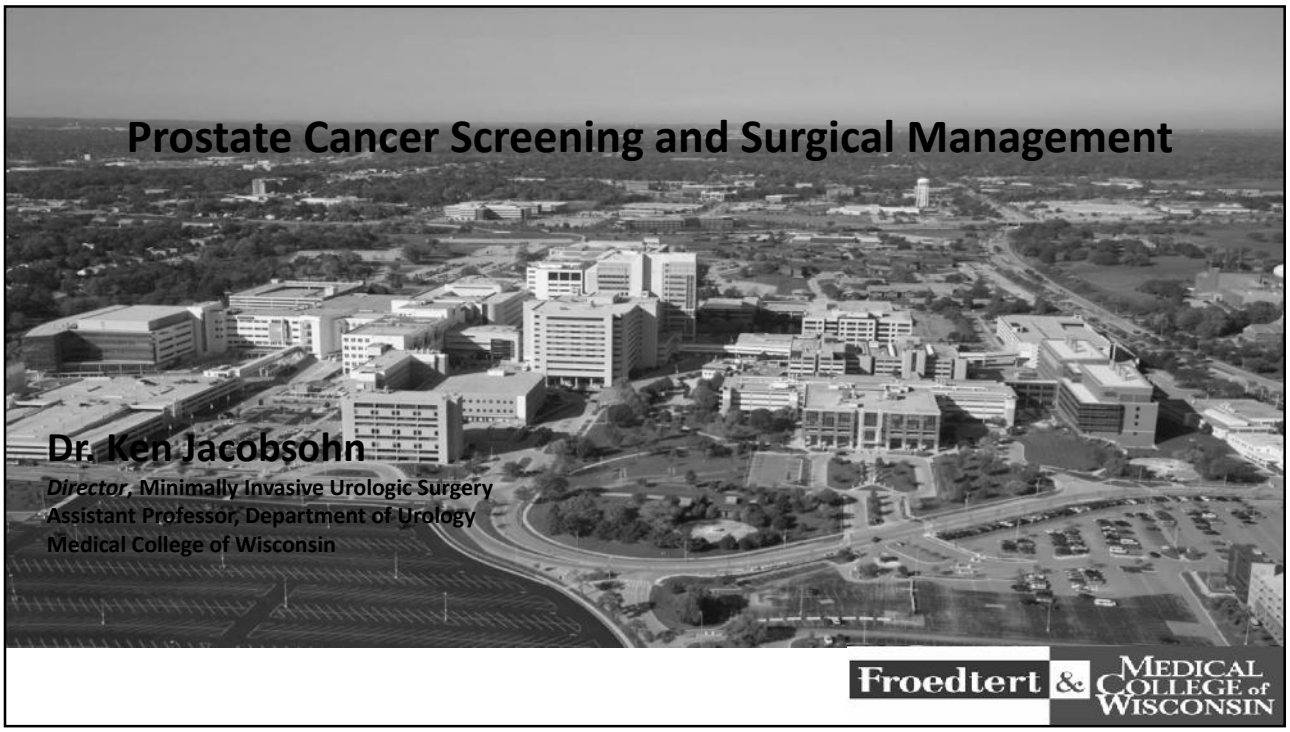
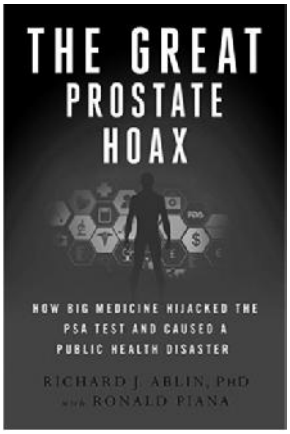


Financial Disclosures

- None

Objectives

- Update the latest prostate cancer statistics
- Review Diagnosis and Staging
- Review data concerning PSA screening:
  - PLCO
  - ERSPC
- Latest AUA Recommendations
- New diagnostic tools
- Treatment Options



"*The Great Prostate Hoax* is the answer to my prayers, finally getting the message out to millions of men in jeopardy of undergoing unnecessary and debilitating treatments. *Hoax* sends a clear message that those who profit from PSA testing are doing so at the expense of countless men. A must-read."
—ALVIN COX, PROSTATE CANCER SURVIVOR WHO DEFIED A NATIONALLY RENOWNED UROLOGIST

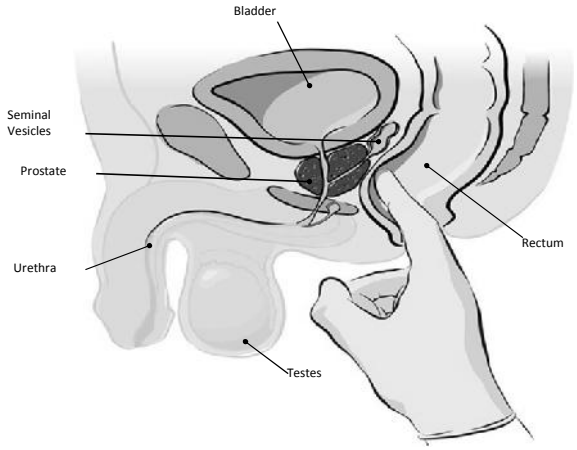
Early Detection

- Best prognosis follows early detection
- Recent data on lower mortality rates of prostate cancer
- Affords patients many options for treatment

Froedtert & Medical College of Wisconsin

Early Detection

- Digital Rectal Exam (DRE)
- Prostate Specific Antigen (PSA) blood test
- Any abnormality in the PSA or DRE will require
  - Biopsy of the prostate
    - Ultrasound guided
    - Usually performed in the office
    - Short procedure



Froedtert & Medical College of Wisconsin

Staging of Prostate Cancer

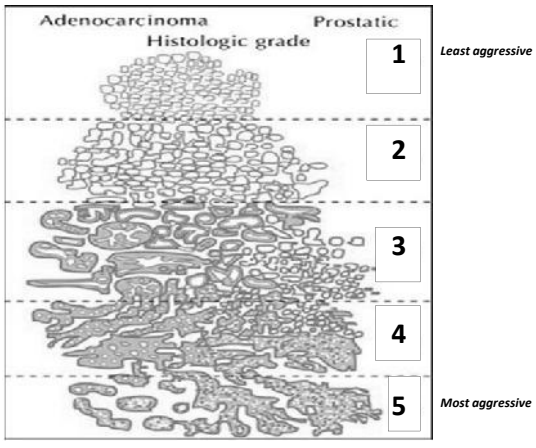
- PSA
- Digital Rectal Exam
- Trans Rectal Ultrasound
- Gleason Score
- Bone Scan
- +/- CT scan or MRI
- Biopsy and TNM staging system
  - Tumor, Nodes, Metastases

Froedtert & Medical College of Wisconsin

Biopsy Results

- **Prostate cancer graded on appearance of cancer cells**
- **Gleason grading system**
  - Gleason grade ranges from 1 (least aggressive) to 5 (most aggressive)
- **Gleason score (2-10)**
  - Most common cell grade (first) added to second most common cell grade, e.g., Gleason 7 (3+4)

Gleason Grading



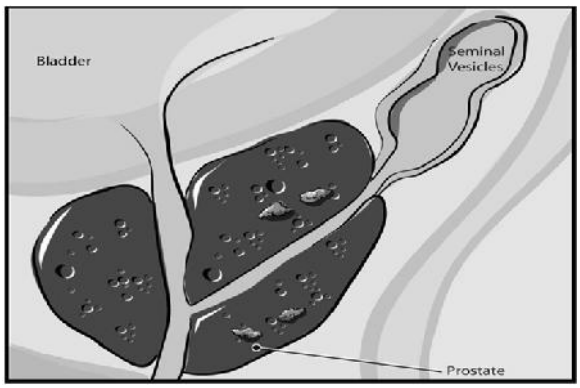
Froedtert & Medical College of Wisconsin

Table 2 The update to the Gleason scoring system

Traditional Gleason score	New ISUP score
6	1
3+4=7	2
4+3=7	3
8	4
9–10	5

ISUP, International Society of Urological Pathology.

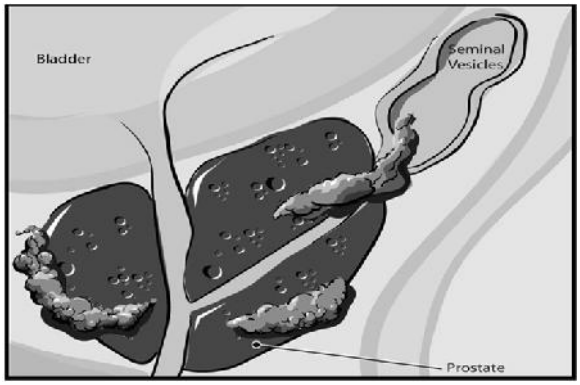
Prostate Cancer T1 Disease



- Tumor cannot be felt
- T1a – cancer found in ≤ 5% TURP specimen
- T1b - cancer found in ≥ 5% TURP specimen
- T1c – cancer found as a result of PSA elevation only

Froedtert & Medical College of Wisconsin

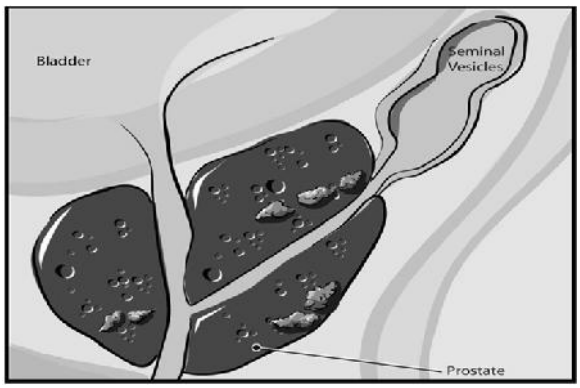
Prostate Cancer T3



- Cancer has spread beyond the prostate
- T3a – extra capsular extension
- T3b – tumor invades seminal vesicle(s)

Froedtert & Medical College of Wisconsin

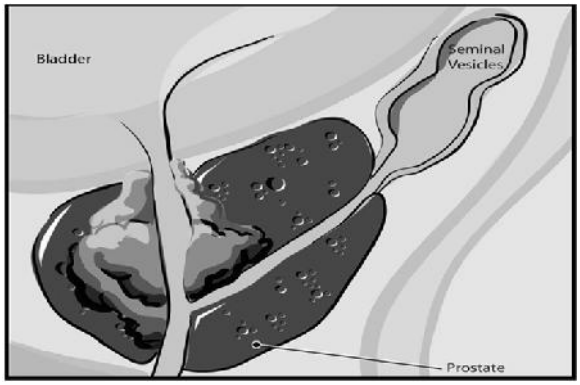
Prostate Cancer T2



- Tumor can be felt during DRE (digital rectal exam)
- T2a – felt on ≤ one half of one side of prostate
- T2b – felt on ≥ one half of both sides of prostate
- T2c – felt on both sides of prostate

Froedtert & Medical College of Wisconsin

Prostate Cancer T4

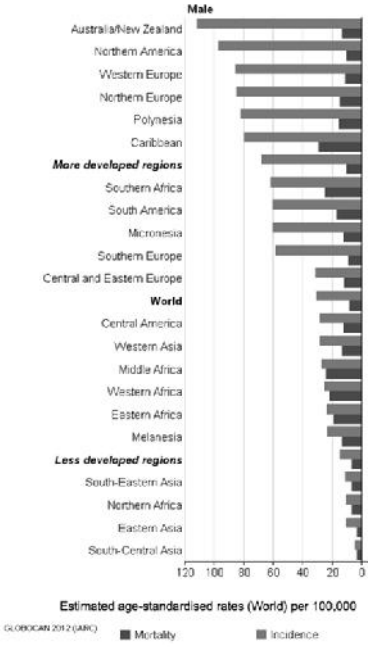


- Cancer has invaded local organs/tissues
  - Bladder muscle
  - Pelvic side wall
- May cause pain in joints and back

Froedtert & Medical College of Wisconsin

Epidemiology

- ➢ Prostate cancer is a global problem
- ➢ Today we focus on the debate of prostate cancer in the US and Europe
- ➢ We often overlook the fact that prostate cancer is really a global phenomenon
- ➢ Some of the highest mortality rates found in the least developed regions of the world: Caribbean, South America, and Africa



Epidemiology

- Prostate cancer is the most common
- 116,360 cases
- 26,150 deaths
- Now third leading cause of cancer deaths (lung and colon kill more men)

Estimated New Cases

Males			Females		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,360	3%
All Sites	**836,150**	**100%**	**All Sites**	**852,630**	**100%**

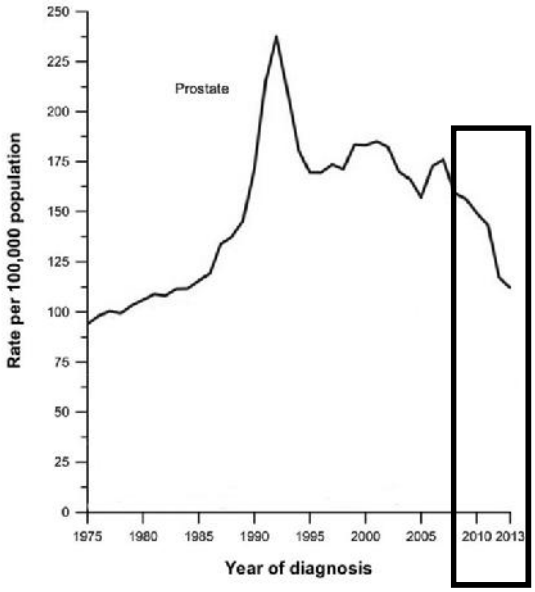
Estimated Deaths

Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,510	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017.
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

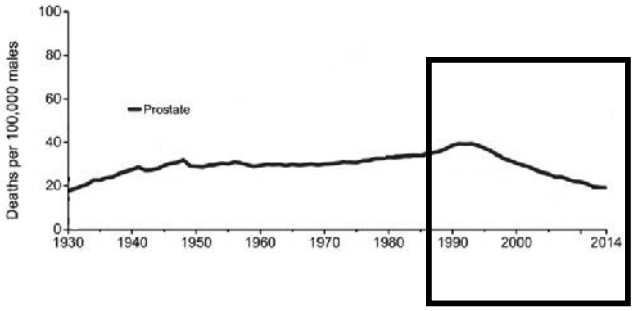
Epidemiology

- Prostate cancer projections, 2017
  - Highest incidence among men
  - Third leading cause of cancer death in men (down from #2)
- Nevertheless, the number of men diagnosed is decreasing, compared to the 1990s



Epidemiology

- Mortality rates are declining in the PSA era
- APC -3.4% (2005-2014)
- 10,000 lives saved



Evidence Synthesis
Number 90

Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force

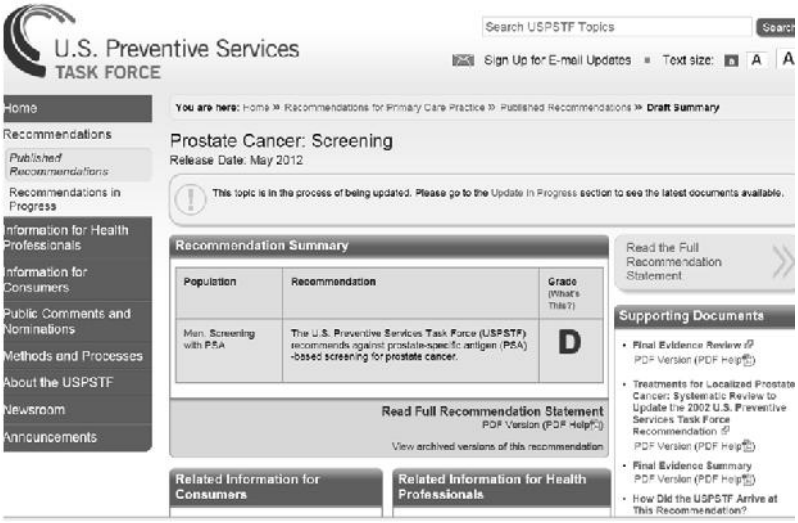
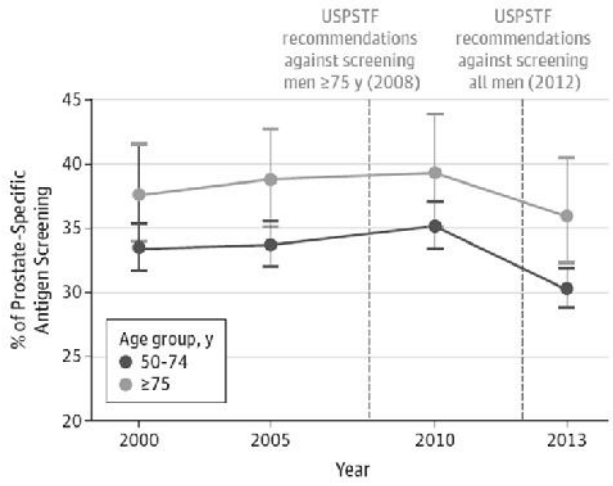
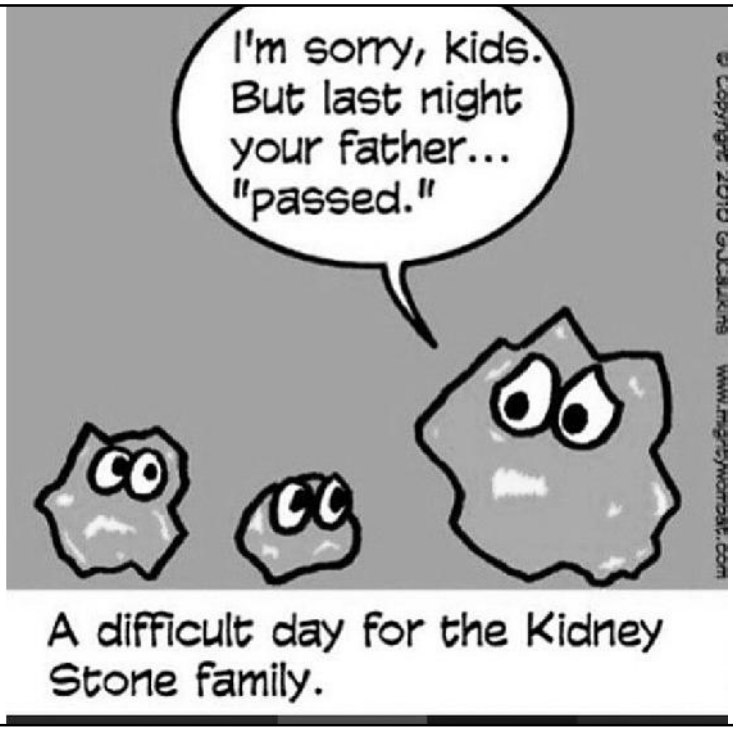
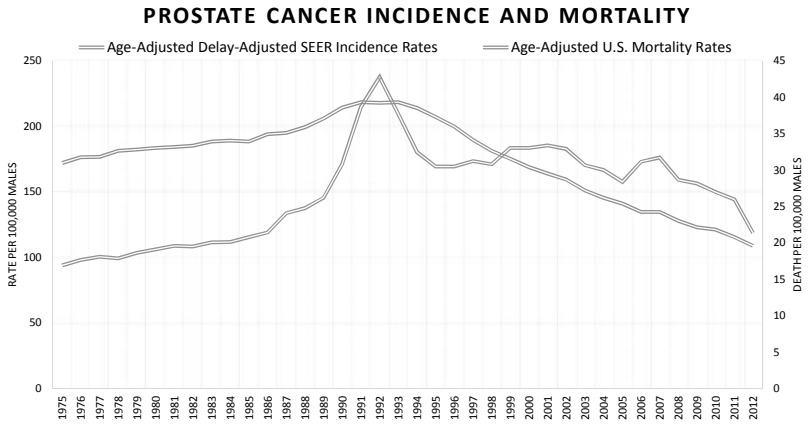


Figure. Prevalence of Prostate-Specific Antigen Screening From National Health Interview Survey (2000, 2005, 2010, and 2013)





But, a fact: SEER, 2015



RCT's Prostate Cancer Screening

Two studies:

US – PLCO. Rigorous. Conducted in US

Problem: PSA testing had already taken off like wildfire in the U.S.

Europe – ERSPC – PSA testing. A*dvantage: little background PSA testing.*

Problem: almost a meta-analysis of several different trials.

Screening Trials

ARTICLE

Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up

Gerald L. Andriole, E. David Crawford, Robert L. Grubb III, Saundra S. Buys, David Chia, Timothy R. Church, Mona N. Fouad, Claudine Isaacs, Paul A. Kvale, Douglas J. Reding, Joel L. Weissfeld, Lance A. Yokochi, Barbara O'Brien, Lawrence R. Ragard, Jonathan D. Clapp, Joshua M. Rathmell, Thomas L. Riley, Ann W. Hsing, Grant Izmirlian, Paul F. Pinsky, Barnett S. Kramer, Anthony B. Miller, John K. Gohagan, Philip C. Prorok; for the PLCO Project Team

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-Håkan 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*

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

METHODS

From 1993 through 2001, we randomly assigned 76,693 men at 10 U.S. study centers to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects). Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years. The subjects and health care providers received the results and decided on the type of follow-up evaluation. Usual care sometimes included screening, as some organizations have recommended. The numbers of all cancers and deaths and causes of death were ascertained.

The PLCO Clinical Trial

PLCO Design

- 1993-2001
- 77,000 men randomized to annual screening for 6 years vs. “usual care”
- Men w/ PSA WNL prior to enrollment included
- Men w/ elevated PSA prior to enrollment excluded

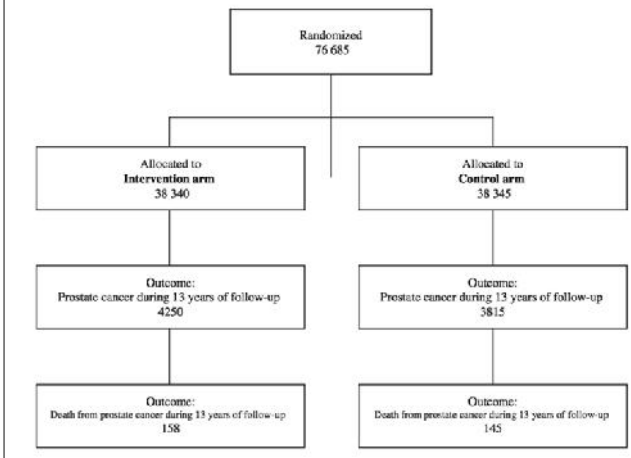
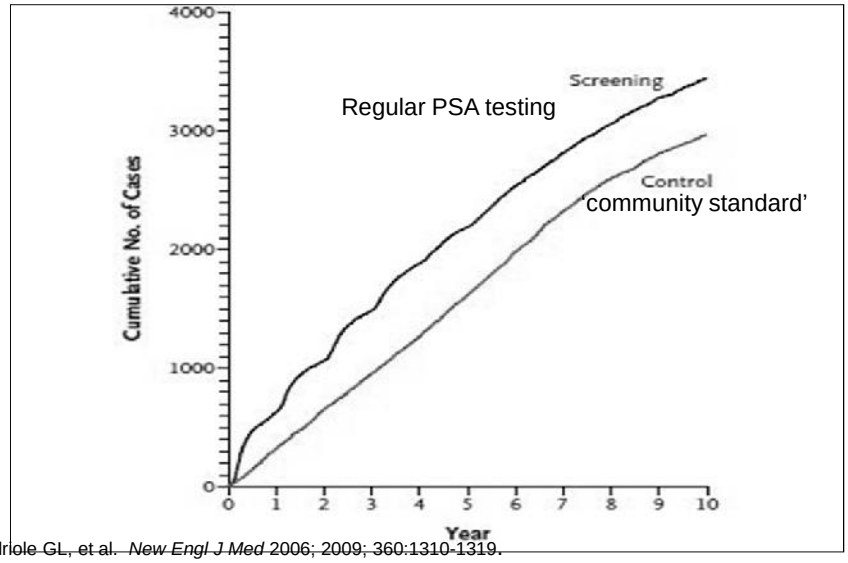


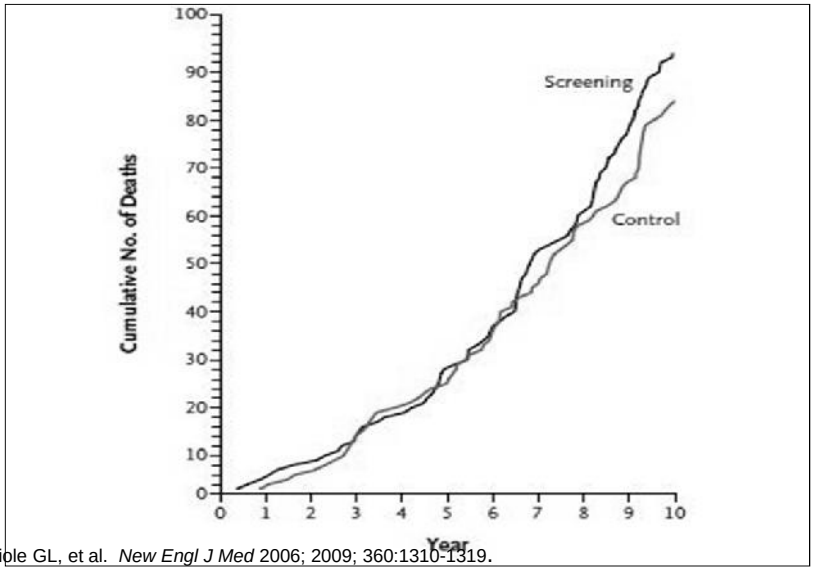
Figure 1. Flow diagram for male participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

PLCO: More cancers detected



Andriole GL, et al. *New Engl J Med* 2006; 2009; 360:1310-1319.

PLCO: No reduction in deaths



Andriole GL, et al. *New Engl J Med* 2006; 2009; 360:1310-1319.

PLCO Summary

Criticisms

- Changing definition of "usual care" in the 1990s
- 44% of participants had >/ 1 PSA prior to enrollment
- 90% contamination of "usual care" group
  - Shoag, Mittal NEJM 2016
- Biopsy rates for elevated PSA only 30-40%

Conclusions

- PLCO is not "screening vs. no screening"
- More accurate: "annual vs. opportunistic" screening
- PLCO should not be included in analysis of screening trials
- PLCO is not evidence that screening doesn't improve PCSM

The NEW ENGLAND JOURNAL of MEDICINE

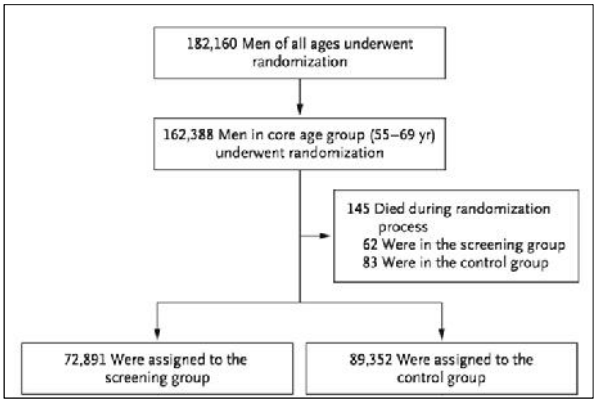
ESTABLISHED IN 1812 MARCH 15, 2012 VOL. 366 NO. 11

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*

ERSPC Design

- 1991-2003
- 182,000 men randomized
- Majority screened every 4 years
- Majority biopsied for PSA >/4
- Less contamination, larger risk profile differences between groups



ERSPC Results

- At 9 years, 21% relative risk reduction in PCSM
- After adjustment for contamination, even higher risk reduction (29%)
- NND = 37 at 11 years follow-up

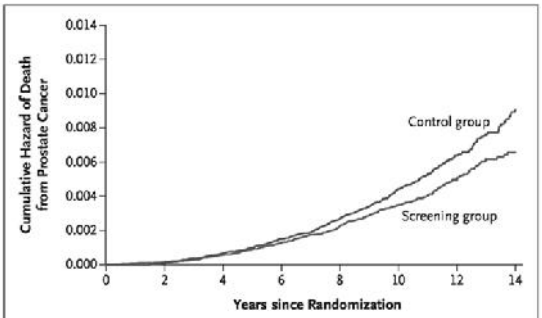


Figure 2. **Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.**
Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.

ERSPC Summary

Criticisms

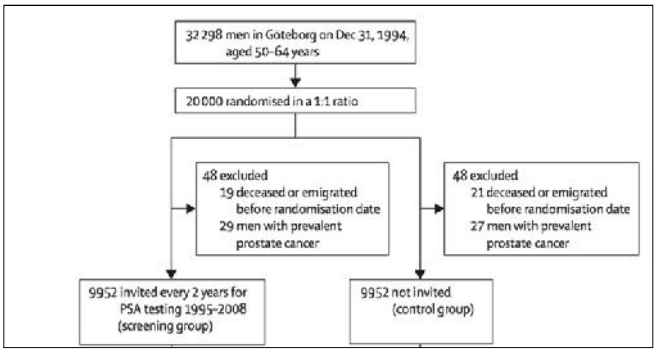
- NND at 11 years follow up is still too short to be accurate
- Predictive models with 25 years follow up show NND = 2-9

Conclusions

- ERSPC is an imperfect but valid study of prostate cancer screening
- The true magnitude of screening benefit is unknown because of inadequate follow-up

Goteborg Design

- 1994-2008
- Nearly 20,000 men randomized to PSA screening every 2 years, or no screening until age 69
- Median age was 56: youngest of 3 major trials



Goteborg Results

- 14 years of follow-up
- 44% relative risk reduction in PCSM
- NND = 12
- Diverging survival curves at the end of follow-up period

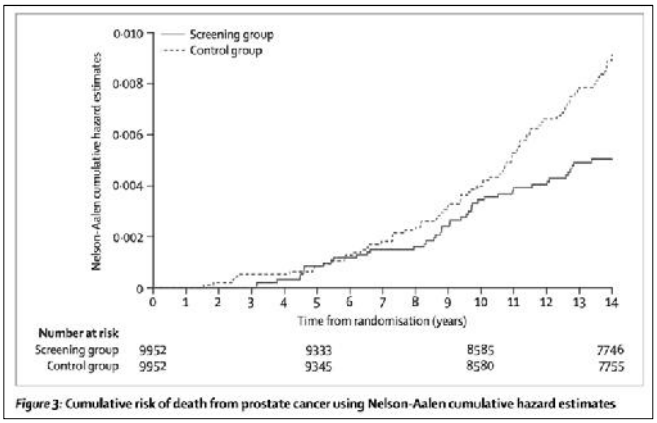


Figure 3: Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates

Summary of RCTs in Prostate Cancer Screening

- Of the 3 major screening trials, only 2 are valid to answer the question
  - Conclusions from ERSPC and Goteborg are concordant
- Data from PLCO should not be included in the discussion
  - This is *not* controversial
- Bottom Line: PSA screening reduces prostate cancer specific mortality

May, 2012: USPSTF Recommendations

- Outcome:
  - The USPSTF recommends against PSA-based testing for prostate cancer (Grade "D")
- Origin of Controversy
  - Underappreciation of benefit
    - Emphasis on PLCO and ERSPC trials
    - No extrapolation of ERSPC data via modeling for NND
    - Goteborg Trial ignored

May, 2012: USPSTF Recommendations

Origin of Controversy

<u>Overestimation of Harms</u>

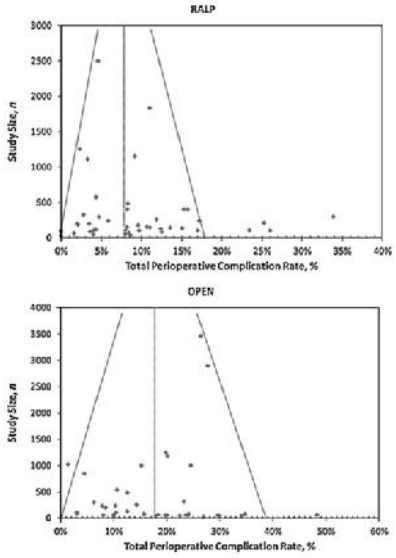
- Emphasis on false positives
- Men prefer to be designated cancer free, even if negative biopsy required.

Screening health state	Ranked as 'best' state	Ranked as 'worst' state
A	7 (4.2%)	146 (86.9%)
B	96 (57.1%)	3 (1.8%)
C	65 (38.7%)	19 (11.3%)

A = no cancer, no PSA test and no biopsy; B=no cancer and a favourable (negative) PSA test; C = no cancer, an unfavourable (positive) PSA test and a favourable (negative) biopsy.

May, 2012: USPSTF Recommendations

- Origin of Controversy
  - Overestimation of Harms
    - Focus on morbidity data from treatment of prostate cancer
      - Cites 0.5% complication rate from Medicare data in open prostatectomy era
      - More contemporary data shows lower morbidity rates (<0.1%)



May, 2012: USPSTF Recommendations

- Origin of Controversy
  - Overestimation of Harms
    - Ignores contemporary attitude that uncouples diagnosis from intervention
    - Men who enlist in active surveillance avoid operative morbidity

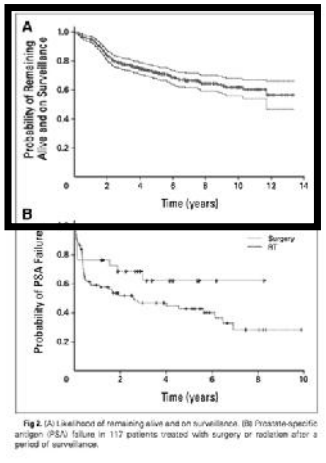


Fig 2. (A) Likelihood of remaining alive and on surveillance. (B) Prostate-specific antigen (PSA) failure in 112 patients treated with surgery or radiation after a period of surveillance.

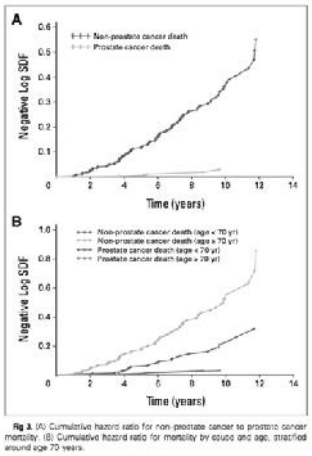


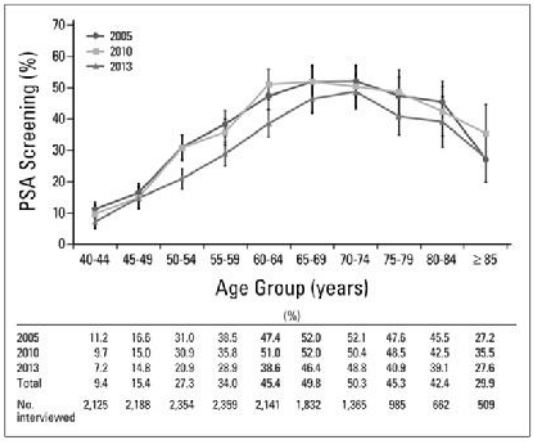
Fig 3. (A) Cumulative hazard ratio for non-prostate cancer vs prostate cancer mortality. (B) Cumulative hazard ratio for mortality by cause and age, stratified around age 70 years.

Impact of the USPSTF Recommendation

- Screening
- Biopsy
- Diagnosis
- Stage Migration

Impact of the USPSTF: Rates of screening across age groups- Survey Data

- Prostate cancer screening rates have declined since 2012
  - NHIS used to estimate screening rates based on 9-year mortality index for men >40
  - 2005, 2010, and 2013 compared
    - Age 50-59 rates 33→24% (p<0.01)
    - Age 60-74 rates 51→43% (p<0.01)
    - Age >75 rates 44→27% (p=0.03)



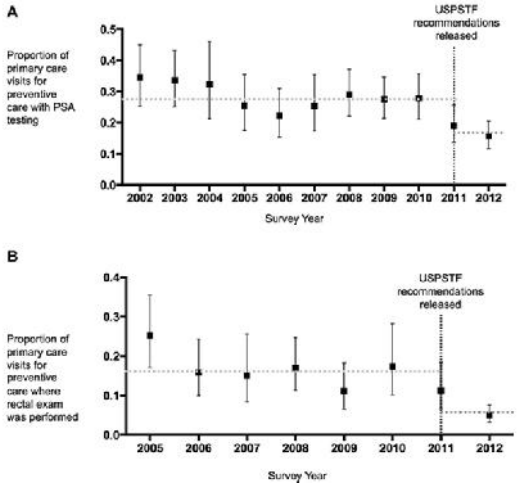
(%)

	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥ 85
2005	11.2	16.6	31.0	38.5	47.4	52.0	52.1	47.6	45.5	27.2
2010	9.7	15.0	30.9	35.8	51.0	52.0	50.4	48.5	42.5	35.5
2013	7.2	14.8	20.9	28.9	38.6	46.4	48.8	40.9	39.1	27.6
Total	9.4	15.4	27.3	34.0	45.4	49.8	50.3	45.3	42.4	29.9
No. interviewed	2,125	2,188	2,354	2,399	2,141	1,832	1,365	985	662	509

Fig 1. Proportion of men, by 5-year age group, who saw a physician in the year prior and received a prostate-specific antigen (PSA) test for screening purposes.

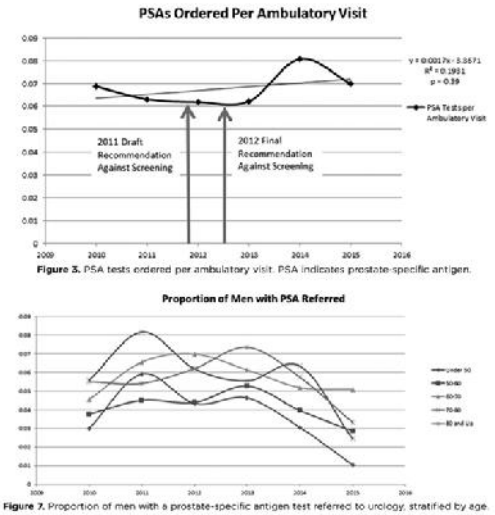
Impact of USPSTF: Rates of screening across age groups- Survey Data

- Prostate cancer screening rates have declined since 2012
  - NAMCS of primary care visits where DRE and PSA performed
  - DRE rates 65% decrease
  - PSA rates 39% decrease



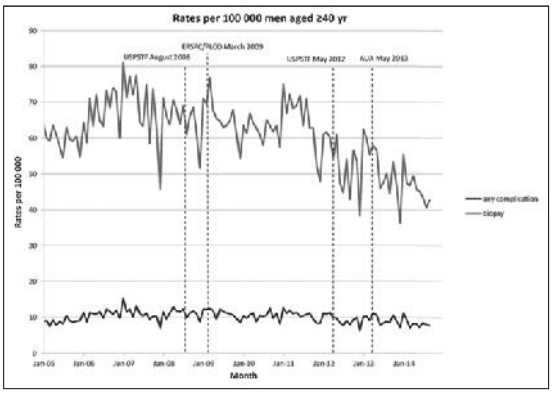
Impact of USPSTF: Rates of screening across age groups- Claims/EMR data

- Prostate cancer screening rates have not declined since 2012
  - UTSW review of institutional PSA orders and urology referrals
  - The number of PSAs per ambulatory visit and urology referrals were unchanged



Impact of USPSTF: Rates of prostate biopsy

- Prostate biopsy rates have declined
  - Claims data from >5 million men with Medicare and private insurance
  - 2005-2014: 33% drop in prostate biopsies
  - 64→43 biopsies per 100,000 men



Impact of USPSTF: Rates of diagnosis-localized disease

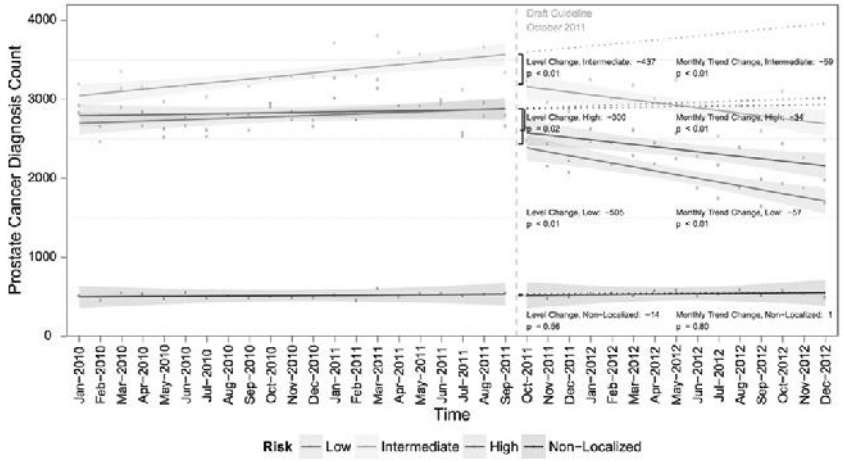
Barocas et al, JUrol, 2015

- NCDB Analysis
- 2010-2012

Group	Monthly Slope before Guideline Change*		Level Change Immediately after Guideline Change†		Monthly Slope Change after Guideline Change Relative to before Guideline Change‡		Estimated Change in Monthly Diagnoses 1 Yr after Guideline Change§	
	Absolute Change	% Change	Absolute Change	% Change	Absolute Change	% Change	Absolute Difference	% Difference
Cancer type:		p(int)=0.31‖		p(int)=0.04		p(int)=0.03		
Prostate	39	0.4	−1,373	−12.2	−164	−1.8	−3,181	−27.9
Colon	3	0.1	4	0.2	−27	−0.5	−298	−5.1
Prostate cancer subgroup:								
Disease risk stratum:		p(int)=0.31		p(int)=0.30		p(int)<0.01		
Low	9	0.3	−505	−16.9	−57	−2.7	−1,134	−37.9
Intermediate	26	0.8	−437	−12.9	−59	−1.9	−1,090	−28.1
High-risk	4	0.1	−300	−10.1	−34	−1.4	−674	−23.1
Non-localized	2	0.3	−14	−2.7	1	0.1	−6	−1.1

Impact of USPSTF: Rates of diagnosis-localized disease

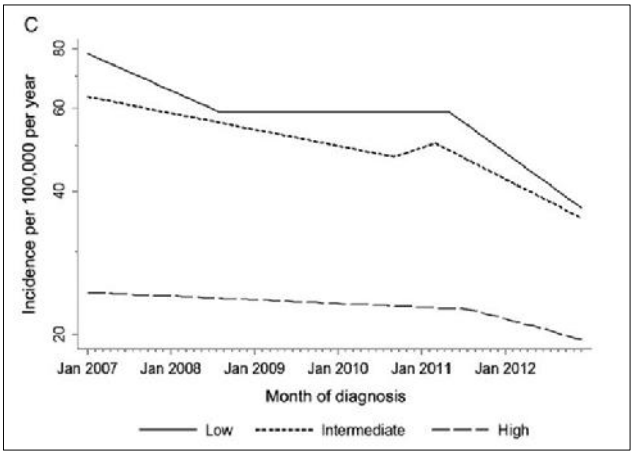
Barocas et al. JUrol, 2015



Impact of USPSTF: Rates of diagnosis-localized disease

Herget et al, JUrol, 2016

- SEER analysis
- 2007-2012
- Rate of decline by risk group
  - Low risk
    - 18% 2007-2008, then 29% after 2011
  - Intermediate risk
    - 8% 2007-2010, then 21% after 2011
  - High Risk
    - 2% 2007-2011, then 11% after 2011

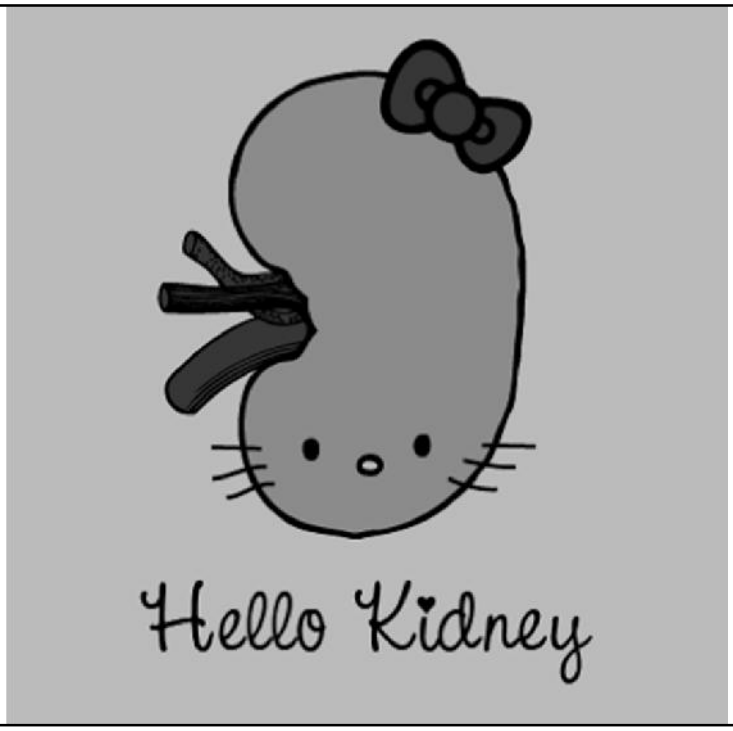


Impact of the USPSTF: Reverse stage migration

- Statistical models exist to project effect of screening discontinuation
  - As high as 50% increase in metastatic cases at presentation
  - 20% increase in prostate cancer deaths
- Actual data to evaluate this is immature and inconclusive

Impact of the USPSTF: Summary

- The USPSTF recommendations had notable effects on screening/biopsy/diagnosis rates in a very short time period



AUA Guidelines Update 2013

- Meanwhile, the AUA released an updated guideline in 2013
- Represented a systematic review of the evidence by noted experts
- Emphasis on an individualized, risk adapted approach through shared decision making

AUA Guidelines: Statement 1

- The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C)
  - In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.

AUA Guidelines: Statement 2

- The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)
  - For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions regarding prostate cancer screening should be individualized.

AUA Guidelines: Statement 3

- For men ages 55 to 69 years the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B)
  - The greatest benefit of screening appears to be in men ages 55 to 69 years.

AUA Guidelines: Statement 4

- To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening.

AUA Guidelines: Statement 5

- The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)
  - Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.

Other agencies follow suit…

- American College of Physicians, 2013
  - "ACP recommends that clinicians base the decision to screen for prostate cancer using the prostate-specific antigen test on the risk for prostate cancer, a discussion of the benefits and harms of screening, the patient's general health and life expectancy, and patient preferences."
  - "ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 to 15 years."

Update to USPSTF Recommendations

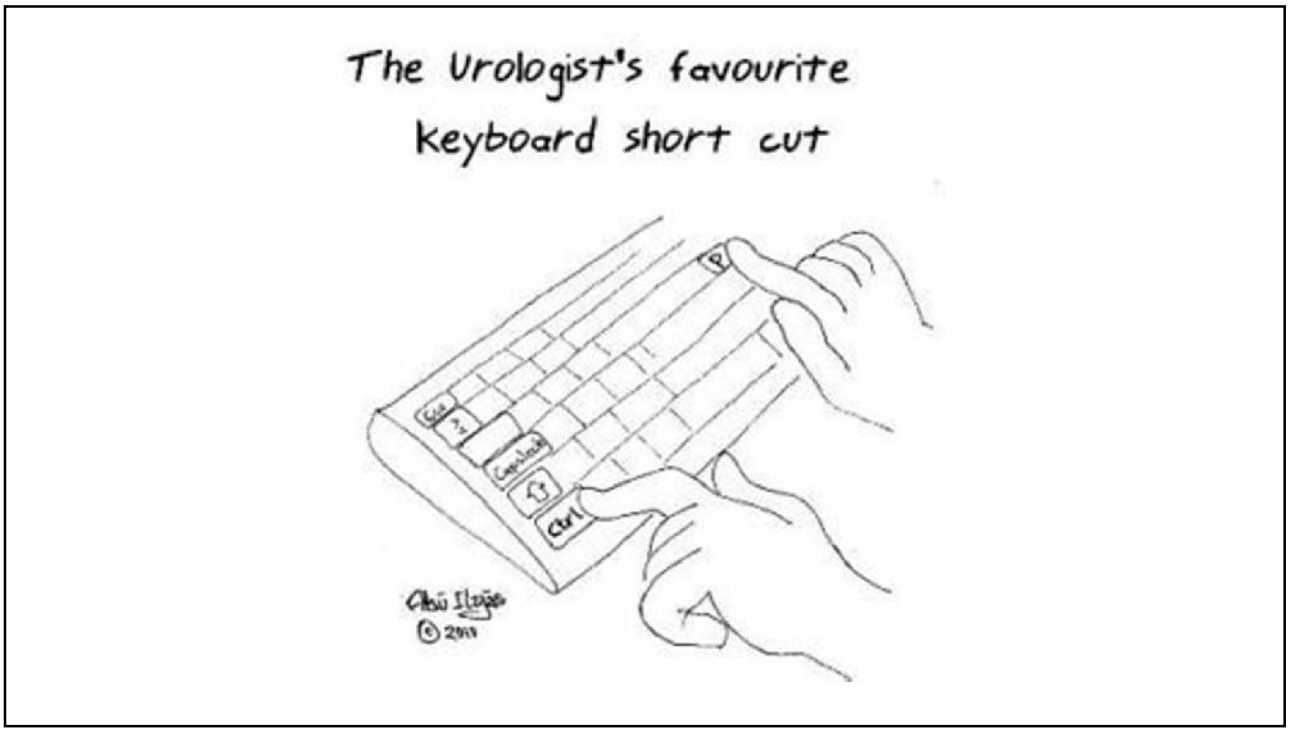
- May 8, 2017
  - USPSTF releases draft update upgrading screening recs for men 55-69 to grade "C"
  - For men >70, grade remained "D".

> *"The decision about whether to be screened for prostate cancer should be an individual one. The USPSTF recommends individualized decision making about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision."*

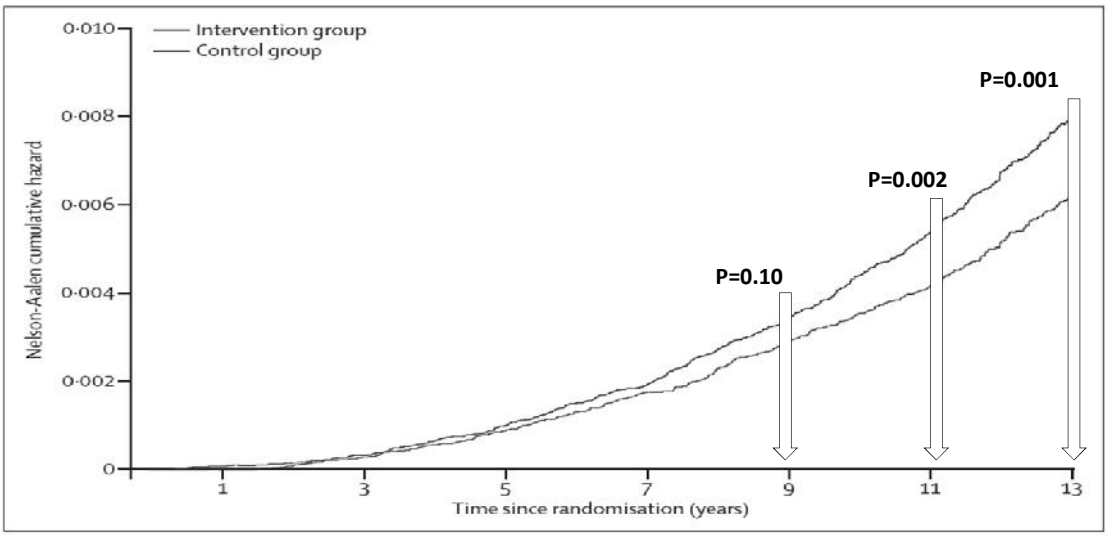
Where does prostate cancer stand in 2018?

- **We are at a cross-roads.**
- Screening of healthy, young, well-informed men with serum PSA significantly reduces the risk of dying from prostate cancer (21-44%)
- *However, does so at the risk of over-detection of* low-grade tumors which would not have become clinically apparent over a patient's lifetime if left untreated
- Although enthusiasm has grown for surveillance *over-detection and over-treatment remain are tightly linked*
-

Cancer Cases Control 19:175; NEJM 360:1320; Lancet Oncol 2010 11:725;NEJM 2011;364:1708

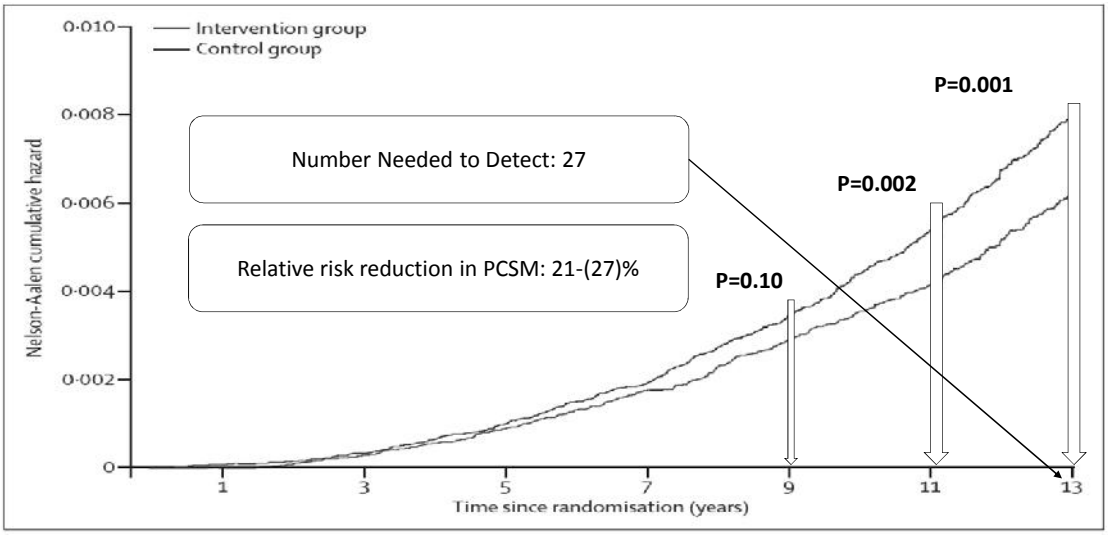


Cumulative prostate cancer mortality



Schroder et al., Lancet 2014

ERSPC: Cumulative prostate cancer mortality

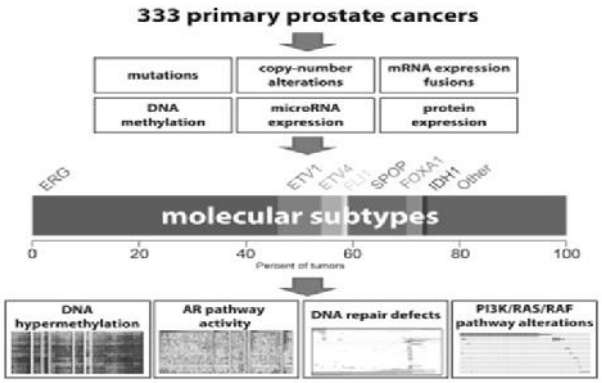


Schroder et al., Lancet 2014

Challenges: molecular and clinical heterogeneity

- Substantial heterogeneity exists among primary prostate cancers
  - Clinically, Biologically
- Slow growing "indolent"→ lethal malignancy
- Distinct molecular subtypes may underlie the highly varied clinical behavior
- ***Need to develop single, widely accessible screening tests assess this complexity***

TCGA Molecular Analysis



TCGA Network, Cell. 2015 Nov 5; 163(4): 1011-25

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

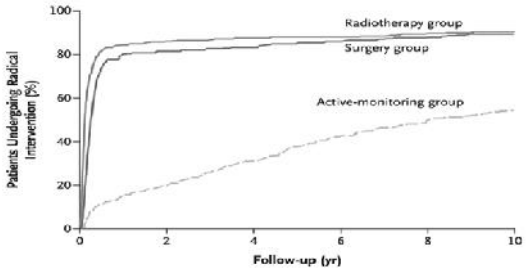
10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

- 82,249 men screened with PSA aged 50-69 between 1999-2009
  - 2,664 diagnosed with PCa → 1,643 randomized
- Median f/u 10 years
- Three arms:
  (1) "AS" (n=545); (2) RP (n=553); (3) RT (n=545)
- **Primary Outcome: *PCSM* at median of 10 year f/u**
- **Secondary: disease progression, metastasis, ACS**

Hamdy FC et al. NEJM, Sept 2016

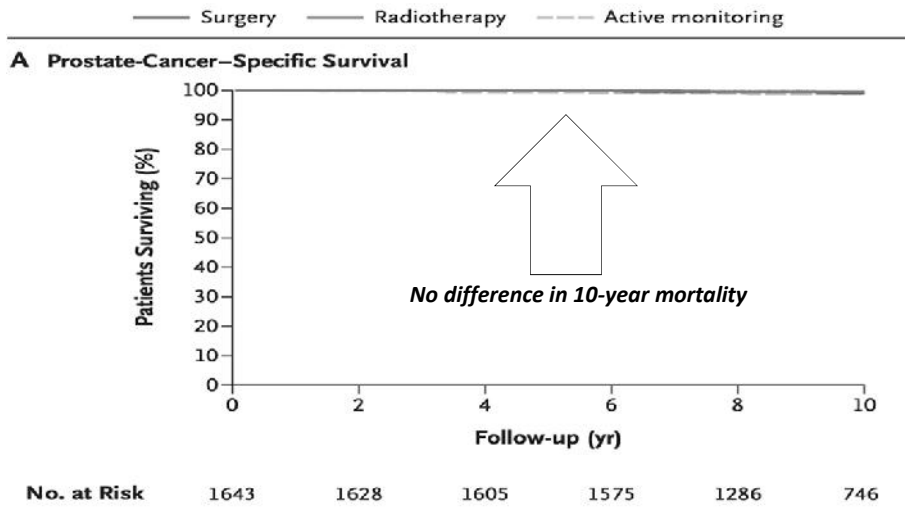
How relatable was surveillance protocol?

- Some (9) with Gleason >6 (5 in AS)
- Surveillance protocol: PSA monitoring every 3 months in the first year and then every 6-12 months
- Increases of 50% over 12 months triggered review and potentially treatment
- Period biopsy not mandated
- ***54.8% of patients initially enrolled in surveillance were treated***



Hamdy FC et al. NEJM, Sept 2016

ProtecT: Take Home Points

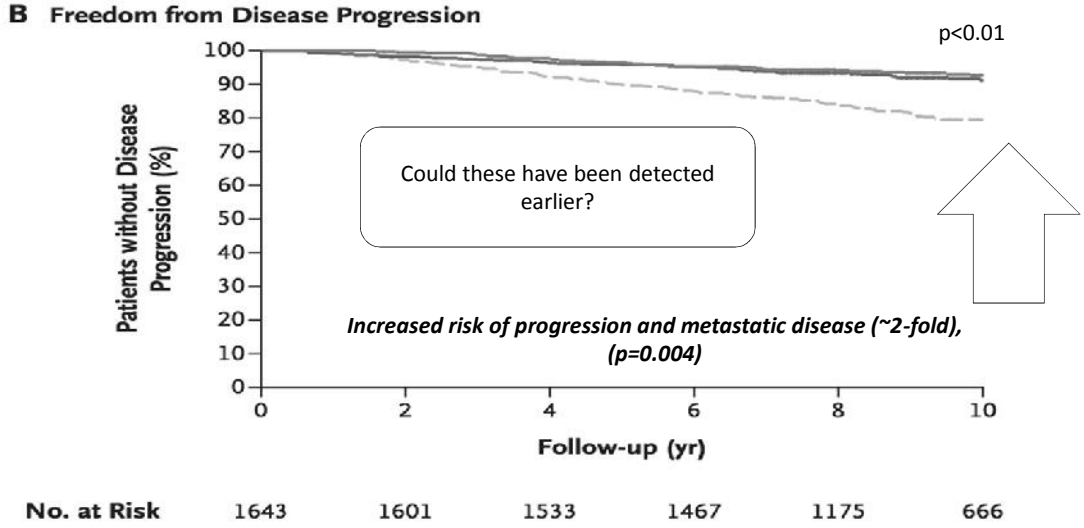


p=0.48

No difference in 10-year mortality

Hamdy FC et al. NEJM, Sept 2016

ProtecT: Take Home Points



p<0.01

Could these have been detected earlier?

Increased risk of progression and metastatic disease (~2-fold), (p=0.004)

Hamdy FC et al. NEJM, Sept 2016

ProtecT: Take Home Points

- **At 10 year follow-up, mortality from low-risk prostate cancer is *low*, regardless of treatment assignment**
  - ***Implications for who we screen and offer treatment***
- Definitive treatment associated with **lower** rates of disease progression and metastasis than active monitoring
- Surveillance protocol was largely PSA based which does not mirror contemporary standards
  - **We cannot freeze frame at diagnosis**
  - **Reinforces need to optimize protocols, tools, and endpoints**

Hamdy FC et al. NEJM, Sept 2016

We need to improve on current standard

- ✓PSA is an imperfect biomarker for prostate cancer
  - ❑Incidental detection of indolent tumors threatens to erode early detection altogether!
- ✓**Initial clinical risk stratification is inadequate and lead to over-treatment**
  - ❑High reclassification rate
- ✓Endpoints during surveillance may detect progression after it has occurred

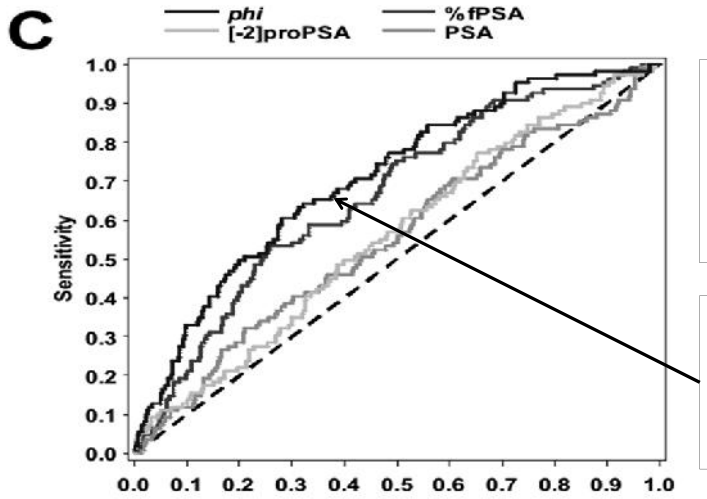
- The inherent limitations of "standard" clinical tools including PSA are associated with unacceptably poor specificity for detecting high grade disease
- An array of new biomarkers, and genomic assays have been ***validated*** predictors of numerous, actionable endpoints
  - ***Aggressive disease at biopsy***
  - ***Adverse pathology***
  - ***Recurrence/metastasis/mortality after treatment***
- Preliminary data suggests that the use of these tools are effective in influencing behavior
- **Skepticism is good!**-- but we should not fear new tools!

Can we refine biopsy selection using better markers?

- *Promise is held in the development and validation of novel biomarkers that possess greater **specificity** for high risk disease*
- **Many exist:** PCA3, TMPRSS2-ERG (MiPS), ExoDx
- Better selection for biopsy may reduce *over-diagnosis*
- **Prostate Health Index (PHI):** [-2]proPSA: splice-variant isoform of total PSA
  - AUC for detection of biopsy Gleason ≥3+4=0.707among 658 men with PSA 4-10
- **4-Kallikrein Panel (4K):** Kallikrein-related peptidase 2 (hK2), intact PSA, free and total PSA
  - AUC for detection of biopsy Gleason ≥3+4=0.821 among 1,012 men with *any total PSA*

Parekh DJ et al. Eur Urol 2014 Loeb S et al. J Urol 2015

Detection of Gleason ≥3+4



Overall AUC=0.707

% free=0.661
[-2]proPSA=0.558
PSA=0.551

**PHI outperforms individual components*

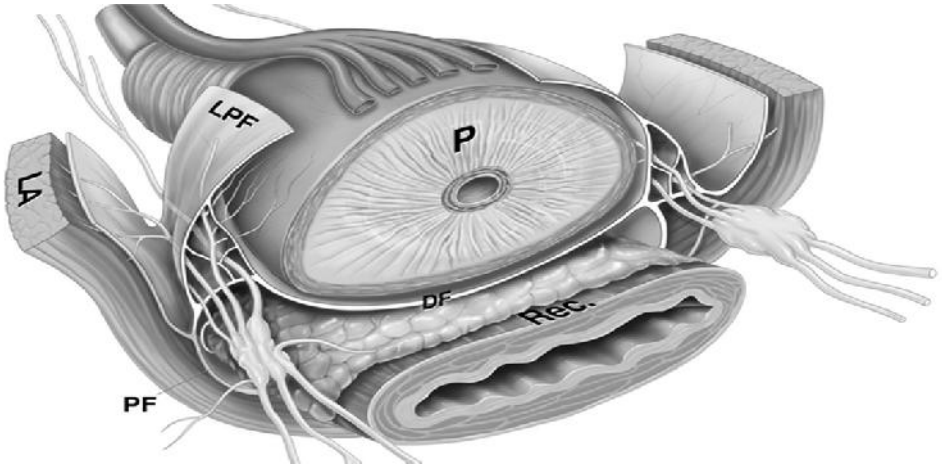
Loeb S et al. J Urol 2015

Have these markers been directly compared?

- Comparison of **531** men with PSA levels between 3-15 ng/mL undergoing *first time* biopsy 2010-2012
- **AUC for prediction of *any grade* and *high grade (Gleason ≥3+4 PCa) not significantly different***
  - *4K: 0.69 (any grade); 0.718 (high grade)*
  - *PHI: 0.704 (any grade); 0.711 (high grade)*
- Both models saved 29.6% of biopsies at a cost of missing 10% of higher grade tumors (at 10% 4K result or 39 PHI cut-off)
- Both models showed limited benefit on decision curve analysis

Nordstrom T et al. Eur Urol 2015 Jul; 68(1): 138-46

MRI in Prostate Cancer Diagnosis



MRI Prior to Biopsy

- Initial Diagnosis
  - High negative predictive value (85-90%)
  - Images clinically significant cancers best
  - Increases biopsy detection rate when combined with standard 12 core biopsy
  - Cost and infrastructure are concerning

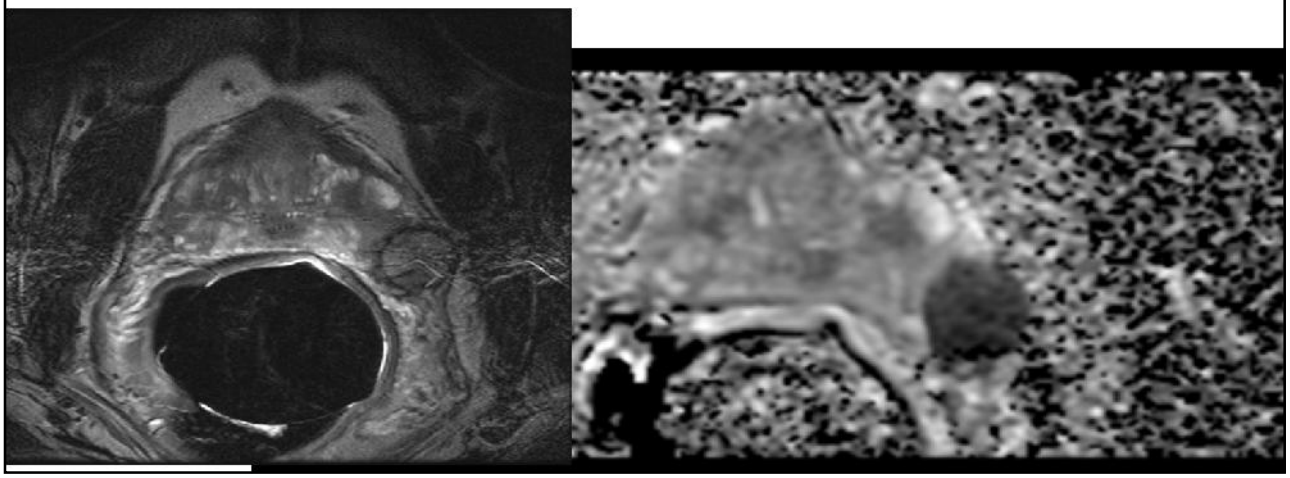
MRI Prior to Biopsy

- Initial Diagnosis
  - High negative predictive value (85-90%)
  - Images clinically significant cancers best
  - Increases biopsy detection rate when combined with standard 12 core biopsy
  - Cost and infrastructure are concerning

Active Surveillance/Prior negative biopsy

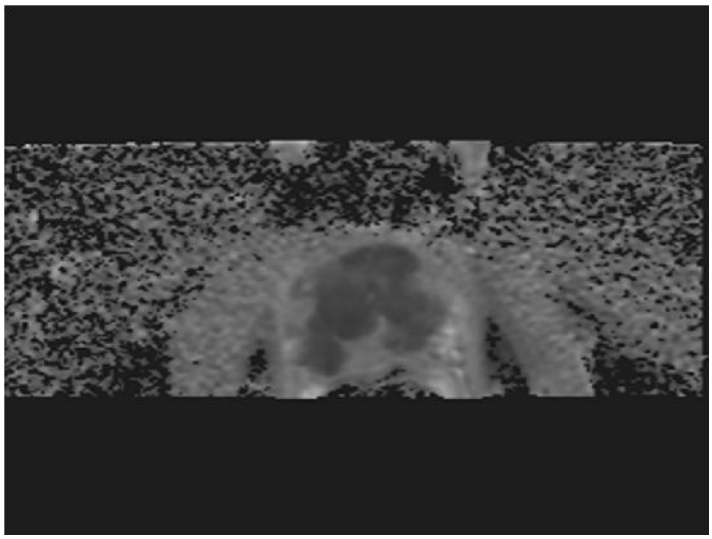
- 53 yo AA male
- Significant family hx
- PSA 7

Active Surveillance selection



Active Surveillance

- 73 yo male, PSA 5
- 1 core gleason 6 on outside biopsy
- MRI after winter in FL



Active Surveillance

- pT3aN0 gleason 5+4=9, ductal variant
- PSA is undetectable 3 years later

Active Surveillance

- pT3aN0 gleason 5+4=9, ductal variant
- PSA is undetectable 3 years later

Treatment Planning

- 57 yo male
- 3/6 cores on the right with gleason 8, left negative

Active surveillance

- Final path = pT3aN0 4+3=7, ductal variant

Prostate Cancer Treatment Options

Froedtert & Medical College of Wisconsin

Treatment Options

Depend upon…

- Stage of disease
- Patient's age and health
- Patient's personal preference

Froedtert & Medical College of Wisconsin

Treatment Options (Early Diagnosis)

- Watchful waiting or active surveillance
- External beam radiation therapy (EBRT) includes IMRT
- Brachytherapy (radioactive seeds)
- Cryosurgery (freezing prostate)
- Surgery (radical prostatectomy)
  - Open surgery
  - Conventional laparoscopic surgery
  - *da Vinci* Prostatectomy (robotic-assisted laparoscopic surgery)

Froedtert & Medical College of Wisconsin

Goals of Radical Prostatectomy

- Remove the prostate and cancer
- Preserve urinary function
- Preserve erectile function
- Analyze the prostate after surgery to assess risk of recurrence of cancer

Froedtert & Medical College of Wisconsin

Surgery: Gold Standard Treatment for Localized Prostate Cancer

"Because the entire prostate gland is removed with radical prostatectomy, the major potential benefit of this procedure is a cancer cure in patients in whom the prostate cancer is truly localized."

--(2007 AUA clinical guidelines[2])

Froedtert & Medical College of Wisconsin

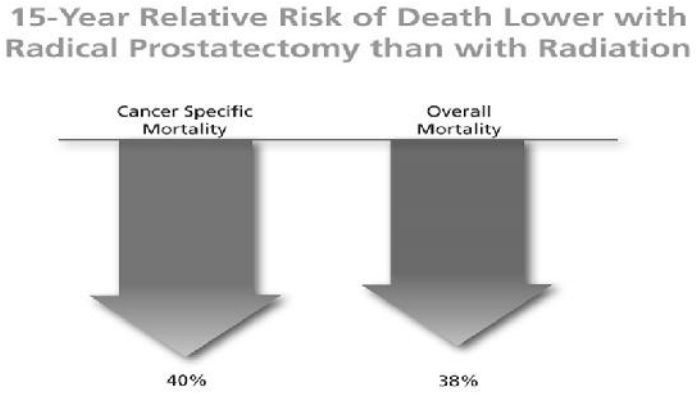
Benefits of Surgery

- Up to 35% of tumors can actually be more aggressive than the pre-surgery assessment and biopsy results indicated[3]
- Choosing surgery can:
  - Enable easier detection of cancer recurrence through PSA monitoring after a radical prostatectomy than after radiation therapy[4]
  - Preserve your treatment options if there is a recurrence[5]

Froedtert & Medical College of Wisconsin

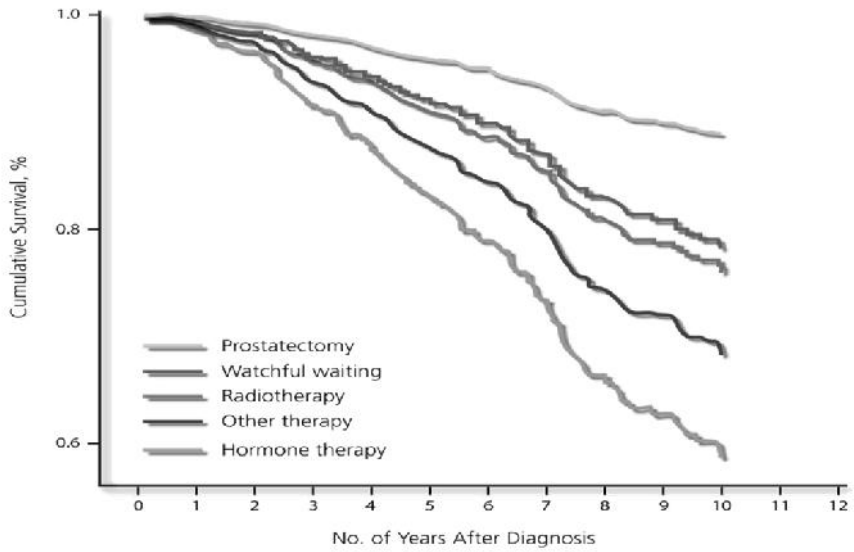
Long-Term Survival and Localized Prostate Cancer

A study of 3,159 patients found that 15 years after treatment, those who had undergone radical prostatectomy had a 40% lower risk of death from prostate cancer than radiation patients.[6]



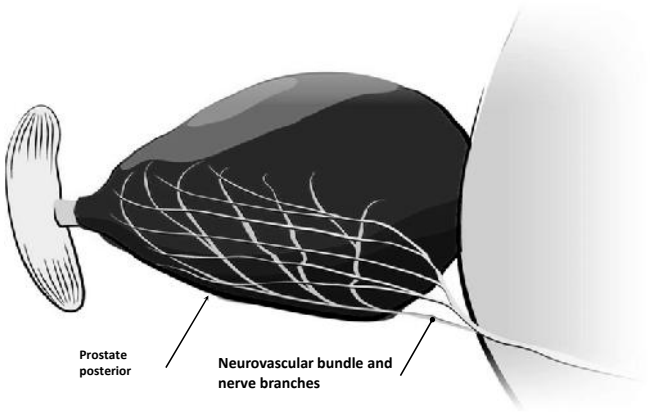
Froedtert & Medical College of Wisconsin

Surgery: Longer Survival vs. Any Other Treatment



Nerve-Sparing Prostatectomy

- Preserve nerves responsible for erections
- Nerves run alongside prostate
- *da Vinci* System permits surgeon to spare nerves
  - Enhanced magnification
  - Three-dimensional view
  - Robotically enabled *EndoWrist*® instruments



Froedtert & Medical College of Wisconsin

Robotic-Assisted Surgery Access

Open Surgical Incision

***da Vinci*® Prostatectomy Incision**

Froedtert & Medical College of Wisconsin

How can we overcome the drawbacks of laparoscopy?

- Provide a high-resolution 3D image
- Insert a computer between the surgeon's hand and the instrument tip
- Increase the surgeon's dexterity for the difficult aspects of the procedure, e.g.
  - Sparing the nerves to preserve erectile function
  - Preserving continence
  - Preserving quality of life

Froedtert & Medical College of Wisconsin

Clinical Concerns for Prostatectomy

"The Big 3"

1. Cancer Control – Margins
2. Urinary Control – Continence
3. Sexual Function – Potency

Froedtert & Medical College of Wisconsin

Conclusions

- Prostate Cancer diagnosis is controversial
- Patient selection is critical
- The answers point to more questions