Prostate Cancer PSA Controversy and Emergence of Active Surveillance

Christopher J. Kane MD
Professor of Surgery, Chief of Urology
C Lowell and JoEllen Parsons Chair in Urology

UC San Diego
SCHOOL OF MEDICINE

Disclosures

- NCI Kidney Cancer Task Force Co-Chair
- Intuitive surgical grant support and CME support
- AMGEN honoraria
- Janssen Inc. consultant and honoraria
- Genprobe consultant
- Dendreon consultant

UC San Diego
SCHOOL OF MEDICINE

Prostate Cancer in Developed Countries –*Known 2012*

- **•39% Reduction in mortality; Accounting for 20% of the overall reduction in cancer mortality in men.**
- *–Half of this appears related to early detection*
- **•Screening of healthy, young, well -informed men with serum PSA *reduces significantly the risk of dying of prostate cancer* (21% –44%)**
- **•It does so at the *risk of over detection*–detecting disease which would not have become clinically apparent over a patient's lifetime if left untreated**
- **•Detection and treatment (over-treatment) are, currently, too tightly linked**

UC San Diego
SCHOOL OF MEDICINE

USPSTF

- Gives prostate cancer screening a D grade.
- The definite evidence of harm far outweighs the unproven benefit of PSA screening
- 8,000 comments received concerning the recommendation in the first 30 days (comment period).

UC San Diego
SCHOOL OF MEDICINE

Why?

- The randomized trials of PSA screening show little improvement in mortality at a high cost of treatment
- PSA is a poor screening test with poor specificity so many men get prostate biopsies and worry and don't have cancer
- Many men who are treated had bad side effects, surgical complications, erectile dysfunction and incontinence and don't benefit from treatment

UC San Diego
SCHOOL OF MEDICINE

Recent studies

Screening revisited:

•PLCO (Prostate, Lung, Colorectal and Ovary) - Andriole GL, Crawford ED, Grubb RL, et al.: Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009, 360:1310–1319.

•ERSPC (European Randomized Screening for Prostate Cancer) - Schroder FH, Hugosson J, Roobol MJ, et al.: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009, 360:1320–1328

UC San Diego
SCHOOL OF MEDICINE

Screening

PLCO:

- Randomization 50-74 yo men from 1993-2001
  - 38,350 men to intervention vs 38,355 to control
  - Screening: Annual PSA (6 yrs) and DRE (4 yrs)
  - Control: NO screening
  - Follow for ≥ 13 years

- Goal: whether or not screening reduces *Prostate Cancer Mortality*

UC San Diego
SCHOOL of MEDICINE

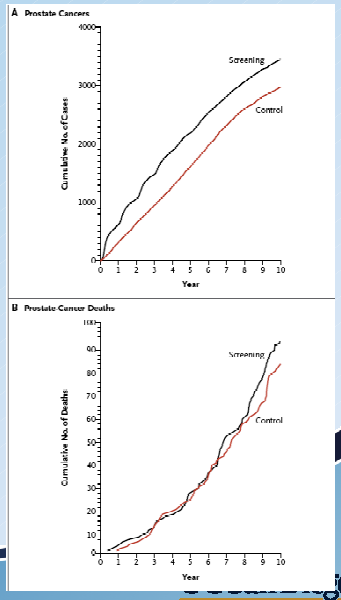
Screening

PLCO:

- Findings after median 11.5 yrs

  - Prostate Ca diagnosis:
    - Screened-9% vs Control-7.8%

  - Prostate Ca Mortality:
    - Screened-0.24% vs Control-0.21%



Andriole et al, NEJM, 2009

UC San Diego
SCHOOL of MEDICINE

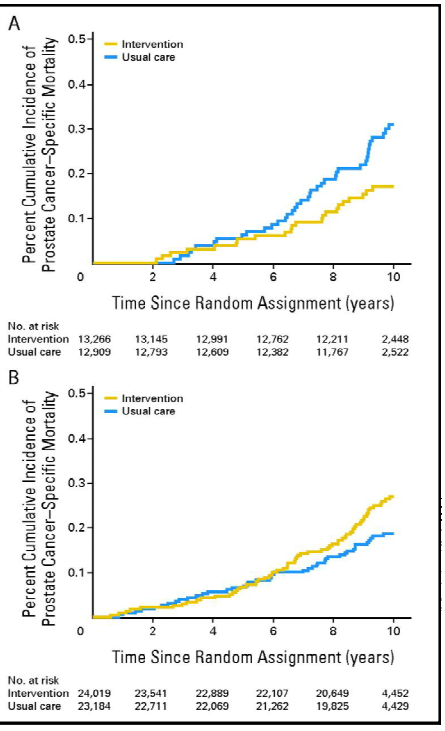
PLCO Contamination:

- Flaws:
  - Assumed that 10% with prev screening in control arm would continue
  - In actuality, Control Arm,
    - 44% of men in each arm had ≥1 PSA test before randomization
    - During trial, 52% had undergone PSA screening and 46% with DRE
  - Controls:
    - Only 15% decreased diagnosis
    - 93% of cancers were asymptomatic, organ-confined
  - Follow-up was 11.5 years from randomization, NOT treatment

UC San Diego
SCHOOL OF MEDICINE

- Re -analyzed PLCO
- Stratified by co – morbidity
- 35.7% of men had minimal co –morbidity
- Significant decreased risk of prostate cancer mortality in those with minimal or no co - morbidity, *HR 0.56*
- NNS/NNT *723 and 5*

Crawford E D et al. JCO 2011;29:355-361



Screening

ERSPC:

•162,243 men 55-69 yo randomized from 1991-2003

•Median follow-up - 9 years

•Screening:

- •Did NOT require annual PSA – only 2.1 tests averaged over course of study
- •DRE variable, but usually only if equivocal PSA

UC San Diego SCHOOL OF MEDICINE

ERSPC:

•Prostate Cancer diagnosis: Screened-8.2% vs Control-4.8

•Death from prostate cancer: screened arm RR was 0.80 (95% CI 0.67–0.95; P=0.01)

- •Curves began to diverge at 7-8 years

•NNS to prevent 1 death=1410; NNT=48

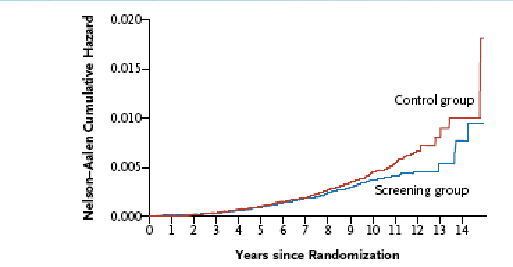


Figure 2. Cumulative Risk of Death from Prostate Cancer.

Schroder et al, NEJM, 2009

UC San Diego SCHOOL OF MEDICINE

Screening - Newer data

Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

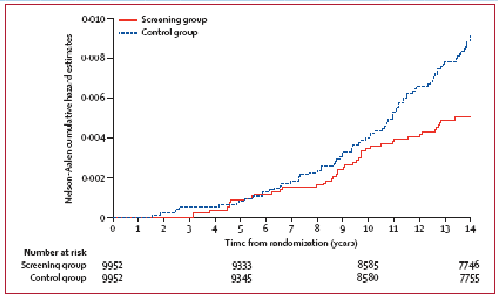
Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

- 20,000 men aged 50-64 yrs
- Screened every 2 years
- Followed median 14 years
- Screened:
  - Prostate cancer diagnosed: Screened-12.7% vs Control-8.2%
  - Prostate cancer death: Screened-0.5% vs Control-0.9%
    - RR Reduction = 0.56 (95%CI, 0.39-0.82, p=0.002)
      - *Compared to ERSPC = 0.8*

Hugosson et al, Lancet Oncol 2010

UC San Diego SCHOOL OF MEDICINE

Screening - Newer data



- Younger patients – more likely to have incurable cancer at first screen
- Lower PSA threshold for biopsy (2.5-3 vs 4) and more frequent screening (2 vs 4 yrs)
- Lower contamination (3% vs 44%)
- ***Longer follow-up with improved RR***
- NNS = 293 and NNT = 12 to prevent 1 Death
  - Not significantly different from Breast or Colorectal cancer

UC San Diego SCHOOL OF MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

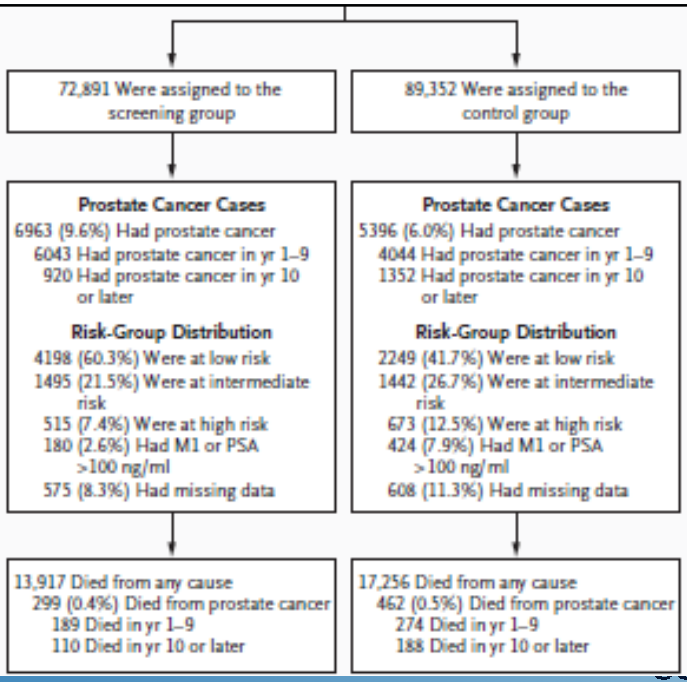
ESTABLISHED IN 1812 MARCH 15, 2012 VOL. 366 NO. 11

Prostate-Cancer Mortality at 11 Years of Follow-up

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Alvaro Páez, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Sigrid Carlsson, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Paula M. Kujala, M.D., Bert G. Blijenberg, Ph.D., Ulf-Hakan Stenman, M.D., Andreas Huber, M.D., Kimmo Taari, M.D., Matti Hakama, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

- Now with 11 years of follow-up, the relative reduction in the risk of death from prostate cancer is 21% (RR 0.79, 95% CI 0.68-.91 p=0.001), 29% after adjustment for noncompliance.
- NNS now 1055, NNT 37.

UC San Diego SCHOOL of MEDICINE



UC San Diego SCHOOL of MEDICINE

Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.

UC San Diego SCHOOL of MEDICINE

So in what ways were they wrong?

- There is strong evidence that radical prostatectomy saves lives over observation (38% prostate cancer mortality reduction, 25% all cause mortality reduction) at 15 years (Bill-Axelson NEJM 2011; 364:1708-17)
- Diagnostic procedures to detect prostate cancer are common in both screened and unscreened populations, they just occur later in unscreened men.

UC San Diego SCHOOL of MEDICINE

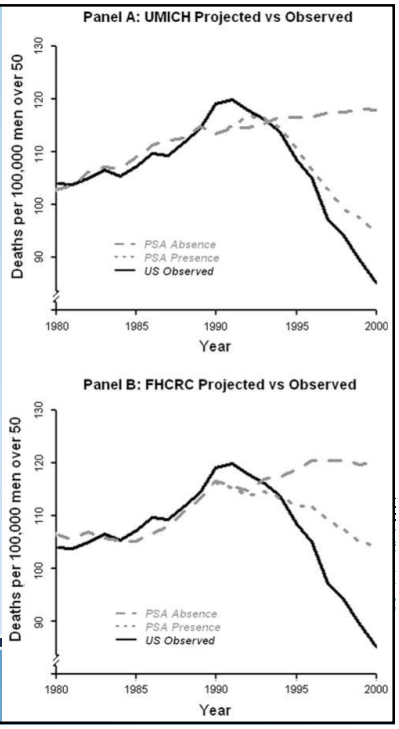
- The task force minimized the burden of living with advanced cancer and primarily looked at survival (bone mets, obstruction, fractures etc…)
- The task force did not adequately consider at risk populations (AA and FH men)
- The task force minimized the epidemiologic data that since PSA testing began in the 1990's there has been a 40% reduction in prostate cancer mortality and 75% reduction in presentation with advanced disease.

UC San Diego
SCHOOL OF MEDICINE

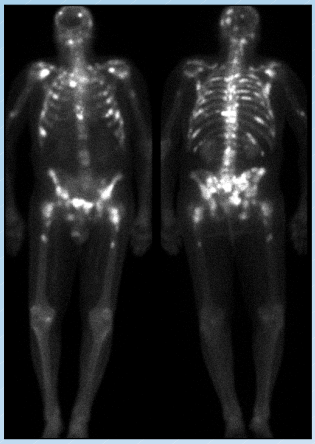
Defining the proportion of mortality reduction from PSA screening and early detection

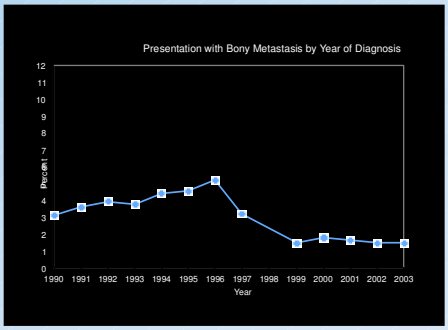
- Two models generated to determine the proportion of decline in mortality from early detection vs. improved treatment
- 45-70% mortality reduction from early detection

Etzioni et al Cancer Causes Control. 2008 Mar;19(2):175-81.



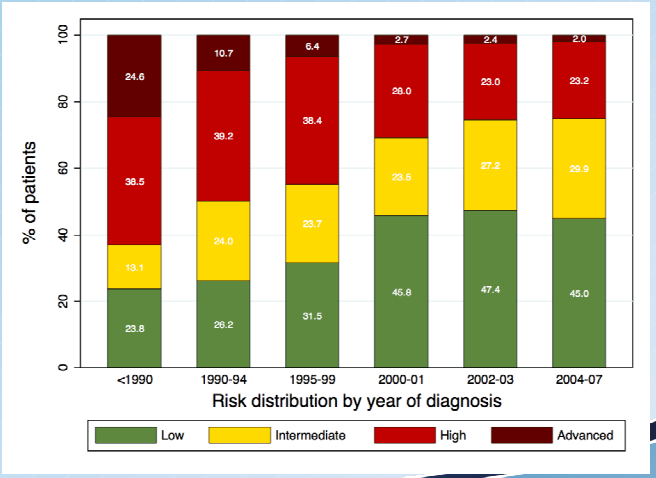
Stage Evolution





UC San Diego
SCHOOL OF MEDICINE

The Changing Face of Prostate Cancer in the United States



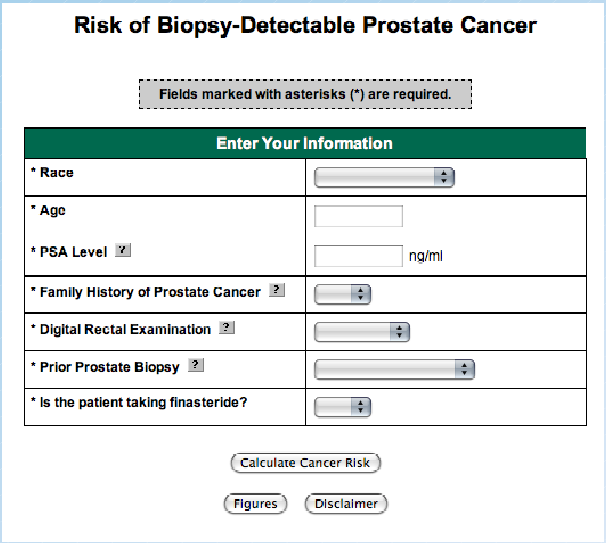
J Urol 2007; 178:S14; J Urol. 2009 Apr;181(4):1622-7

UC San Diego
SCHOOL OF MEDICINE

So how do we answer the screening concerns?

- Improve the specificity of PSA
- Stop screening men who are unlikely to benefit
- Diminish overtreatment by offering active surveillance more than currently

UC San Diego SCHOOL OF MEDICINE



http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp

UC San Diego SCHOOL OF MEDICINE

Rational for Earlier Screening

- A baseline PSA level above the median for age 40 is a strong predictor of prostate cancer
- The age adjusted mortality rate for prostate cancer between ages 50 and 65 is not insignificant. Such men may have been cured by earlier diagnosis and treatment
- Younger men are more likely to have curable cancer
- PSA is a more specific test for cancer in younger men
- Earlier and less frequent testing might reduce mortality and costs compared to annual testing beginning later

JAMA, 284: 1399, 2000, JAMA, 277: 1456, 1997

UC San Diego SCHOOL OF MEDICINE

Chemoprevention Before Age 50

Focusing on high -risk subgroups

- Based on a unscreened cohort from Malmö a single PSA before age 50 is a strong predictor of advanced CaP occurring up to 25 years subsequently
- Data from PCPT were used to model chemopreventive treatment strategies based on PSA level
- Treating men at a certain PSA level reduced the treatment rate by 83% and resulted in a cancer rate only 1.1% higher than treating all men

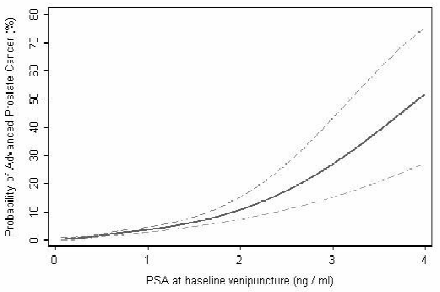


Fig 2 Predicted probability of advanced CaP by PSA at age 44–50

BMC Med. 2008; 6: 6
J Clin Oncol. 2010 Mar 1;28(7):1112-6

UC San Diego SCHOOL OF MEDICINE

Risk Stratification

- PSA
- Clinical Stage
- Gleason Grade
- Number and extent of positive biopsies
- PSA velocity/ PSA kinetics
- Obesity

UC San Diego SCHOOL OF MEDICINE

UCSF CAPRA

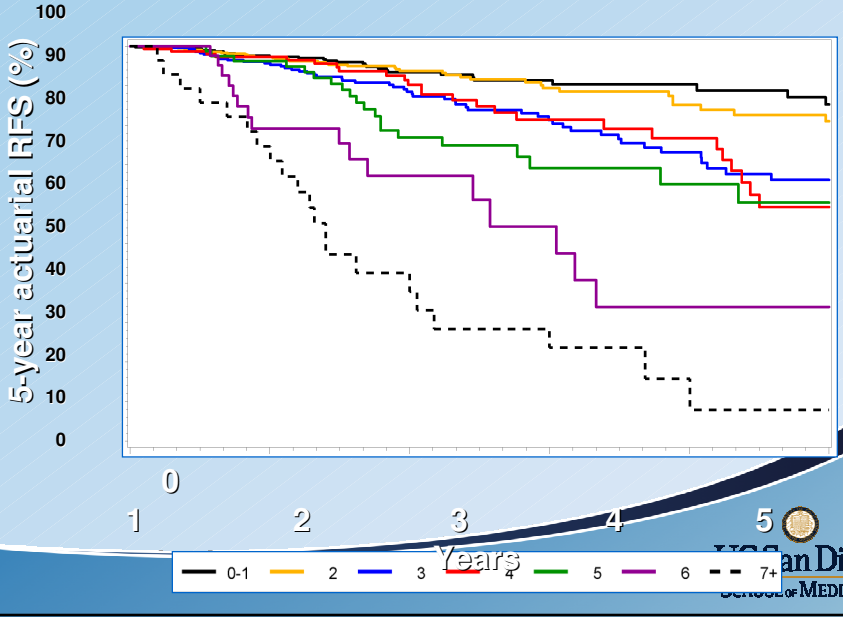
Variable	Level	Points	N	% of cohort	% fail
PSA	2.1-6	0	721	50	9
	6.1-10	1	453	31	14
	10.1-20	2	209	15	28
	20.1-30	3	36	3	33
	>30	4	20	1	55
Gleason	1-3/1-3	0	1068	74	12
	1-3/4-5	1	239	17	20
	4-5/1-5	3	132	9	28
T-stage	T1/T2	0	1410	98	14
	T3a	1	29	2	21
% pos bx	<34%	0	911	63	10
	≥34%	1	528	37	22
Age	<50	0	51	4	6
	≥50	1	1388	96	15

Cooperberg et al J Urol June 2005

Score calculated by totaling each characteristic, range 0-10

UC San Diego SCHOOL OF MEDICINE

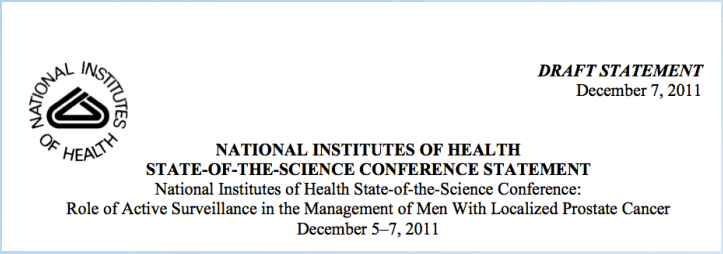
The UCSF-CAPRA



Active Surveillance

- Advantages
  - Avoids risk from surgery or radiation therapy
  - Decreased cost
- Disadvantages
  - Inaccurate staging/grading may put patient at risk for metastases
  - Stress
  - Side effects from repeat biopsy

A busy year for AS



DRAFT STATEMENT
December 7, 2011

NATIONAL INSTITUTES OF HEALTH
STATE-OF-THE-SCIENCE CONFERENCE STATEMENT
National Institutes of Health State-of-the-Science Conference:
Role of Active Surveillance in the Management of Men With Localized Prostate Cancer
December 5–7, 2011

ESO Inside Track Conference
ACTIVE SURVEILLANCE FOR LOW RISK PROSTATE CANCER
January 12-13 , 2012
Rotterdam, The Netherlands

UC San Diego
SCHOOL OF MEDICINE

Clinically Indolent Disease

How to define an "insignificant tumor"?
•Clinical stage T1c or T2a, PSA under 10 ng/ml
•PSA density < 0.15ng/ml/cm^3

<u>And absence of</u>
•Any Gleason pattern 4 or 5
•3 cores involved
•> 50% of core involved
•In a 12 core Bx

Epstein. JAMA 1994;271:368

UC San Diego
SCHOOL OF MEDICINE

Surveillance: Recent Experiences

Institution (PI)	Total (n)	Strict* (n)	Median age	Inclusion criteria
Royal Marsden (Parker)	326	326	67	Gleason ≤3+4, PSA ≤15 ng/ml, cT stage ≤2a, ≤50% of cores positive
University of Miami (Soloway)	230	230	64	Gleason ≤6, PSA ≤10 ng/ml, cT stage ≤2, ≥2 cores, ≤20% of any core positive
Johns Hopkins (Carter)	769	633	66	Gleason ≤3+3, PSAD ≤0.15 ng/ml/ml, cT stage 1, ≤2 cores positive, ≤50% of any core positive
UCSF (Carroll)	640	376	62	Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2, ≤33% of cores positive, ≤50% of any core positive
University of Toronto (Klotz)	453	453	70	Gleason ≤6, PSA ≤10 ng/ml (until Jan 2000, for men >70: Gleason ≤3+4, PSA ≤15 ng/ml)
ERSPC Sites (Schröder)	988	616	66	Gleason ≤3+3, PSA ≤10 ng/ml, PSAD ≤0.2 ng/ml/ml, cT stage 1c-2, ≥2 cores positive
Memorial-Sloan Kettering (Eastham)	238	238	64	Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2a, ≤3 cores positive, ≤50% of any core positive
TOTAL	3644	2872	67	

UC San Diego SCHOOL OF MEDICINE

Cooperberg et al. J Clin Oncol 29:3669, 2012.

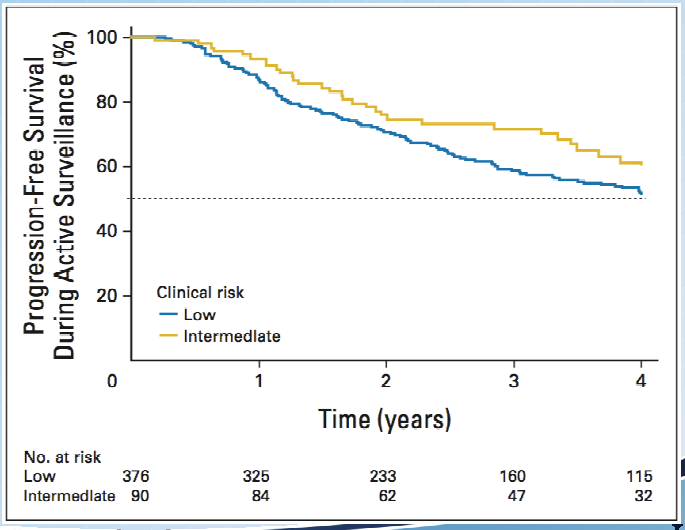
Surveillance: Recent Experiences

Institution	Median follow-up (months)	Progression by grade / volume (%)	Progression by PSA / PSA kinetics (%)	Treatment without progression (%)	OS (%)	CSS (%)	PFS (%)
Royal Marsden	22	13	18	2	98	100	73
University of Miami	32	10	NR	NR	100	100	86
Johns Hopkins	32	14	NR*	9	98	100	54
UCSF	47	35	5/11†	8	97	100	54
University of Toronto	82	9‡	14‡	3	68	97	70
ERSPC Sites	52	NR§	13	18	91	99	68
Memorial-Sloan Kettering	22	13	14	11	n/a	n/a	n/a

UC San Diego SCHOOL OF MEDICINE

Cooperberg et al. J Clin Oncol 29:3669, 2012

Outcomes of Surveillance



UC San Diego SCHOOL of MEDICINE

Cooperberg et al. J Clin Oncol 2011; 29:228

Economic Impact of AS

- The cost of AS is driven by repeated prostate biopsies, clinical visits and imaging
- Other treatments for low risk disease have higher up-front costs (RP<Brachy<IMRT/ADT)
- Costs for AS are lower that curative therapies through 10 years in Markov modeling
- Physician reimbursement for AS is higher than other therapies after 5 years
- Periods of AS with intensive assessment then transitioning to active treatment highest cost

Keegan et al. Cancer. 2012 Jul 15;118(14):3512-8

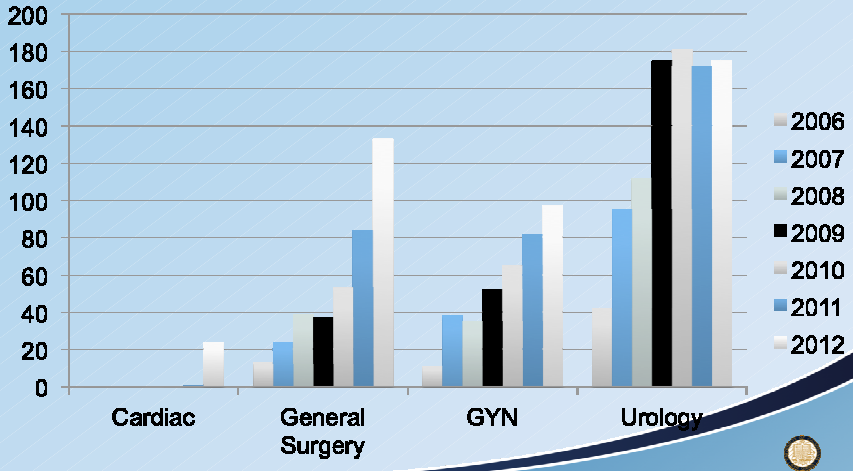
UC San Diego SCHOOL of MEDICINE

Advantages to the RALP

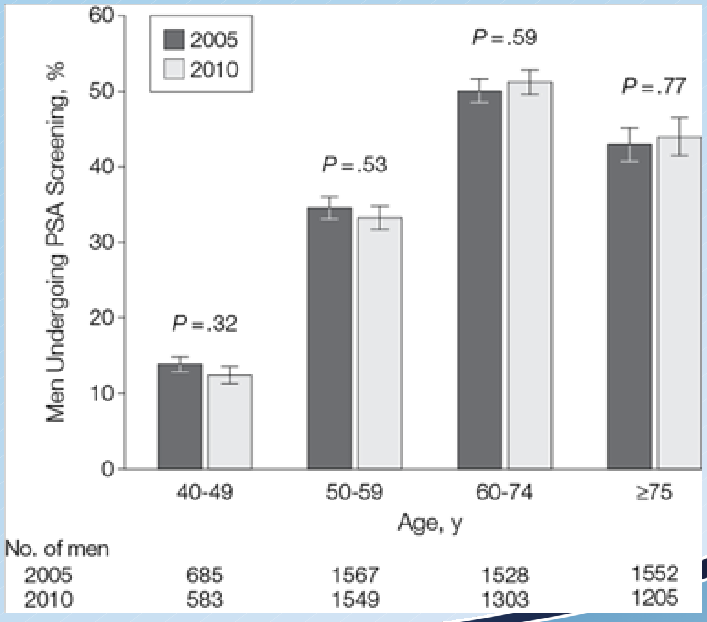
- Data suggesting:
  - Lower blood loss
  - Earlier discharge
  - Quicker return to regular routine
  - Lower rate of bladder neck contraction
  - Earlier return of continence
  - New evidence of decreased complications and perhaps lower mortality!
- Equal cancer cure rates
  - Continence and potency data related to surgeon
  - Safety higher in high volume hospitals

UC San Diego
SCHOOL OF MEDICINE

Robotic Volume by Year
2012 429, 1740 cases overall



UC San Diego
SCHOOL OF MEDICINE



Prasad Sm et al *JAMA*. 2012;307(16):1692-1694.

UC San Diego SCHOOL OF MEDICINE

USPSTF Accountability Act

- USPSTF Transparency and Accountability Act of 2012. This bipartisan legislation, introduced today by Reps. Marsha Blackburn (R-TN-7) and John Barrow (D-GA-12), along with Donna Christensen (D-VI) and Lee Terry (R-NE-2), calls for significant changes to the U.S. Preventive Services Task Force (USPSTF) and the process by which the group makes formal recommendations regarding preventive care services.

UC San Diego SCHOOL OF MEDICINE

USPSTF Accountability Act

- Most importantly, the bill strikes the language added by the 2010 Affordable Care Act (ACA) that directly ties Medicare coverage of a particular preventive service to the grade given by the USPSTF.
- Other key changes called for by the bill include a mandate to ensure a “balanced representation of primary and specialty care providers” and other key stakeholders in the healthcare community are involved in development and review of recommendations.

UC San Diego
SCHOOL OF MEDICINE

Summary

- PSA is an imperfect screening test. High sensitivity but low specificity
- PSA screening does save lives
- Younger men and those at increased risk of prostate cancer benefit the most
- We should stop screening men unlikely to benefit
- We should offer active surveillance to low risk men
- When we treat we should do so expertly with consistently good outcomes

UC San Diego
SCHOOL OF MEDICINE

Summary

- To discourage PSA screening for all men is irresponsible
- The USPSTF methodology is severely flawed
- Lets thoughtfully move forward with prostate cancer detection and treatment that keeps faith with the patients at risk for the second leading cancer killer of American Men

UC San Diego
SCHOOL OF MEDICINE