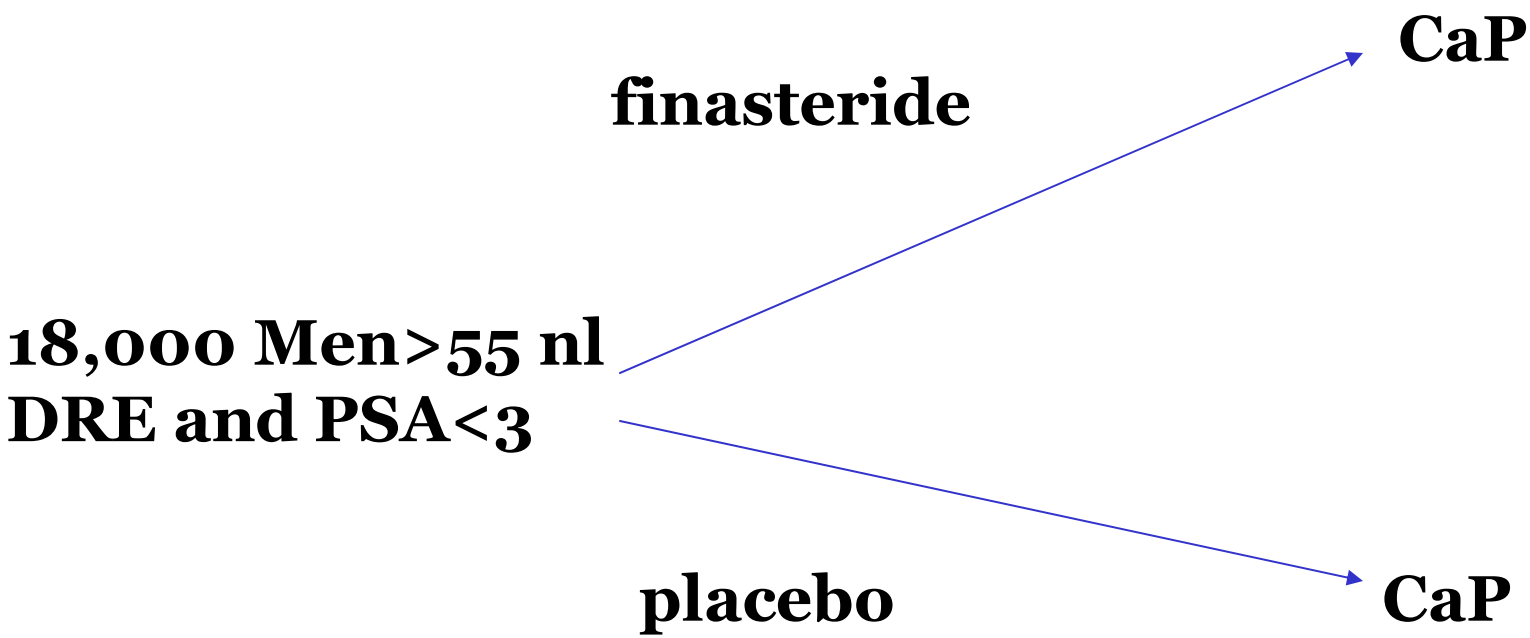
  - Vitamin E vs placebo
  - Selenium vs placebo
- Endpoint: prostate cancer incidence-null (Lippman et al JAMA 2009)
- More prostate cancer seen with Vitamin E supplementation (Klein et al JAMA 2011)

5-alpha reductase inhibitors for prostate cancer prevention

Finasteride Chemoprevention Study (PCPT)



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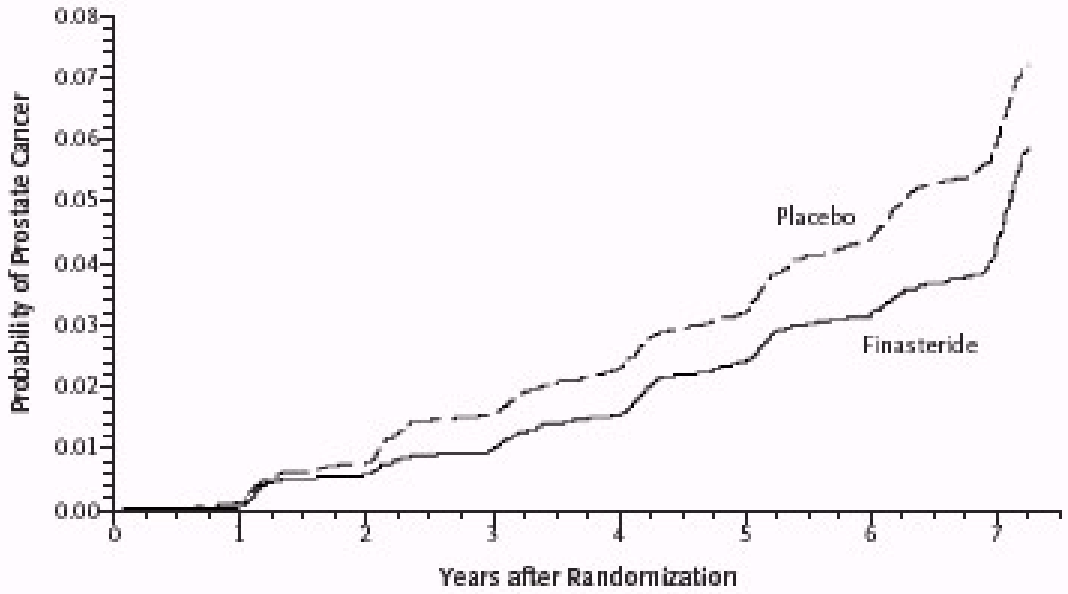


Placebo group							
Biopsy rate (%)	3.0	2.8	2.2	2.9	2.8	2.6	7.1
Total no. of cancers diagnosed	48	71	60	80	92	96	124
No. of grade 7–10 cancers	5	6	15	35	24	24	38
Finasteride group							
Biopsy rate (%)	3.3	2.0	2.1	2.5	2.1	2.2	7.0
Total no. of cancers diagnosed	42	35	39	68	78	51	122
No. of grade 7–10 cancers	11	11	17	31	28	26	64

Figure 1. **Cumulative Incidence of Prostate Cancer Diagnosed in a Biopsy Performed for Cause or after an Interim Procedure.**

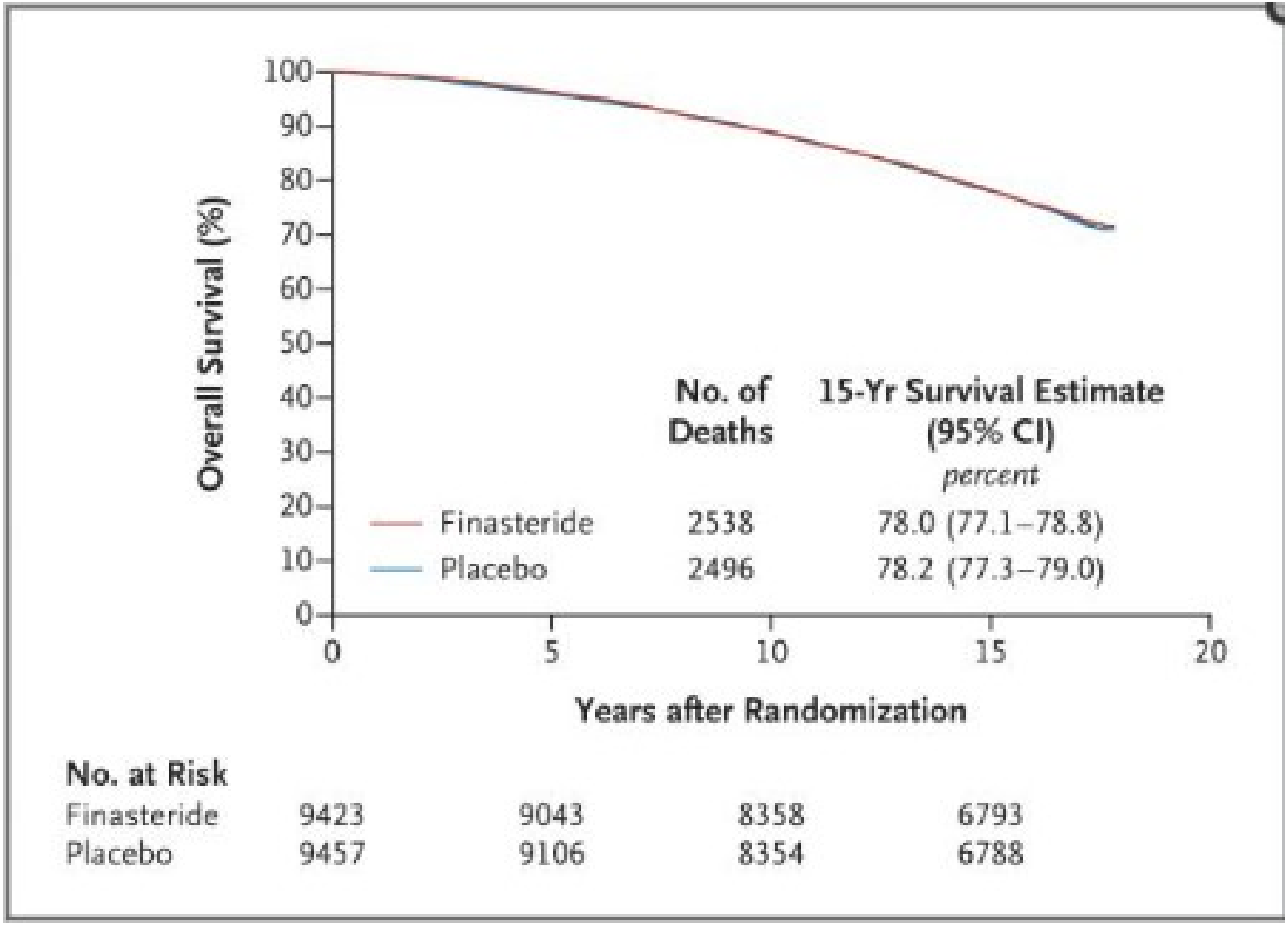
The number at risk is the number of surviving men still being followed who were free of prostate cancer, and the number of events includes all cases of prostate cancer detected on a biopsy performed for cause or after an interim procedure such as transurethral resection of the prostate.

PCPT-Conclusions

- Finasteride reduced the risk of prostate cancer by 25%
- Morbidity was minimal-high in placebo arm
- BUT 20% more Gleason 8-10
  - Biologically plausible or explained by a pathologic artifact?

Thompson et al NEJM 2003

No difference in survival



Thompson et al NEJM 2014

REDUCE Trial

- 8,200 men who had PSA between 2.5 ng/mL and 10 ng/mL (50 to 59 years old) or between 3.0 ng/mL and 10 ng/mL (60 to 75 years old) at initial screening.
- All men had one negative prostate biopsy within six months prior to study entry.
- Participants were randomly assigned to dutasteride or placebo; the study mandated 10 core biopsies at two and four years.
- **Dutasteride was associated with a 23% reduction in prostate cancer cases compared with placebo.**
- Dutasteride did not increase statistically the prevalence of high-grade disease.

Andriole et al NEJM 2010

Chemoprevention

- Antioxidants are not indicated
- 5 ARIs reduce risk of prostate cancer but long term effects are not yet known
  - FDA has chosen not to approve

Does PSA based Screening Reduce Mortality?

- PLCO
- ERSPC study
- Göteborg study

Randomized Screening Studies for Prostate Cancer

- PLCO (JNCI 2012)
  - 150,000 men
  - 52% contamination
  - Median follow-up 13 years
  - **No difference in prostate cancer mortality**
- European Screening Study (NEJM 2012)
  - 162,243 men
  - Median follow up 11 years of
  - **21% reduction in prostate cancer mortality p=0.001**
  - **NNT- 37 needed to be treated to prevent 1 death**
- Göteborg screening trial (Lancet Oncology 2010)
  - 20,000 men
  - Median follow-up of 14 years
  - **44% reduction in prostate cancer mortality (p=0.0002).**
  - **NNT=12 needed to be treated to prevent 1 death**

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Conclusions

- PSA screening likely reduces mortality
- Large amount of over-diagnosis and overtreatment (at least as seen in first 10 years)
- Low mortality of prostate cancer in first 10 years (few deaths occurred)

Impact of Screening

- Diagnosis made 5-10 years earlier (Gann et al JAMA 1995)
- Average age at diagnosis has fallen
- Proportion of advanced cases at diagnosis has decreased
- Proportion of “good risk” patients at diagnosis has increased
- Mortality rates had decreased in US by 25% but are now increasing again

US Preventive Services Task Force 2012 recommendation

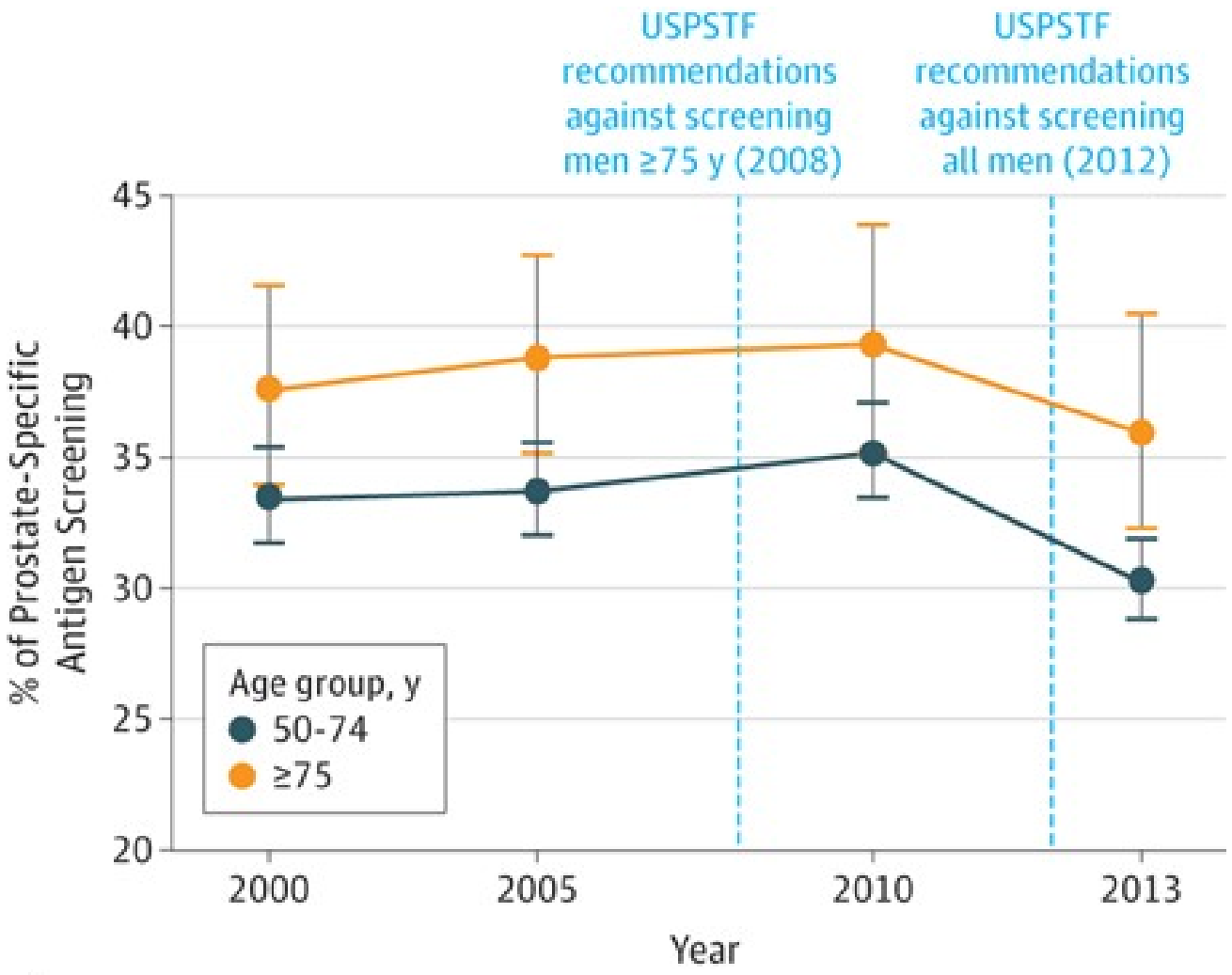
- The USPSTF recommended against PSA-based screening for prostate cancer in all men.

US Preventive Services Task Force 2017 recommendation

- The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)–based screening for prostate cancer.
- The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older.

US Preventive Services Task Force 2018 recommendation

- Clinicians should not screen men who do not express a preference for screening. (C recommendation: There is at least moderate certainty that the net benefit is small.)
- The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older. (D recommendation: There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits).



No. surveyed				
With age ≥75 y	761	834	707	984
With age 50-74 y	3937	4277	3891	5366

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Perhaps a more reasonable approach- PSA drawn early in life (2 studies)

- Men age 40 to 59 years who gave blood before random assignment in the PHS.
- PSA levels measured for 234 patients with PC and 711 age-matched controls.
- Risk of lethal PC was strongly associated with baseline PSA in midlife.
- Over 80% of lethal cases occurred in men with PSA above the median.

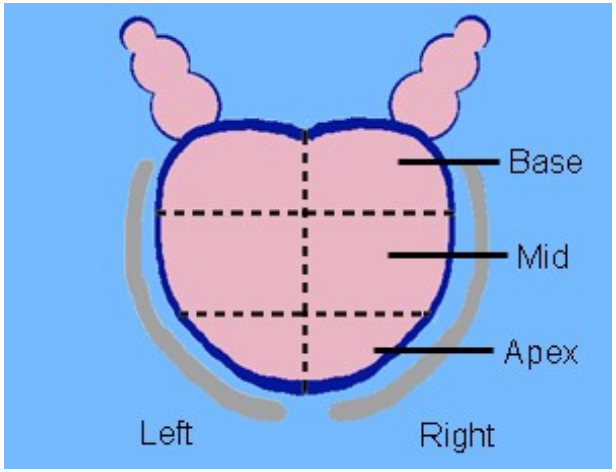
Preston et al J. Clin Onc 2016

Diagnosis Suspected

- Abnormal PSA
- Abnormal DRE
- CaP detected on TURP

How is Diagnosis Made

- Biopsy
  - TRUS guidance
  - > 12 cores by spring-loaded biopsy gun



D'Amico Risk Groups

- Low
  - PSA<10
  - And Gleason 6
  - And T1c or T2a
- Intermediate
  - PSA 10-20 or
  - Gleason 7 or
  - T2b
- High
  - PSA >20 or
  - Gleason 8 or above
  - Stage T2b or above

"Staging"- Characterizing the Primary Tumor

- PSA
- Gleason grade
- Clinical stage
- Volume
  - % positive biopsies
  - % of core that is positive
- PSA velocity prior to diagnosis*
- Multiparametric MRI*

Gleason's Pattern

1. Small, uniform glands
2. More stroma between glands
3. Distinctly infiltrative margins
4. Irregular masses of neoplastic glands
5. Only occasional gland formation

Well differentiated

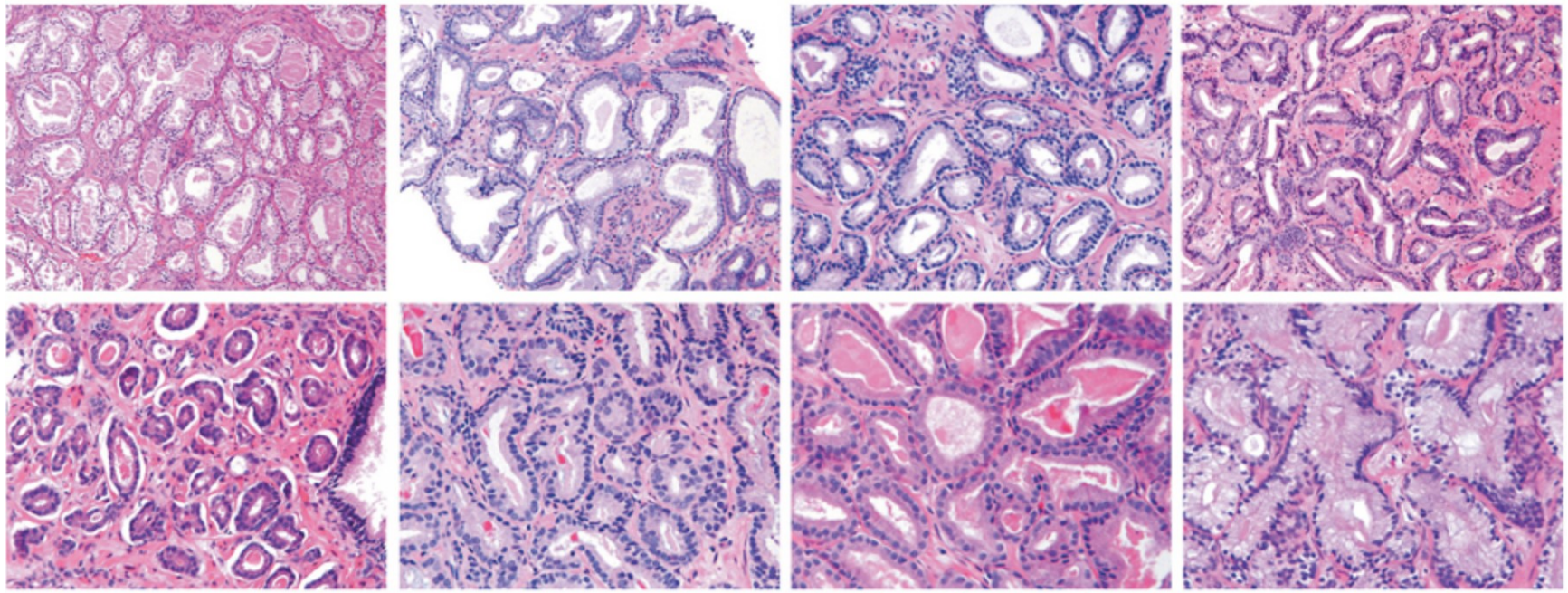
Moderately differentiated

Poorly diff./ Anaplastic

Gleason 3

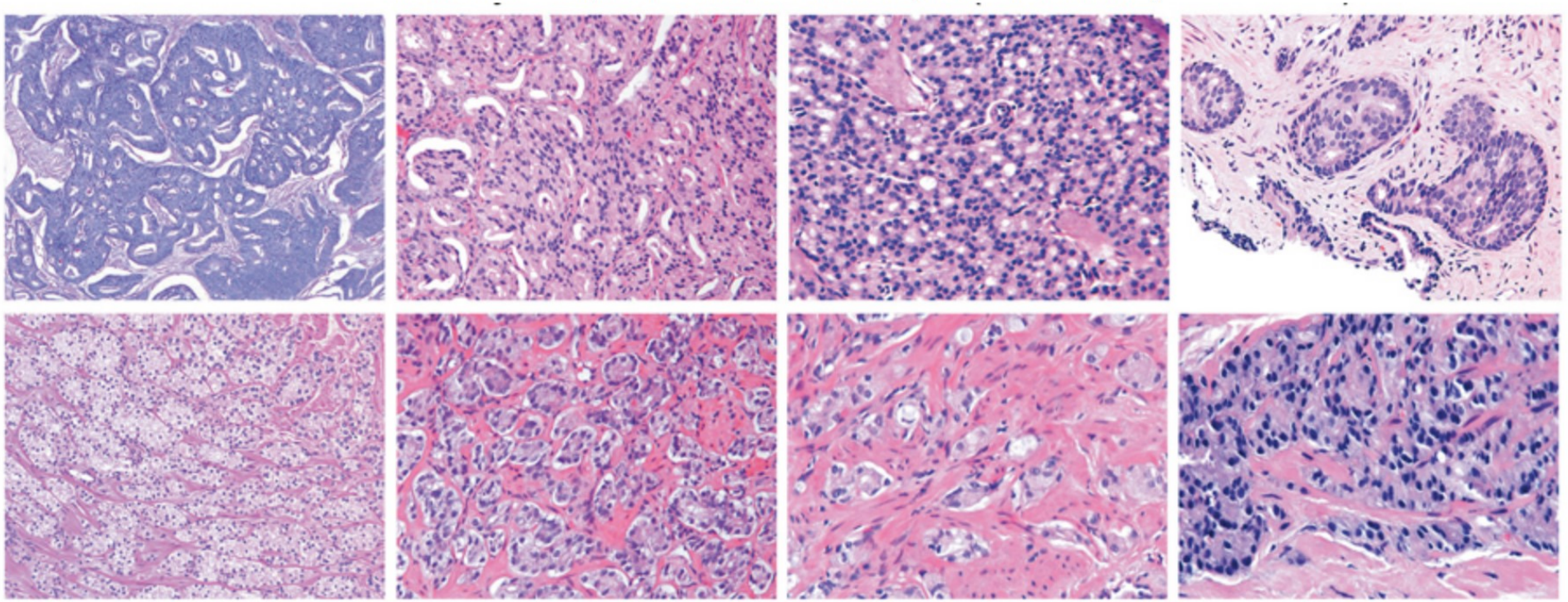
Download PDF version

Discrete Well-formed Glands (Gleason Patterns 1-3)

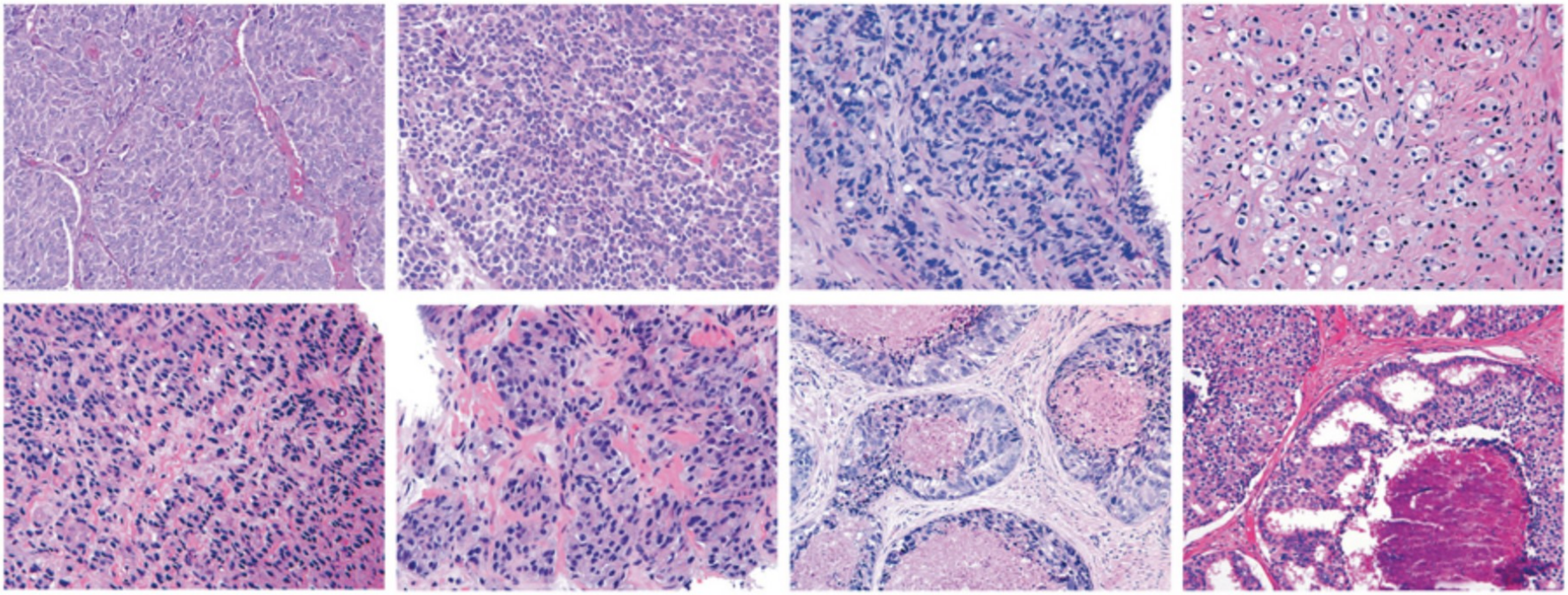


Gleason 4

Cribriform/Poorly-formed/Fused Glands (Gleason Pattern 4)

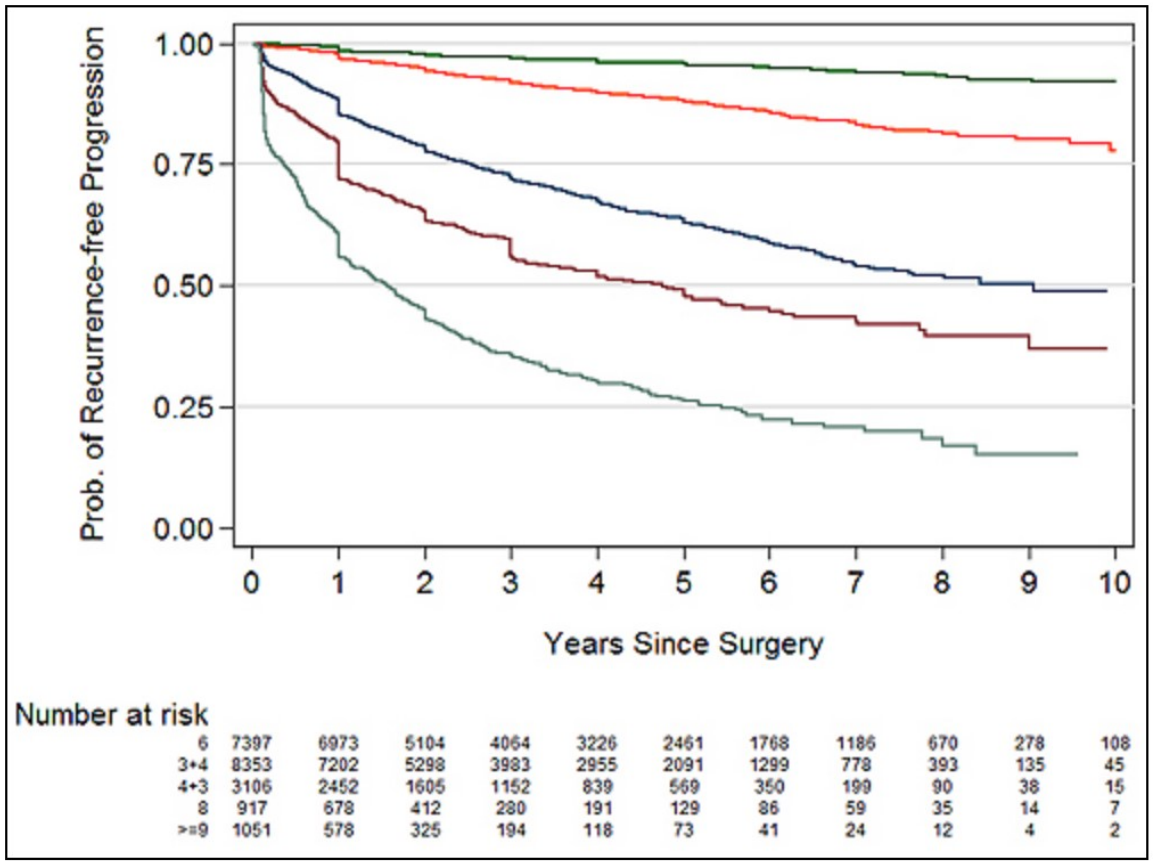


Gleason 5



New Grading System

1. The five-year biochemical recurrence-free progression probabilities for radical prostatectomy Grade Groups 1-5 were 96%, 88%, 63%, 48%, and 26%.



Gleason 3+3-35%
Gleason 3+4-41%
Gleason 4+3-16%
Gleason 4+4-4%
Gleason 9,10-4%

Reasonable Treatment Options

- Low Risk
  - **Active surveillance versus watchful waiting**
  - Radical prostatectomy
  - Brachytherapy
  - External beam XRT

Reasonable Treatment Options

- Intermediate risk
  - Radical prostatectomy
  - XRT+ADT (“short term”)

Reasonable Treatment Options

- High Risk and locally advanced
  - External beam XRT +/- brachytherapy +/- ADT (“long term”)
  - Experimental approaches such as neoadjuvant ADT plus surgery

Adjuvant Therapy

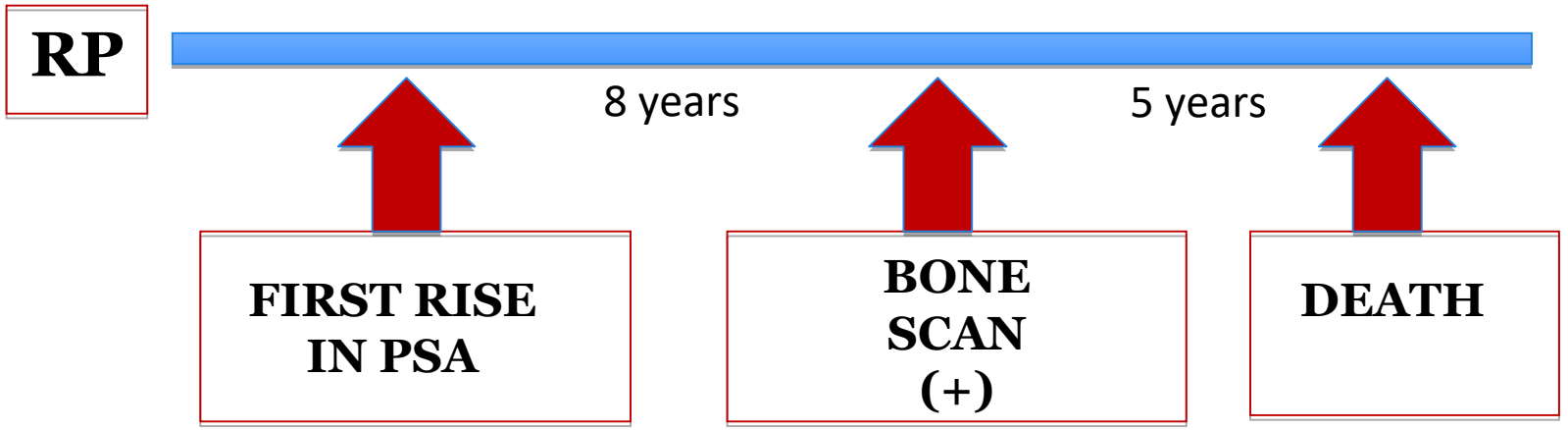
- Adjuvant radiation ie radiation post radical prostatectomy in “high risk” patients
  - Three studies demonstrating PFS benefit
  - One study (SWOG) showed OS benefit
  - Adjuvant versus early salvage still controversial
- Adjuvant chemotherapy
  - No proven benefit
- Adjuvant ADT after RP or XRT
  - ?value of ADT including abiraterone

What is recurrence?

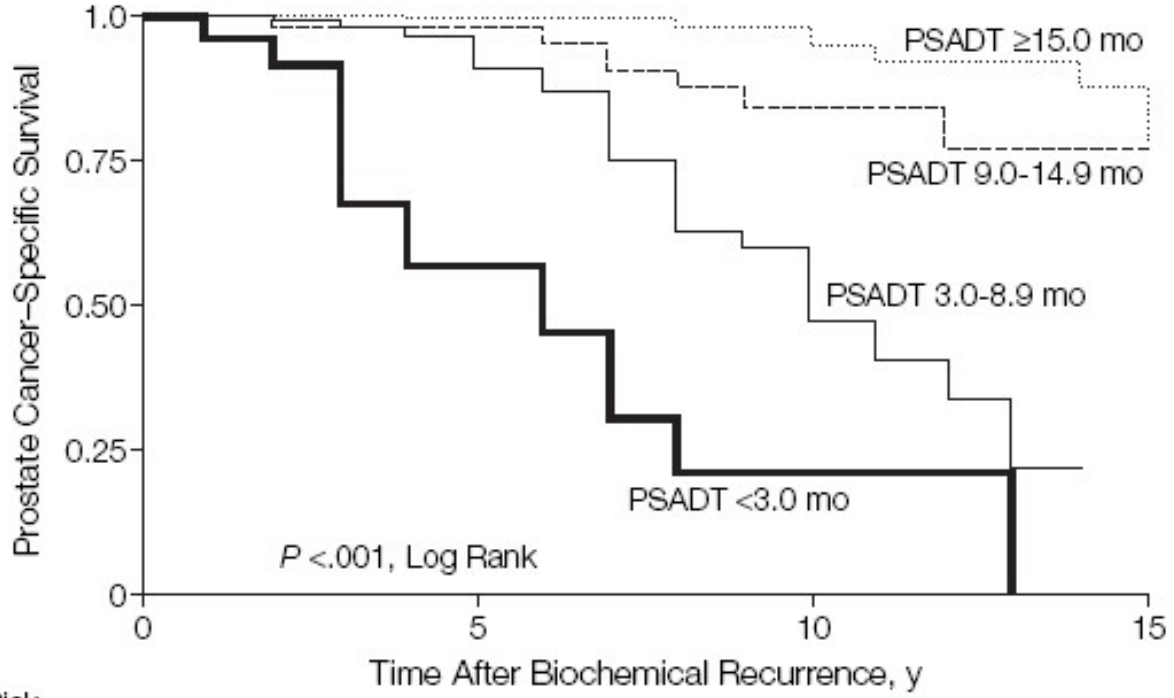
- Prior to PSA, the development of metastases
- With use of PSA
  - After radical prostatectomy
    - Different definitions but a rise in PSA above 0.1 is indicative or relapse
  - After radiation
    - Nadir +2 and rising

What is the natural history of patients who relapse after local therapy?

- 304 men relapsed after surgery;
- No hormones until (+) bone scan; and
- Time to PSA rise, Gleason, PSADT were predictors of survival.



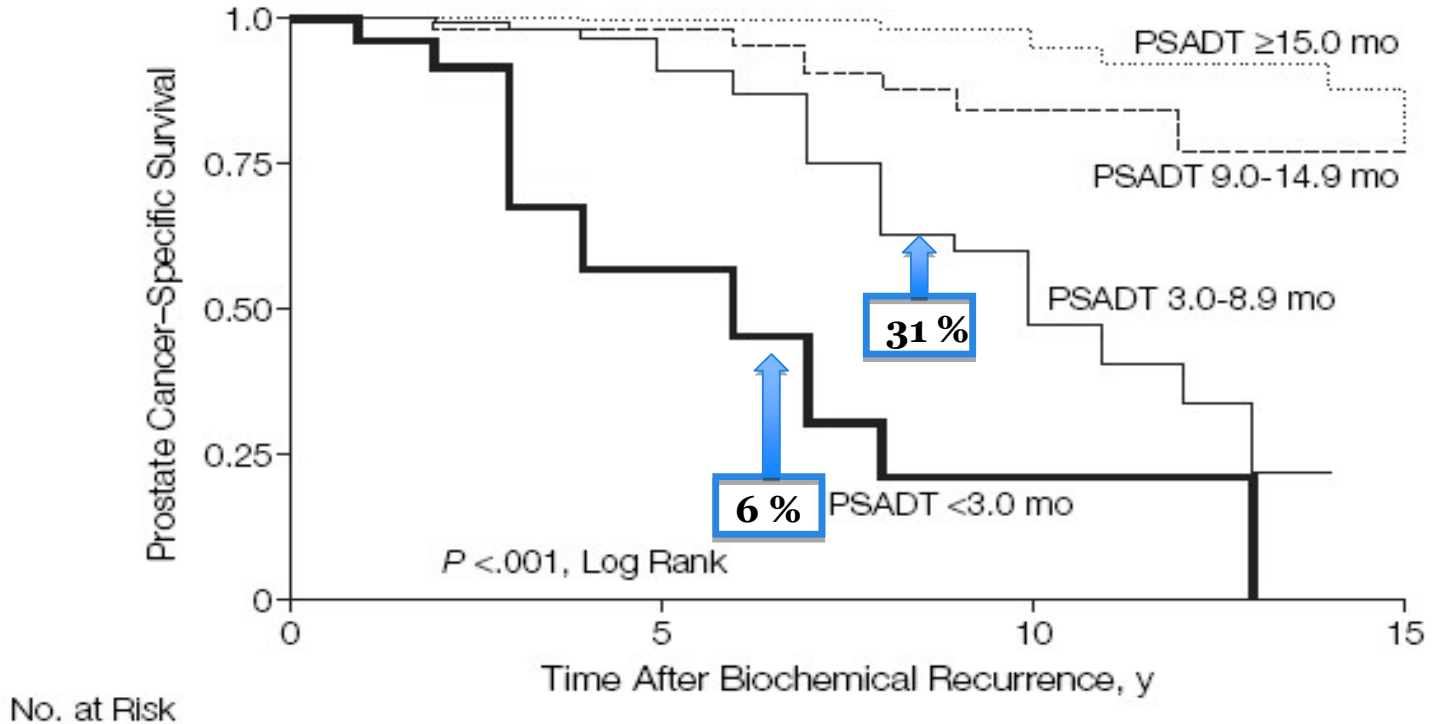
Patients with a Rising PSA- Importance of PSADT



No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

Freedland et al JAMA 2005

Patients with a Rising PSA- Importance of PSADT (continued)



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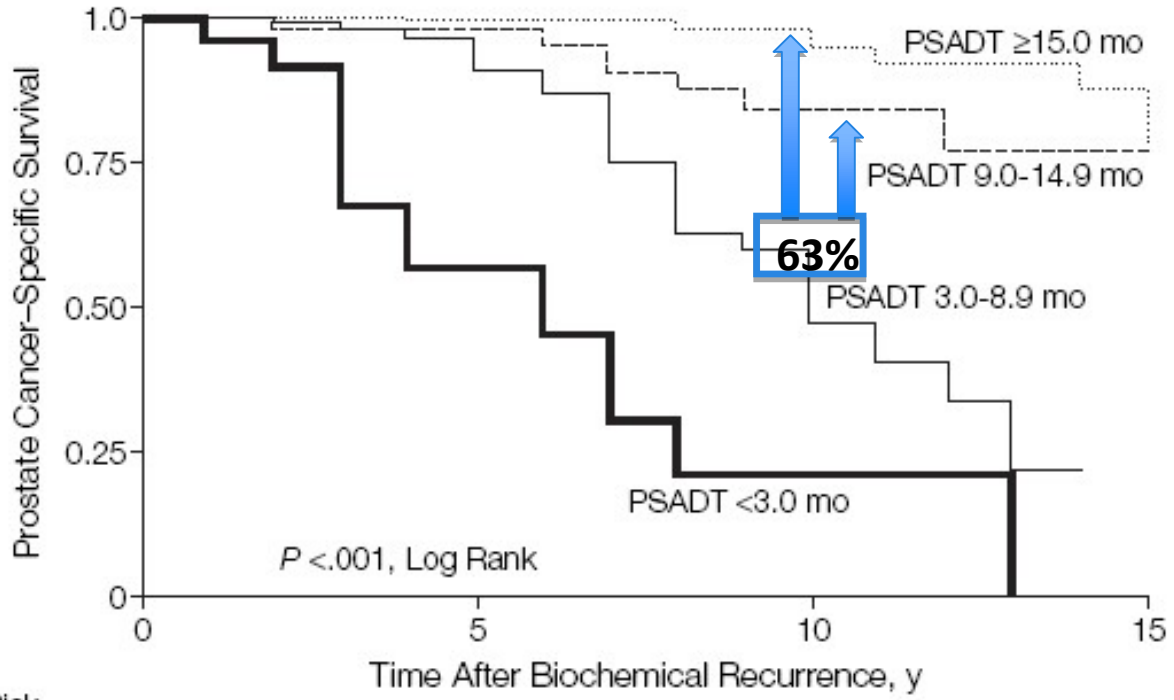

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Androgen Deprivation Therapy (ADT)

- Decreases serum testosterone to “castrate” levels;
- Primary treatment for men with metastatic disease;
  - Most men are treated with ADT before they develop metastases.
- PSA “response rate” very high (>99%); and
- PSA “response rate” is a result of
  - Decreased expression of PSA gene
  - Renders cells quiescent
  - Cell kill-apoptosis

Intermittent versus Continuous ADT

NCIC/PR7-Intermittent vs Continuous: Non-Metastatic Disease

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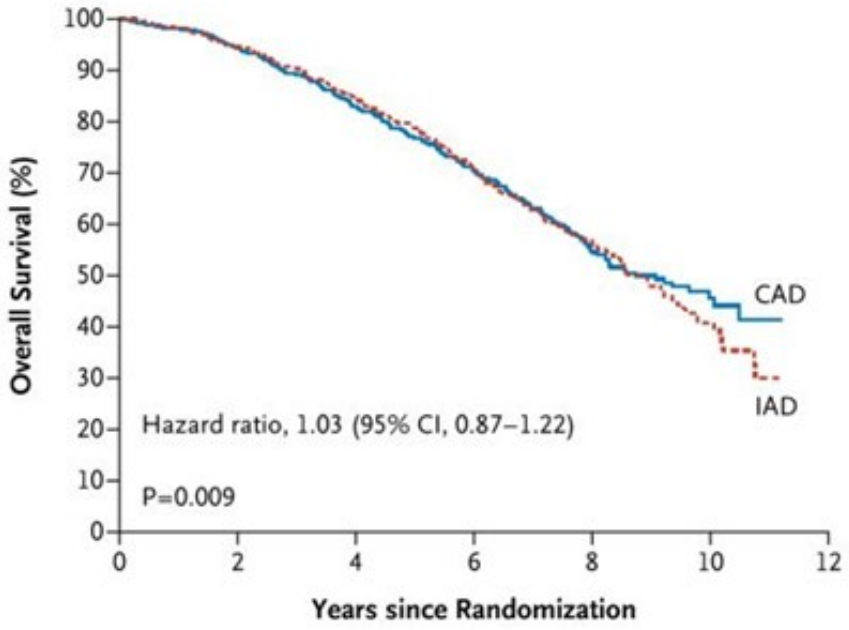

No. at Risk							
CAD	696	652	561	319	125	35	0
IAD	690	651	571	327	140	34	0

Crook et al (NEJM 2010)

SWOG 9346-Intermittent vs Continuous: Metastatic Disease

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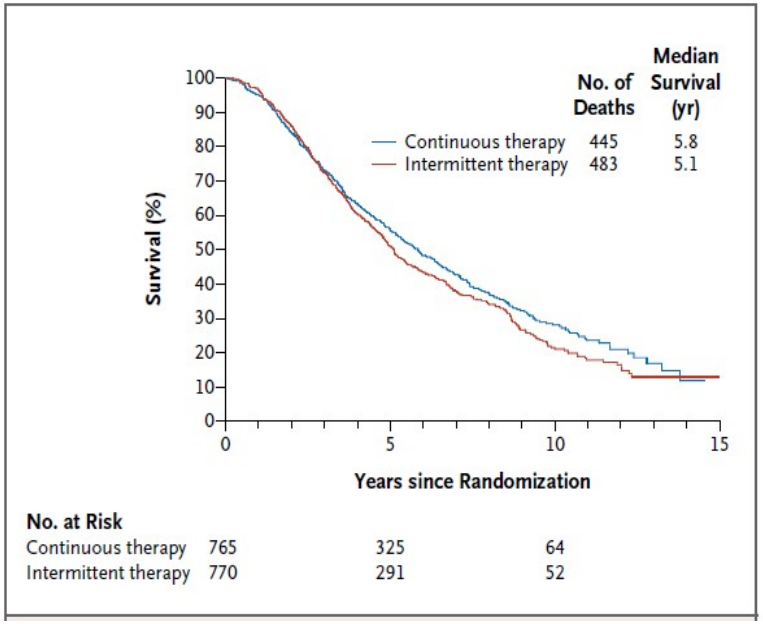
SWOG led Intergroup trial
Metastatic Prostate Ca
Starting ADT (3040 men)

Hazard Ratio for death with int Rx
1.10; 90% CI - 0.99 to 1.23

Exceeded the upper boundary for
noninferiority (cannot rule out a 20%
greater risk of death with int Rx vs Cont)



Hussain et al (NEJM 2013)

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Intermittent versus Continuous ADT

- NCIC/PR7-non metastatic (Crook et al NEJM 2010)-NS difference
- SWOG 9346-metastatic (Hussain et al NEJM 2013)-HR 1.09 (intermittent slightly inferior)
- Intermittent reasonable option and preferable for patients with non-metastatic
- For patients with metastases, needs to be individualized

More sensitive scans can detect “oligometastatic disease”

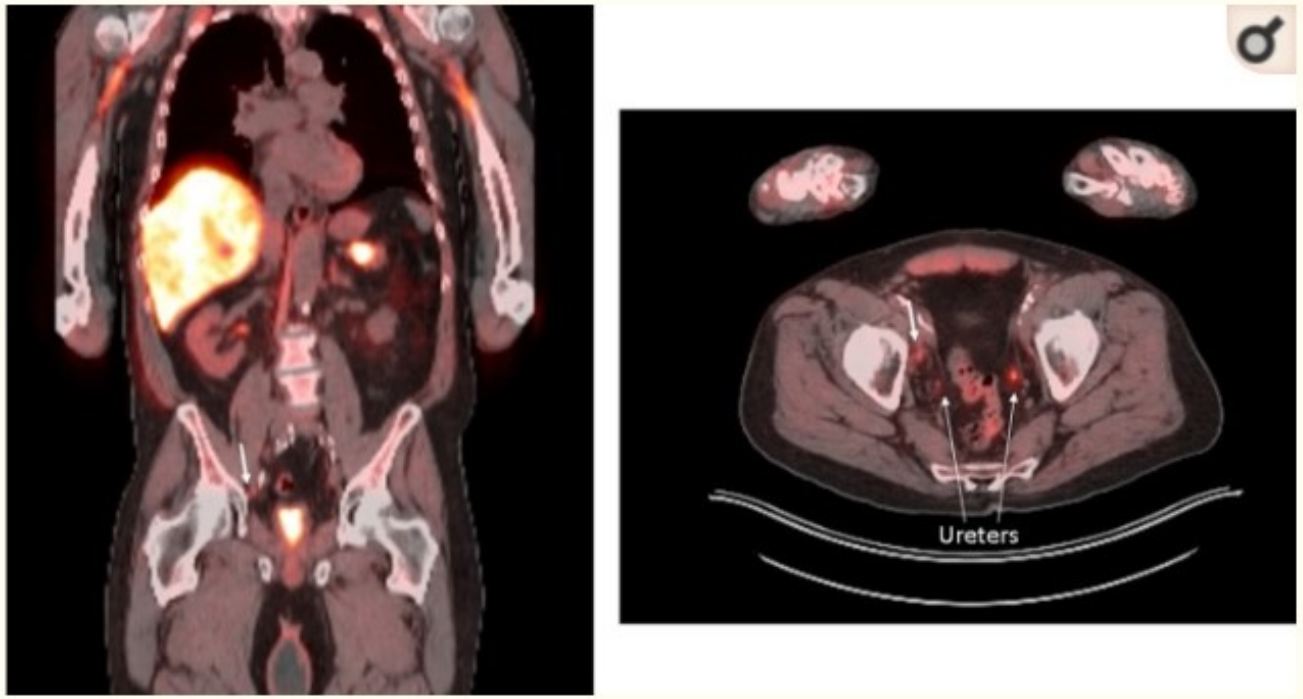

FIG. 1.

Flucicolvine PET/CT scan showing 1.1 × 0.5 cm mildly enlarged *right* pelvic sidewall lymph node with focally increased uptake suspicious for metastatic prostate cancer. The *thick white arrows* point to site of positive lymph node. *Thin white arrows* point to ureters. PET = positron emission tomography.

The Future-preventing or treating recurrence

- Treatment of oligometastatic disease
- Intense androgen deprivation therapy
- Targeted therapy-precision medicine
- Immunotherapy