SHARED CARE ON PROSTATE CANCER PATIENTS

Presented by:

Drs. John Day, Karim Marzouk, Junaid Yousuf

September 13, 2019

WINDSOR REGIONAL HOSPITAL

OUTSTANDING CARE – NO EXCEPTIONS!

COMPASSION is our PASSION

Objectives

1. Explore the pros and cons of prostate cancer screening

2. Review the role of primary care providers and specialty physicians in the prostate cancer journey

3. Explore the heterogenous treatment options for prostate cancer
   - Curative, salvage, palliative

The Case for Screening

- 62 year old, rarely visits office
- *PMHX:* HTN, DDD/Chronic low back pain
- *Meds:* Norvasc 7.5 mg, Tylenol #3 prn. NKDA
- *Family history:* Father CAD, mother breast cancer
- English/Irish
- No previous PSA tests
- Presents to office with “his usual low back pain”

The Case for Screening Continued

- Images show many osteolytic lesions spine
- PSA/bone scan/Pan scan/?others
- Diagnosed with stage 4 prostate cancer
- Referred to Urology
  - "I am sorry, but I can not cure this. We can try to slow it down and control symptoms."

- Referred to Oncology

Referred to Urology (Urologic Oncologist)

- "I am sorry, but I can not cure this… ***But there are excellent treatment options that can help you live longer & improve your QOL***"

- Prior to 2015 only treatment option was Androgen Deprivation Therapy (ADT)

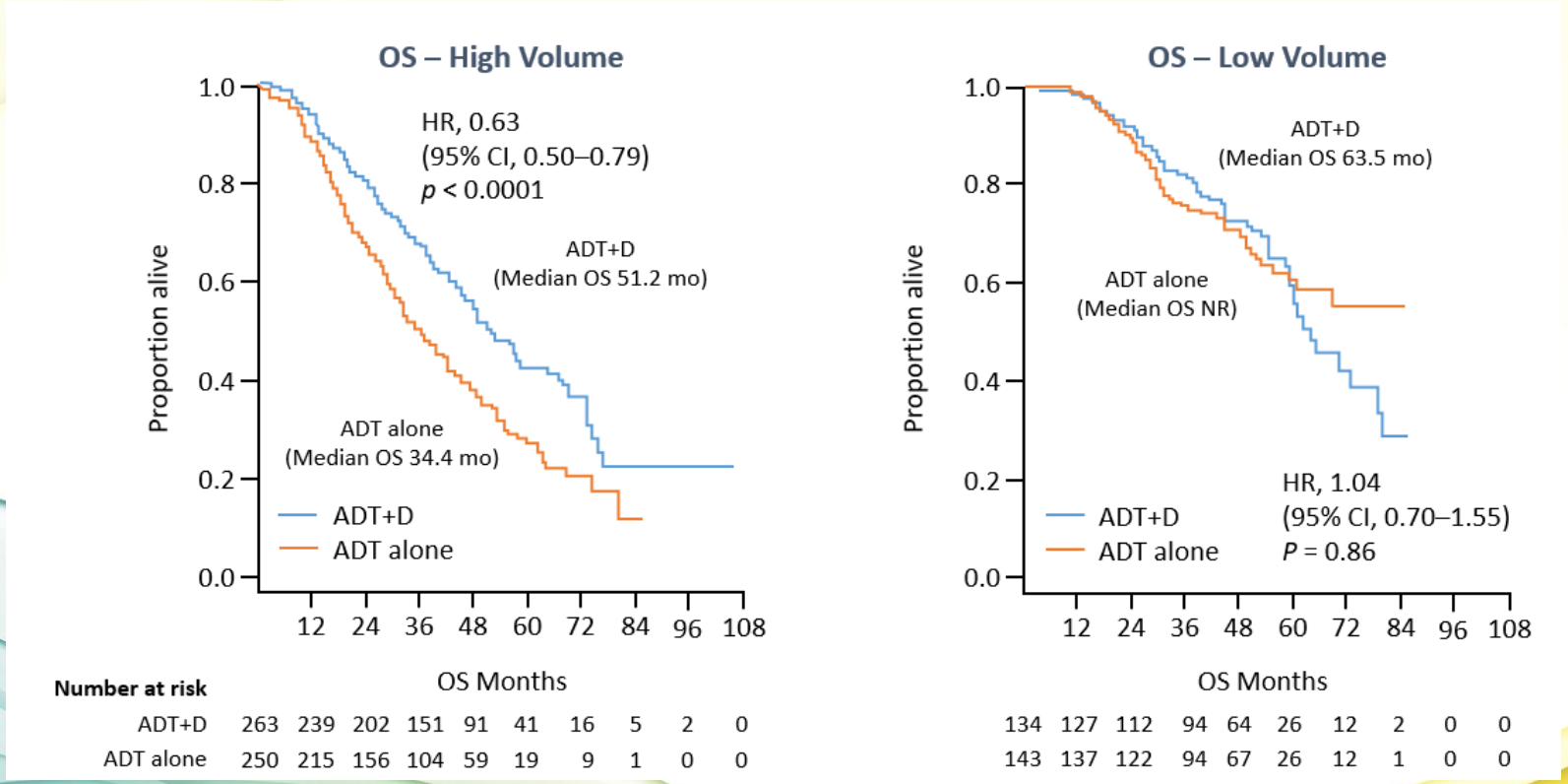
Treatment Beyond ADT Improves Overall Survival in mHSPC

Treatment	Study	Overall survival findings	
		Treatment + ADT	ADT alone
Docetaxel	GETUG-AFU 15 (n = 385)	Median: 62.1 months	Median: 48.6 months
		HR 0.88 (95% CI, 0.68–1.14), p = 0.03	
	CHAARTED (n = 790)	Median: 57.6 months	Median: 44.0 months
		HR 0.61 (95% CI, 0.47–0.80), p < 0.001	
	STAMPEDE-DOC (n = 1776)	Median: 81 months	Median: 71 months
		HR 0.79 (95% CI, 0.66–0.93); p = 0.006	
Abiraterone + prednisone	LATITUDE (n = 1199)	3-year OS: 66%	3-year OS: 49%
		HR 0.62 (95% CI, 0.51–0.76); p < 0.001	
	STAMPEDE-ABI (n = 1917)	3-year OS: 83%	3-year OS: 76%
		HR 0.63 (95% CI, 0.52–0.76), p < 0.001	

OS: overall survival

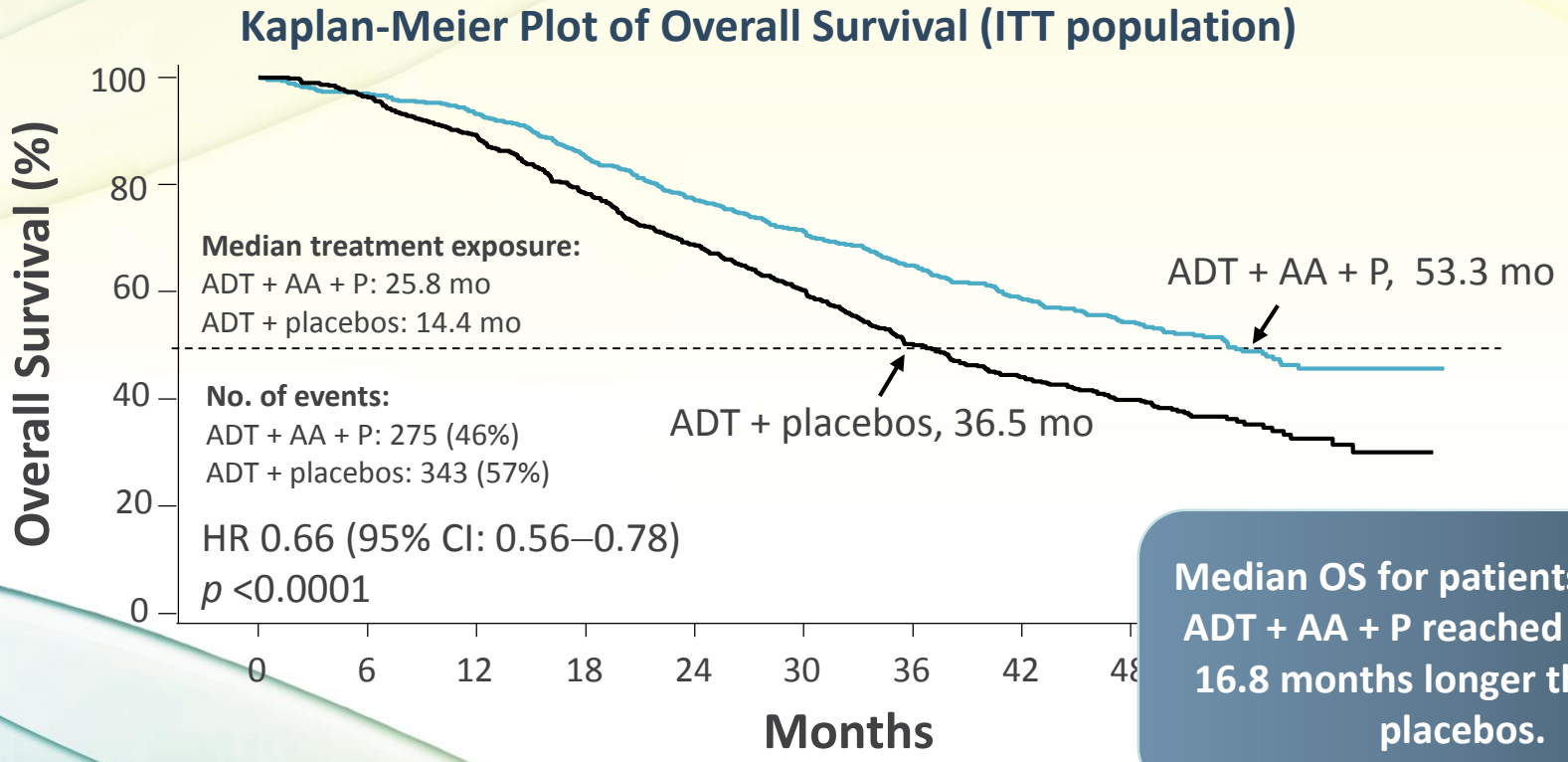
Adapted from McNamara M et al. *Prostate Cancer Prostatic Dis* 2017 Dec 20 [Epub ahead of print].

CHAARTED: Docetaxel in High-Volume Disease



Adapted from Sweeney CJ, et al. Presented at ESMO 2016; Poster #720PD

ASCO-GU 2019: LATITUDE Final Overall Survival



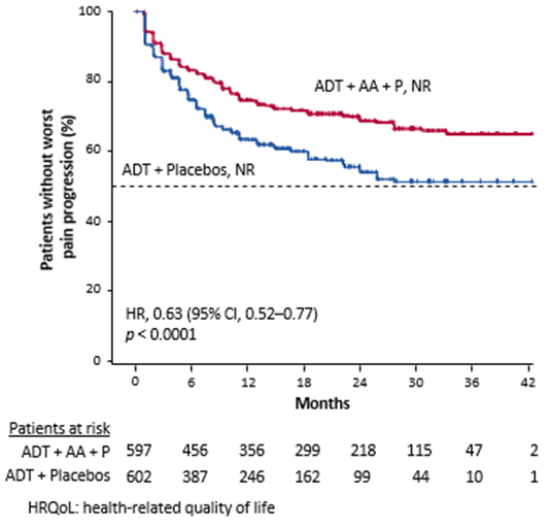
No. at risk

ADT + AA + P	597	565	529	479	425	389	351	311	240	124	40	0
ADT + placebos	602	564	505	432	368	315	256	220	165	69	23	0

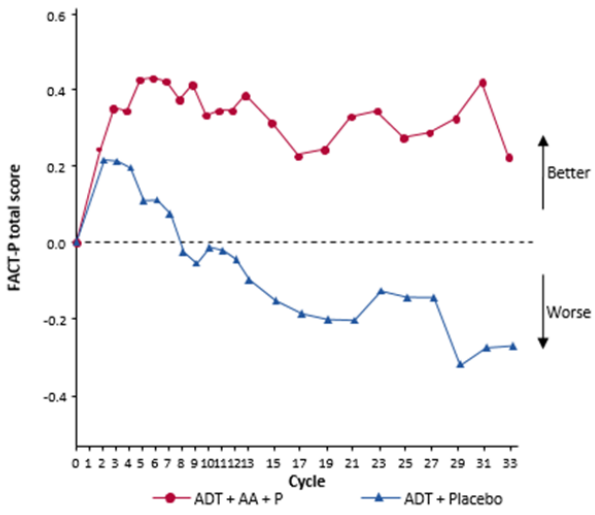
Median OS for patients receiving ADT + AA + P reached 4.5 years, 16.8 months longer than ADT+ placebos.

LATITUDE: Treatment Beyond ADT Improves Patient-Reported Outcomes

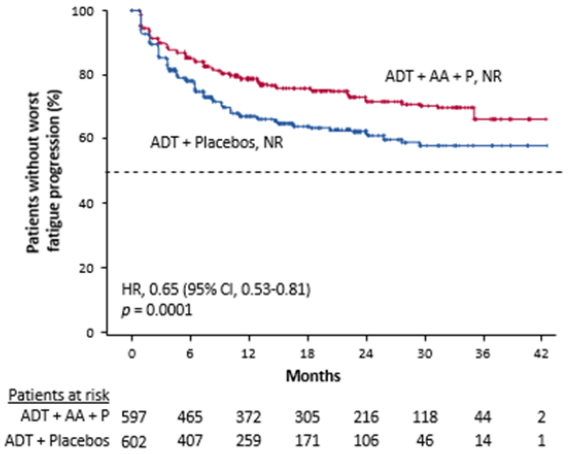
37% Risk Reduction for Worst Pain Progression



Mean HRQoL Change From Baseline Differed From Cycle 5 Onward



35% Risk Reduction for Worst Fatigue Progression



HRQoL: health-related quality of life

Chi K et al. *Lancet Oncol* 2018;19(2)194-206.

The Benefits of Earlier & Integrated Palliative Care

Better outcomes for patients and families:

- ✓ Reduced symptom burden
- ✓ Less anxiety and depression
- ✓ Less caregiver burden
- ✓ Better quality of life
- ✓ Less aggressive treatments
- ✓ More appropriate referral to and use of hospice
- ✓ Lower health care costs

Bone Metastases

Dose Fractionation (SF vs. MF)

- 800 cGy/1 fraction given for uncomplicated bone metastases

- 2000 cGy/5 fractions given for
  - spinal cord compression
  - ? neuropathic pain
  - ? remineralization
  - at the discretion of the treating radiation oncologist

- Median time to pain relief is 3 weeks
- Median duration of pain relief is 3-6 months

Evidence Conclusions

- No significant difference in pain relief between SF and MF palliative RT for bone metastases.

- Higher re-treatment and higher rate of pathologic fracture in SF arms.

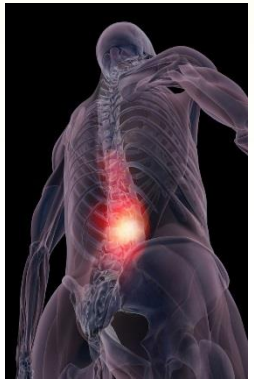
Neuropathic Pain

- One RCT compared 800 cGy/1 vs 2000 cGy/5 for patients with bone metastases causing neuropathic pain.[4]
- SF was not as effective as MFs for the treatment of neuropathic pain; however, it was not significantly worse.
- They recommended that 2000 cGy/5 be the standard.
- Caveats: poor estimated survival, poor KPS status, cost/inconvenience of multiple treatments was a factor, centers with lengthy wait times.

4. "Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05)." (Roos DE, Radiother Oncol. 2005 Apr;75(1):54-63

Remineralization

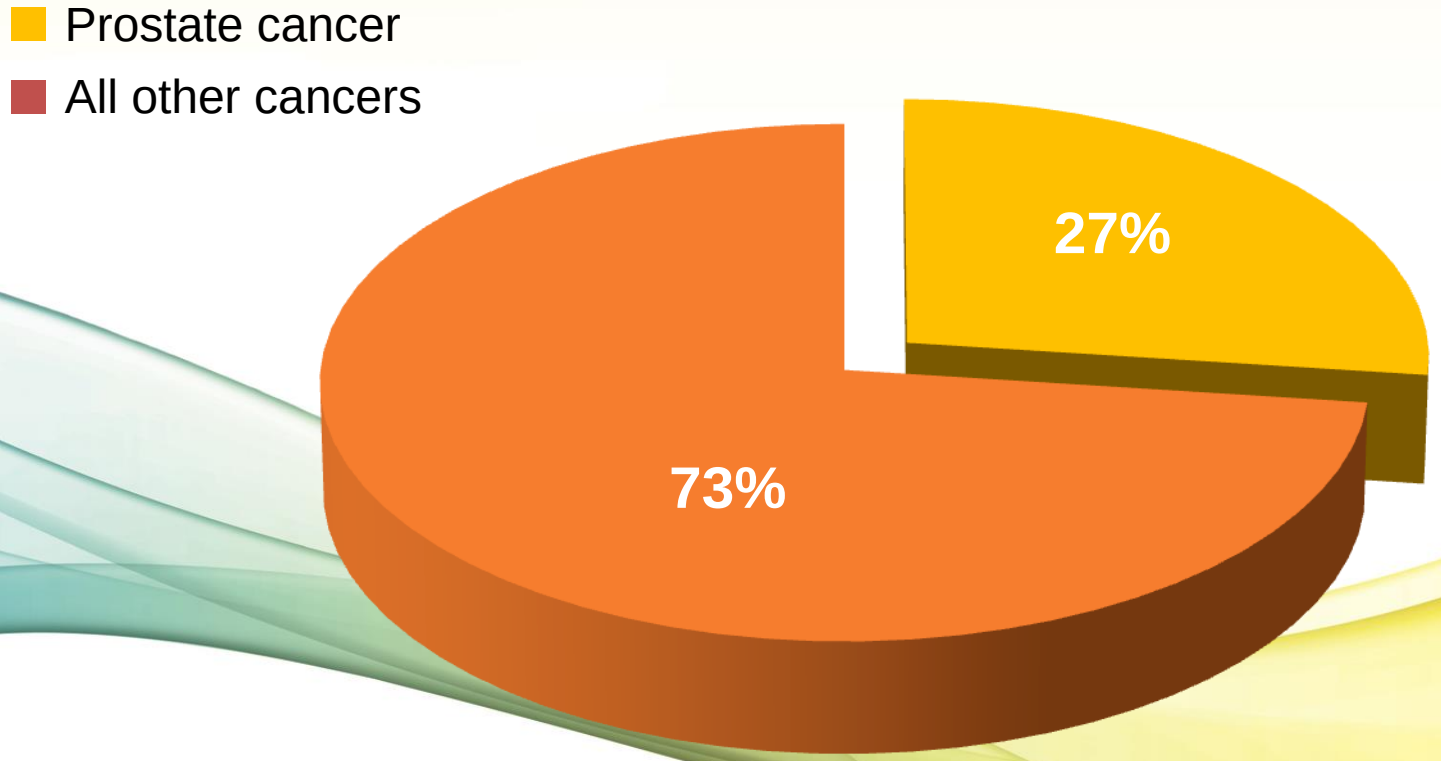
- Koswig et al. 8Gy/1 vs 30Gy/10 found equivalent pain relief, but more remineralization in the MF arm.
- At 6 months MF arm had a mean increase in bone density of 173% vs. 120% (p=s).
- ? Good prognosis patients with single bone metastasis treated with MF.



Why Prostate Cancer Screening is Important

The most common male malignancy

21,600 Canadian men

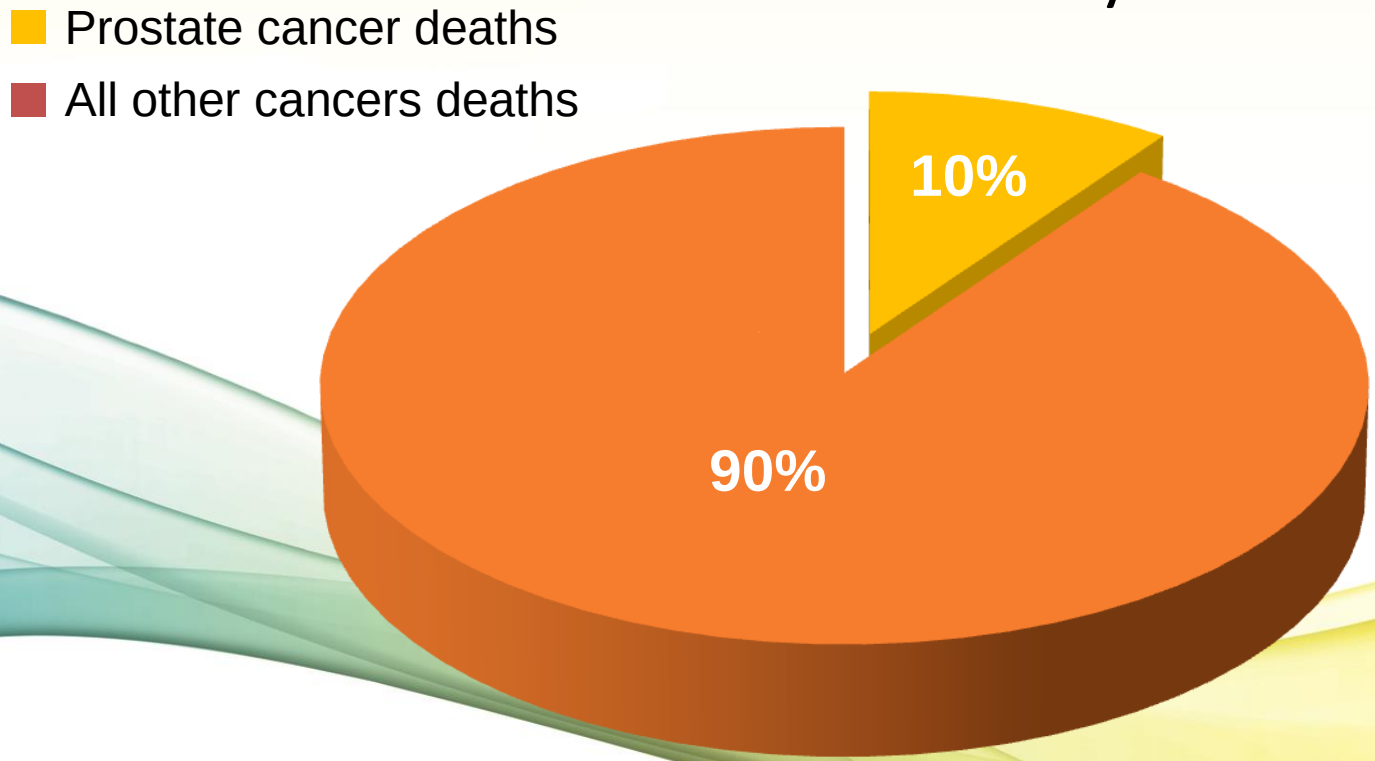


Canadian Cancer Statistics 2018

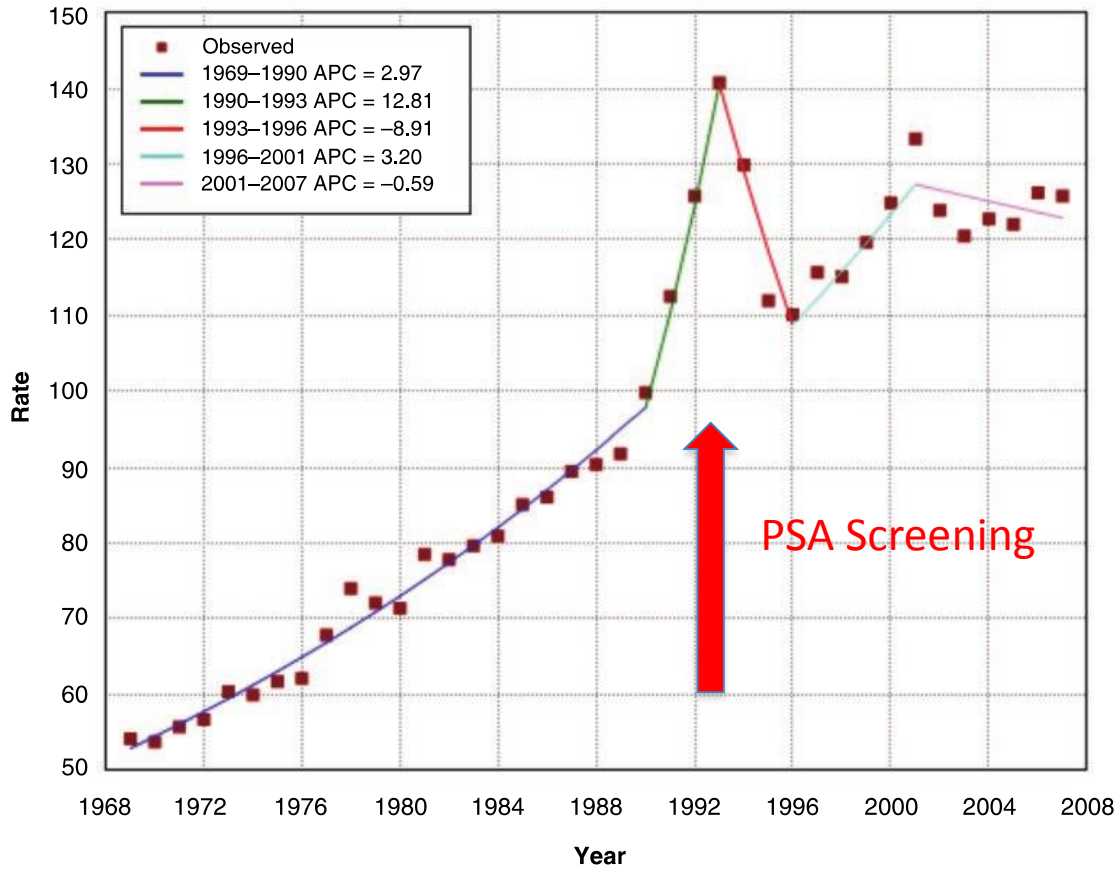
Why Prostate Cancer Screening is Important

2nd leading cause of cancer death

4000 deaths annually



Canadian Cancer Statistics 2018



Age standardized incidence & annual percent change of prostate cancer incidence in Canada

Dickenson et al. CMAJ Open. (2016)

PSA Screening & Prostate Cancer Mortality

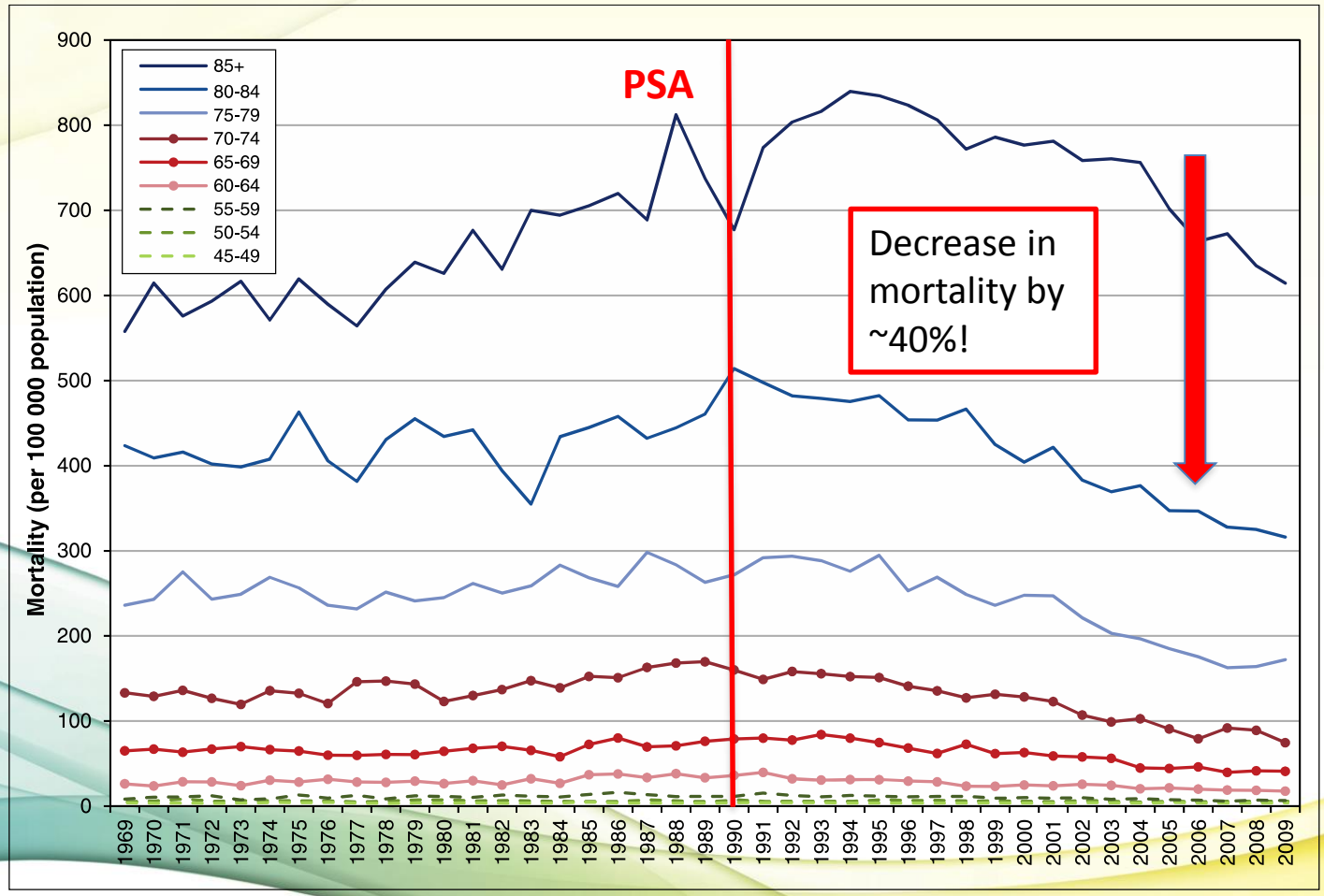


Figure 5: Mortality by age group, 1969–2009, Canada.

Dickenson et al. CMAJ Open. (2016)

U. S. Preventive Services Task Force (USPSTF) 2012 Screening for Prostate Cancer

Grade: D

Definition: The USPSTF recommends against screening for prostate cancer with PSA. There is moderate or high certainty that there is no net benefit or that the harms outweigh the benefits.

Suggestions for practice: Discourage the use of PSA screening.

Recommendations on screening for prostate cancer with the prostate-specific antigen test

Canadian Task Force on Preventive Health Care*

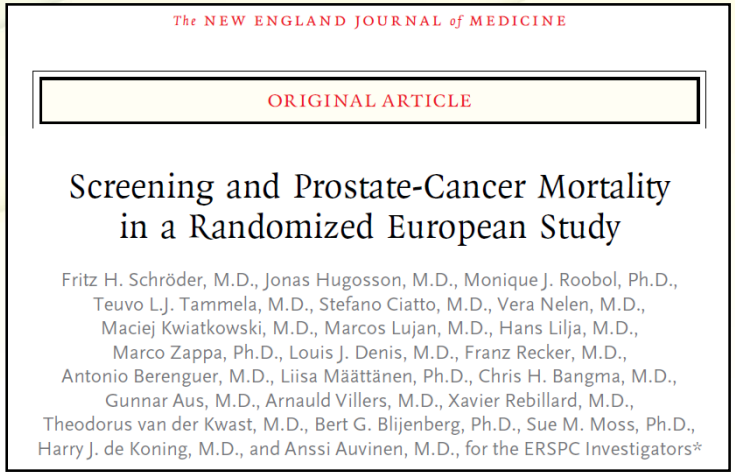
The recommendations apply to all men without a previous diagnosis of prostate cancer.

- For men aged less than 55 years, we recommend not screening for prostate cancer with the prostate-specific antigen (PSA) test. (*Strong recommendation*; *low-quality evidence.*)
- For men aged 55–69 years, we recommend not screening for prostate cancer with the PSA test. (*Weak recommendation*; *moderate-quality evidence.*)
- For men 70 years of age and older, we recommend not screening for prostate cancer with the PSA test. (*Strong recommendation*; *low-quality evidence.*)

Acknowledging the Harms of Screening

- **Screening has not been selective**
  - screening of elderly men with a short life expectancy
- **Large proportion of cancers diagnosed by screening are low-risk**
  - Likely clinically insignificant
- **Too liberal criteria for biopsy**
  - Sepsis rates are increasing
- **Too aggressive treatment of low-risk cancer**
  - Historical underutilization of active surveillance

Two Major PSA Screening Trials



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

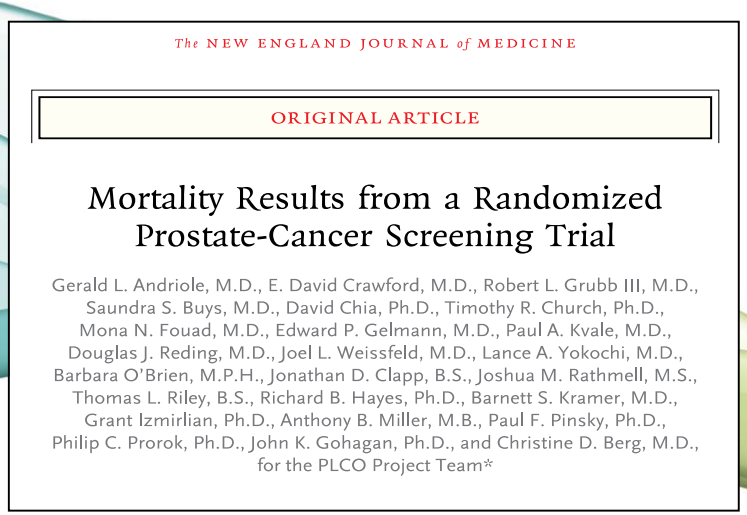
Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

ERSPC

182,000 men, age 55-69

PSA q4 years

21% reduction in PCa mortality



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

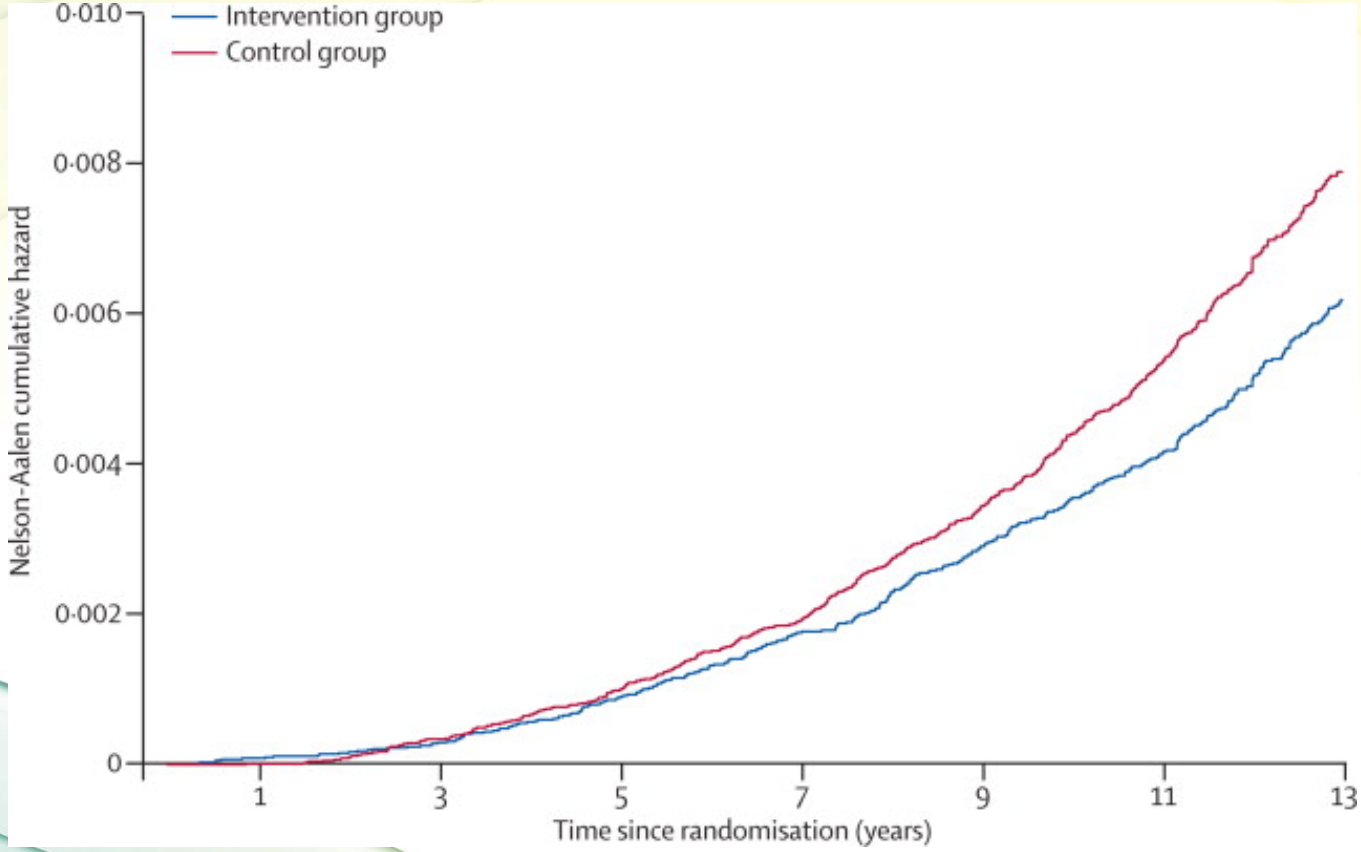
Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, 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., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D., for the PLCO Project Team*

PLCO

76,683 men, age 55-74

PSA annually

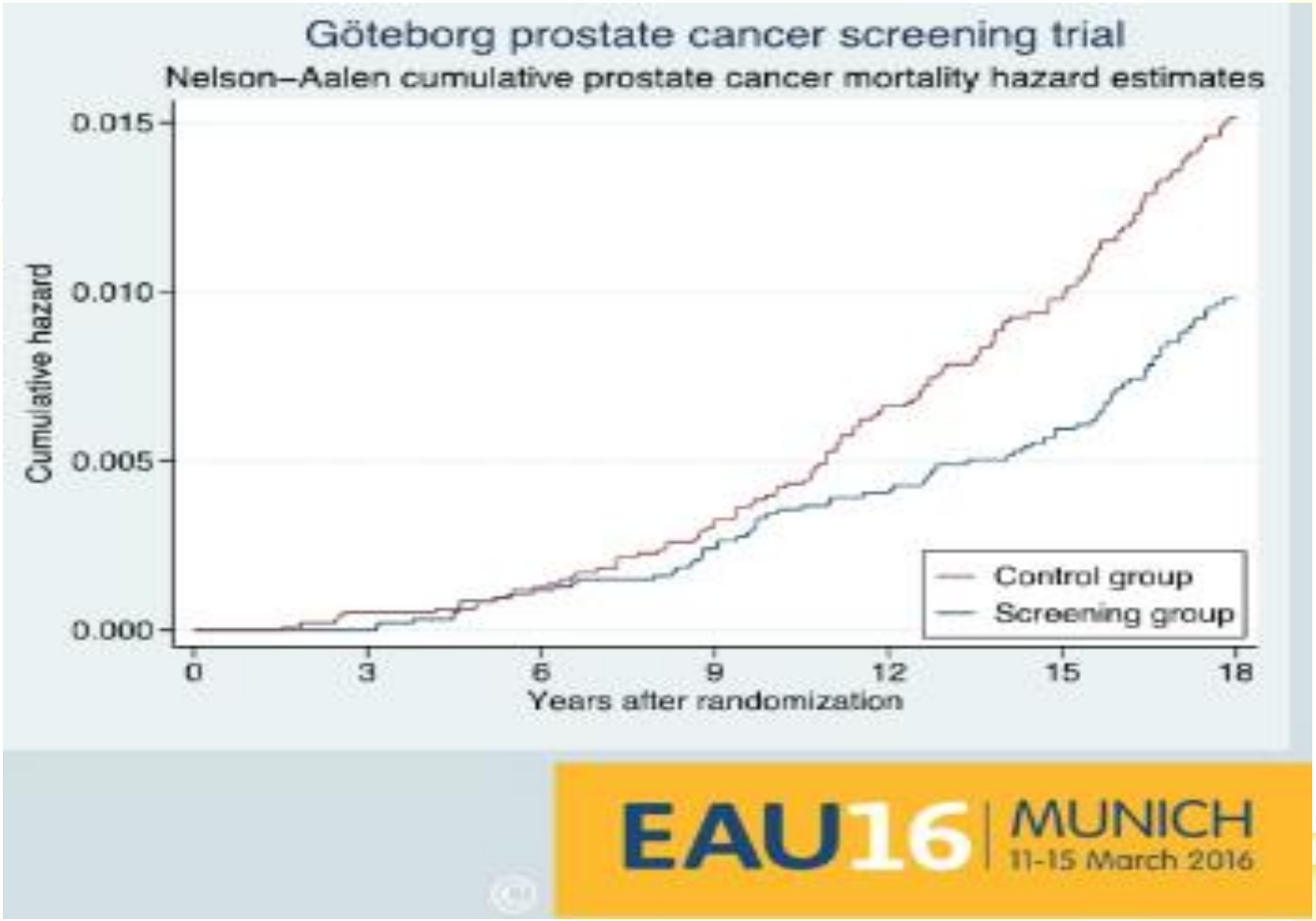
No difference in PCa mortality



ERSPC Trial
13 year f/u

Schroder F et al. The Lancet 2014;384:6-12

Prostate cancer deaths reduced by ≈ 40% at more than 14 years follow-up in Göteborg trial



42%

RR 0.65 at 18 years
(95% CI 0.49-0.87)
S: 0.98%
C: 1.50%

NNS = 139
NND = 13

Courtesy Sigrid Carlsson:
Hugosson, Carlsson, Lilja et al. *Lancet Oncol.* 2010;11:725-32.
Arnsrud Godtman R, et al. *EAU annual meeting* 2016.

NNS: # needed to screen
NND: # needed to diagnose

Why the Discrepancy with PLCO?

- High contamination rates ~90%

Opportunistic vs. Organized screening !!

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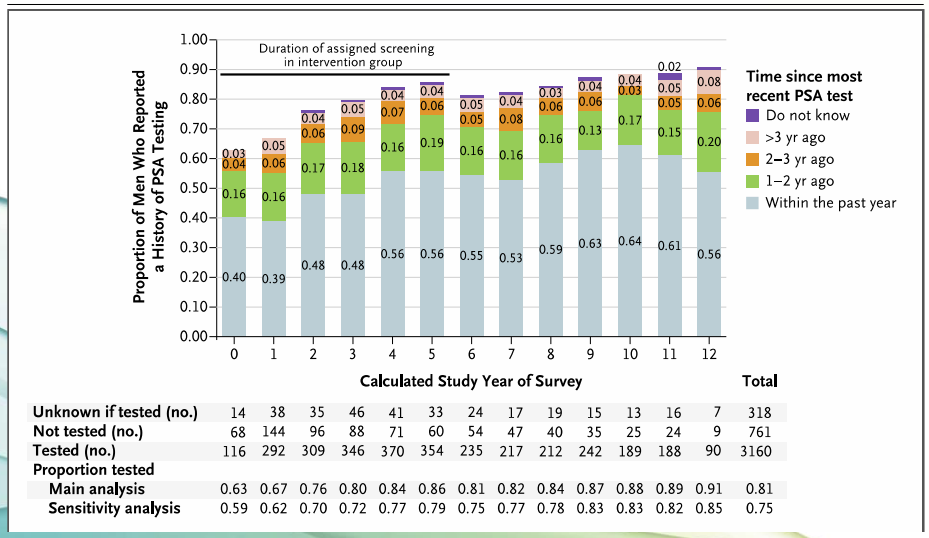


	0	1	2	3	4	5	6	7	8	9	10	11	12	Total
Unknown if tested (no.)	14	38	35	46	41	33	24	17	19	15	13	16	7	318
Not tested (no.)	68	144	96	88	71	60	54	47	40	35	25	24	9	761
Tested (no.)	116	292	309	346	370	354	235	217	212	242	189	188	90	3160
Proportion tested														
Main analysis	0.63	0.67	0.76	0.80	0.84	0.86	0.81	0.82	0.84	0.87	0.88	0.89	0.91	0.81
Sensitivity analysis	0.59	0.62	0.70	0.72	0.77	0.79	0.75	0.77	0.78	0.83	0.83	0.82	0.85	0.75

Years of study	PSA test in Controls PLCO
0-5	78.9%
6-17	85.9%

Shoag J et al NEJM 2016;374:18
Pinsky et al Cancer 2017;123:592-599

Revised USPSTF Recommendations

U.S. Preventive Services TASK FORCE

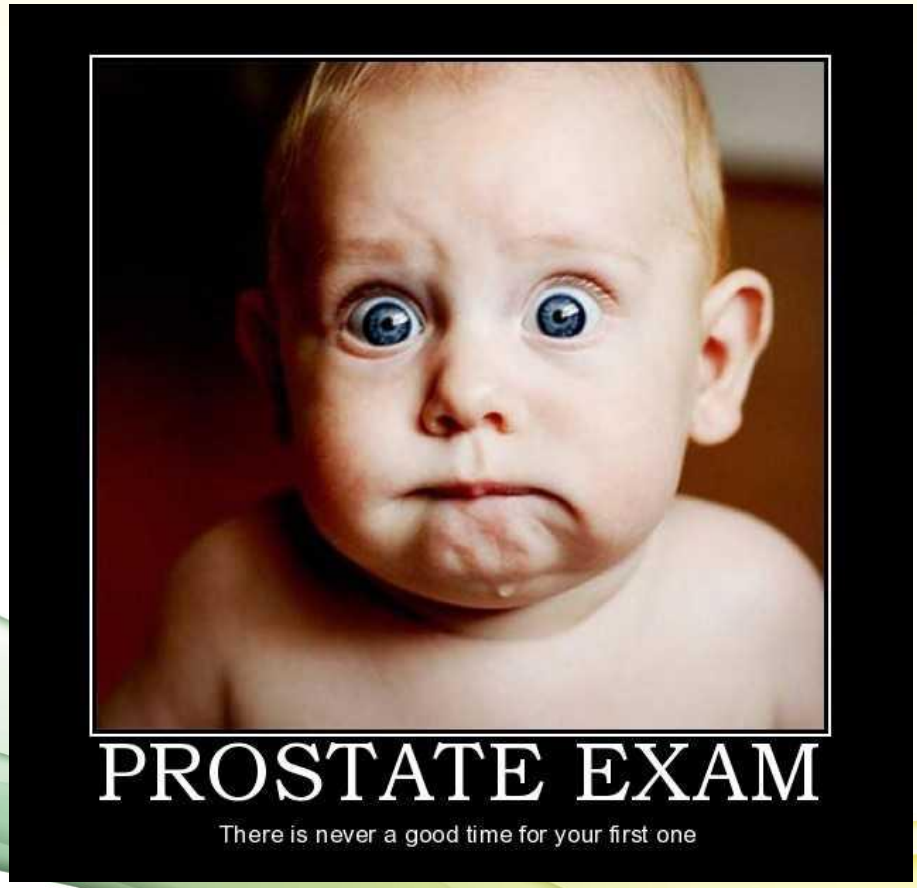
May 2018

Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men ages 55 to 69 years	The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)– 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.	C ?

Canadian Task Force on Preventive Health Care

What age should screening begin?



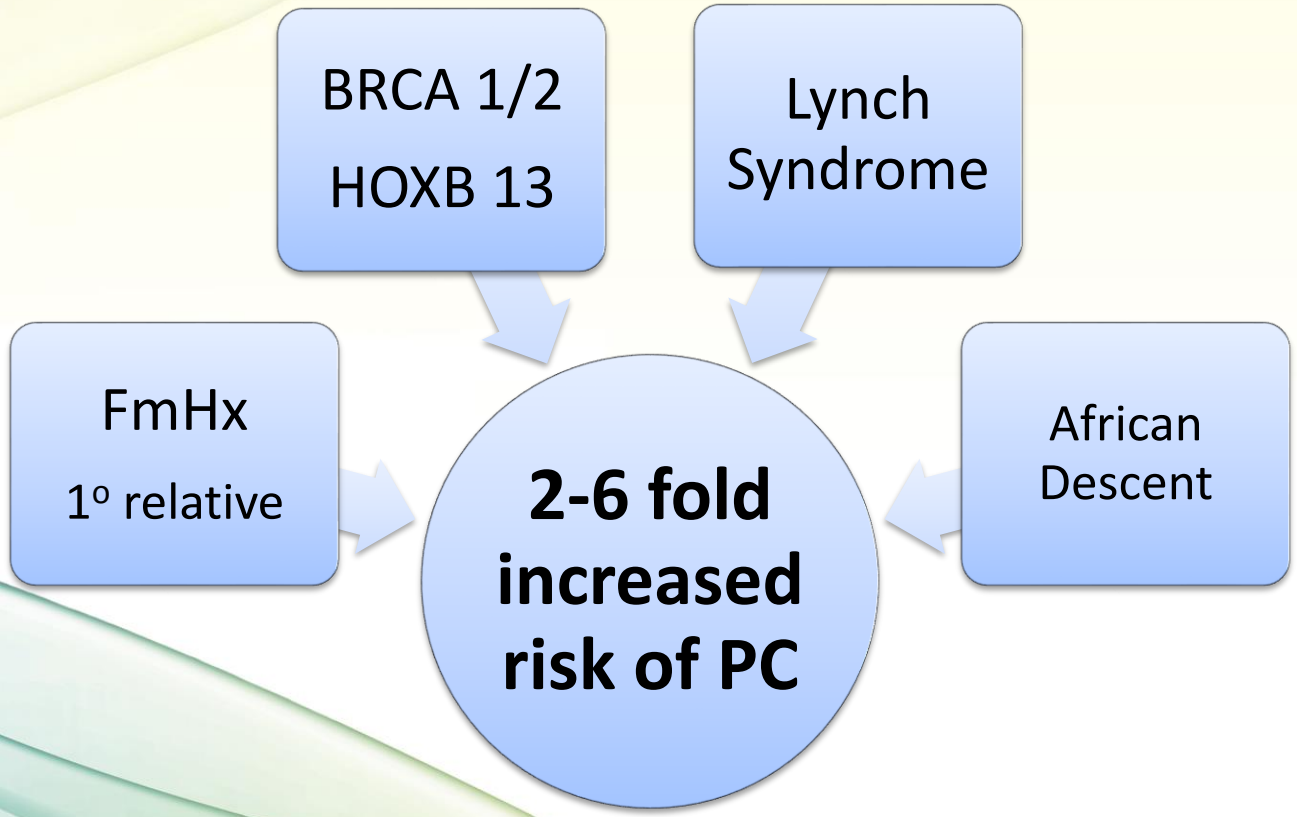
When to Start Screening

Guideline	CUA	NCCN	MSKCC	EAU-ESTRO	ASCO, ACS, ACP	AUA, USPSTF (draft)
Age	50	40-45	45	50; 45 if family history or African-American	50	55

Basis for CUA recommendations

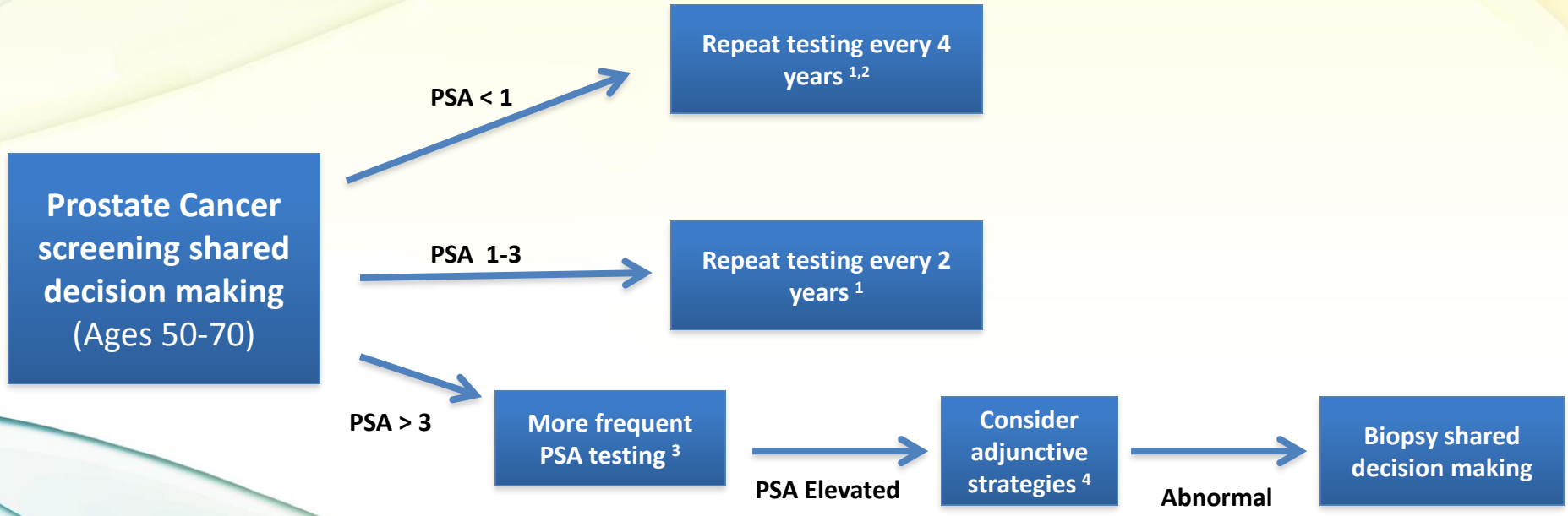
Goteborg – "Level 1" evidence for benefits starting at age 50

High Risk Populations



Consider screening earlier: 40-45 yrs

CUA Guidelines 2017



1. Discontinuation of screening if life expectancy < 10 years
2. Consider discontinuation of screening if Age >60 and PSA remains < 1
3. More frequent testing intervals can be considered, the optimal frequency is unknown
4. ie; Risk calculators, free PSA, biomarkers

Don’t screen men > 60 with PSA ≤ 1 ng/mL

- 10 000 men Gothenburg, Sweden screened for over 15 years

15 year follow up for men aged 60 with PSA ≤ 1 ng/mL

N=1756	Cumulative Incidence
Prostate Cancer Diagnosis	**3.6%**
Prostate Cancer Metastasis	**0.4%**
Prostate Cancer Death	**0.2%**

Carlsson S et al. *BMJ*. 2014; 348:g2296

PSA Screening Summary

Do's

- Discuss screening men 50-70 yrs old (shared decision making)*
- Risk stratify men based on PSA level
- Repeat the PSA if elevated

Don't's

- Screen men < 50 yrs old* & men >75 yrs old
- Screen unhealthy men 50-70 yrs old
  - Multiple significant medical comorbities
  - Life expectancy < 10 yrs
- Act on one PSA
  - Always should be repeated if elevated

CUA Guidelines 2017

CUA GUIDELINE

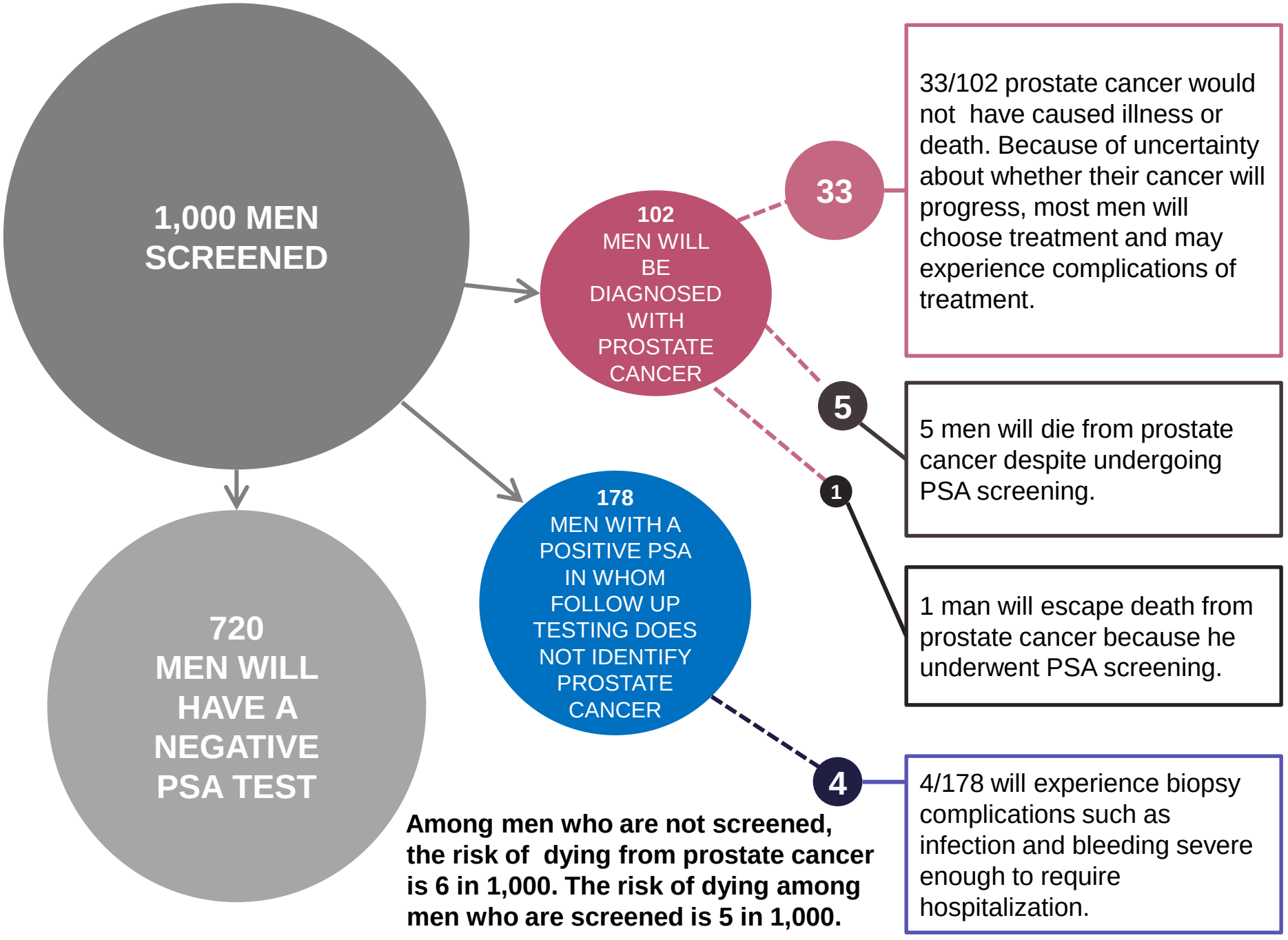
Canadian Urological Association recommendations on prostate cancer screening and early diagnosis

Ricardo A. Rendon, MD[1]; Ross J. Mason, MD[2]; Karim Marzouk, MD[3]; Antonio Finelli, MD[4]; Fred Saad, MD[5]; Alan So, MD[6]; Philippe D. Violette, MD[7,8]; Rodney H. Breau, MD[9]

CUAJ • October 2017 • Volume 11, Issue 10

The Case Against Screening

- Statements from USPTF, Canadian Task Force, CCO
- In AVERAGE risk people, do harms outweigh benefits?
- Consider all patients, intention to screen, no referral bias, unorganized screening
- Other screening intervals, ?other technologies


1,000 MEN SCREENED
720 MEN WILL HAVE A NEGATIVE PSA TEST
102 MEN WILL BE DIAGNOSED WITH PROSTATE CANCER
178 MEN WITH A POSITIVE PSA IN WHOM FOLLOW UP TESTING DOES NOT IDENTIFY PROSTATE CANCER
33
5
1
4
33/102 prostate cancer would not have caused illness or death. Because of uncertainty about whether their cancer will progress, most men will choose treatment and may experience complications of treatment.
5 men will die from prostate cancer despite undergoing PSA screening.
1 man will escape death from prostate cancer because he underwent PSA screening.
4/178 will experience biopsy complications such as infection and bleeding severe enough to require hospitalization.
Among men who are not screened, the risk of dying from prostate cancer is 6 in 1,000. The risk of dying among men who are screened is 5 in 1,000.

When Physicians Fight

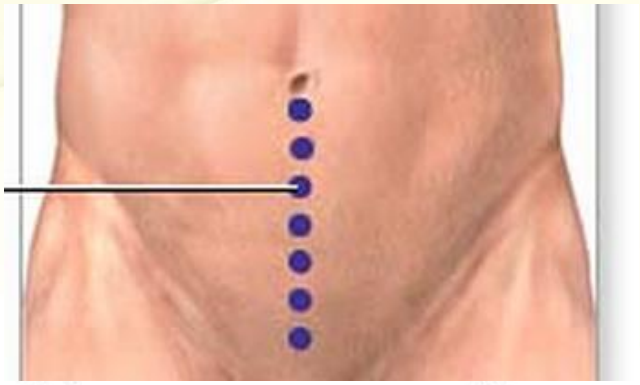
- 62 year old, regular check ups
- HTN, DDD/OA back
- Family hx of prostate cancer (older brother)
- African heritage
- PSA rises: 2.8, 3.4, 6.2
- Urology consult, bx completed
- Gleason 7
- Confined to prostate? How do we know?

When Physicians Fight

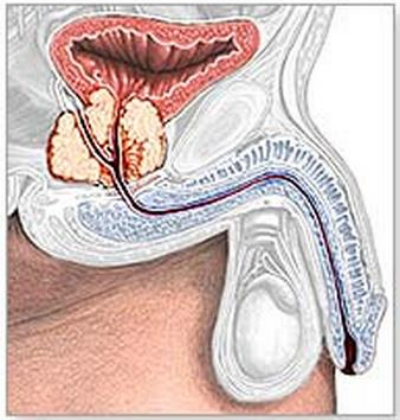
- Urology offers surgery
- Patient returns to family doctor, scared of surgery
- Referred to radiation oncology: offered brachytherapy
- Patient returns to family doctor, scared of radiation
- Patient wants to know what family doctor would do if it was his/her brother

Key Evidence Suggests

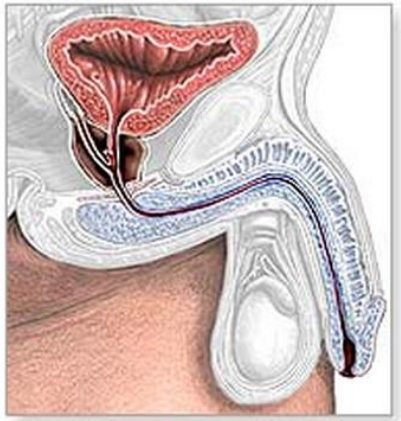
Radical Prostatectomy



Before



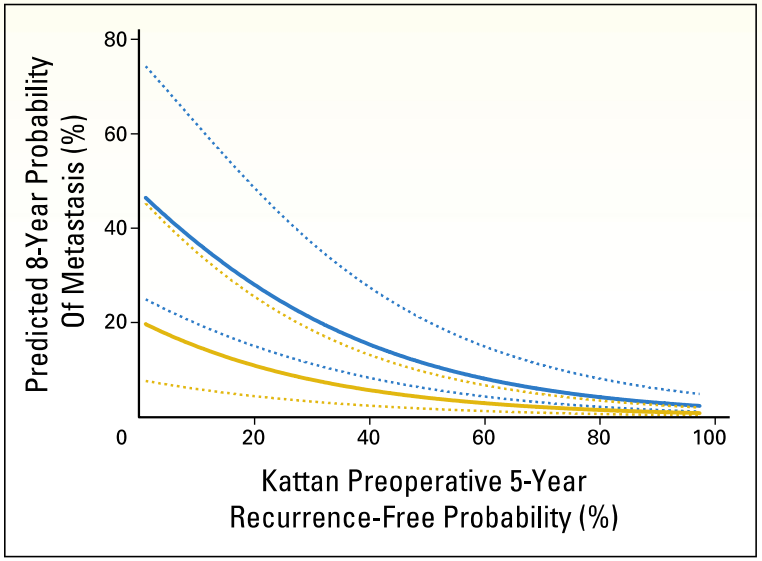
After



The Case for Surgery

Pros

- MIS allowed for faster recovery
- Allows for staging & tx of lymph nodes
- Excellent treatment option for men with obstructive LUTS
- Young men with high risk disease

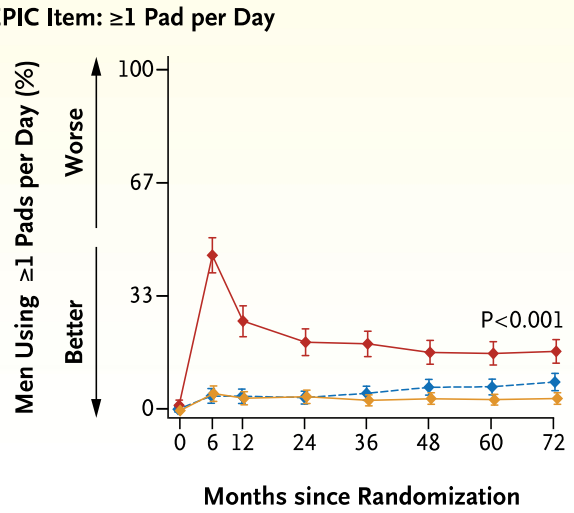


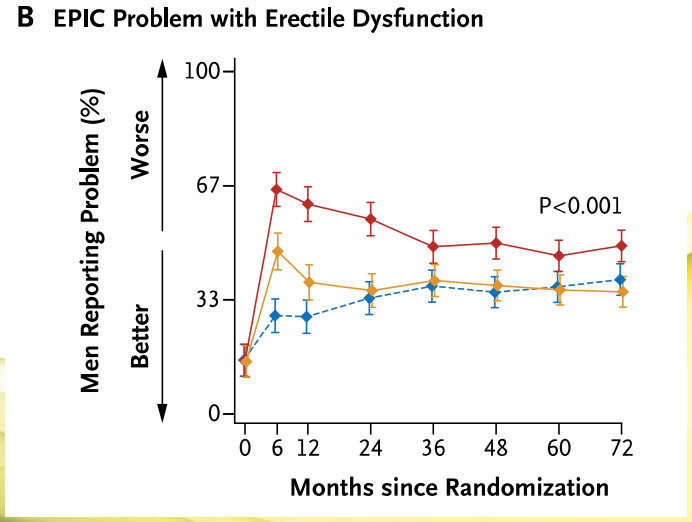
Zelefsky et al. JCO (2010)

The Case for Surgery

Cons

- It's still surgery
  - Not an option for everyone
- Cost for robotic surgery
- Functional outcomes
  - Erections
  - Incontinence

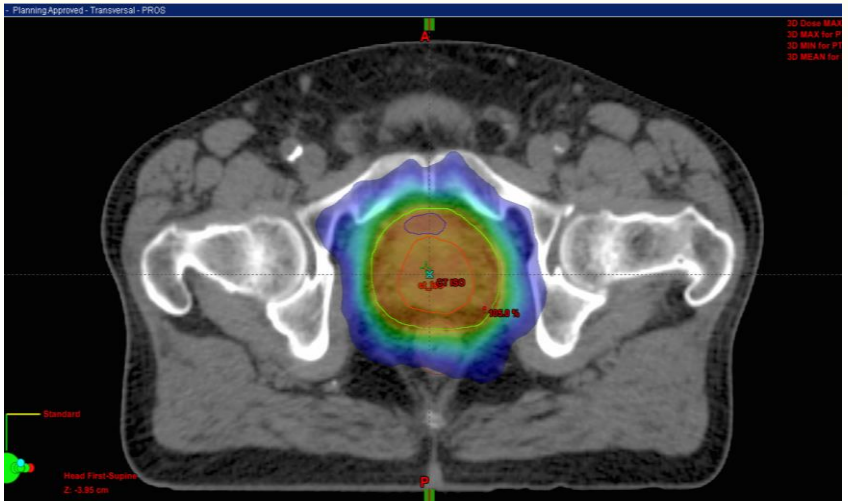




Radical prostatectomy
Radical radiotherapy
Active monitoring

Donovan et al. NEJM (2017)

External Beam Radiotherapy



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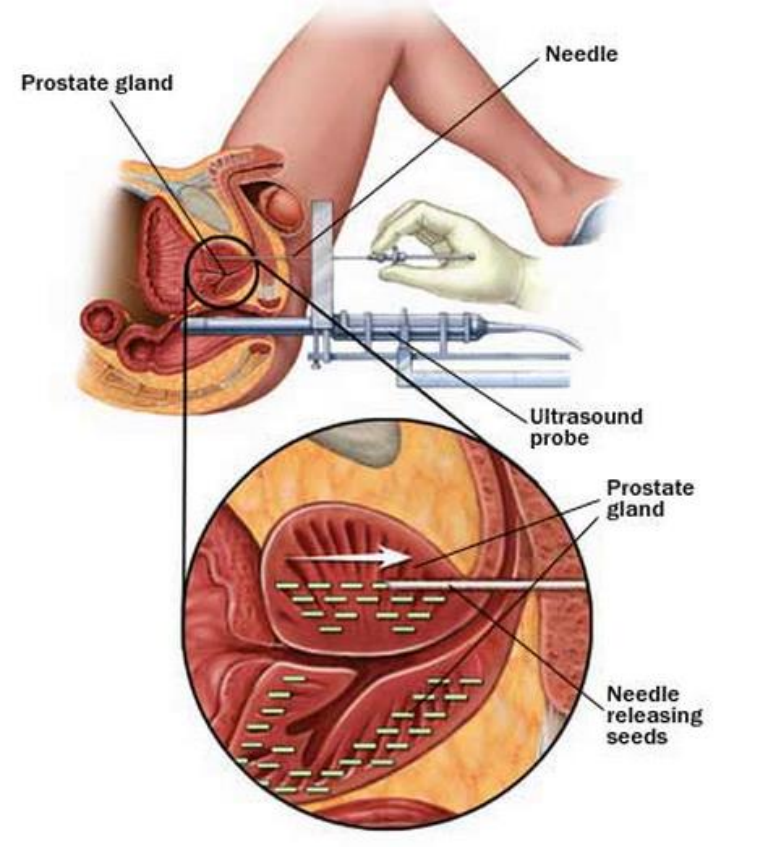
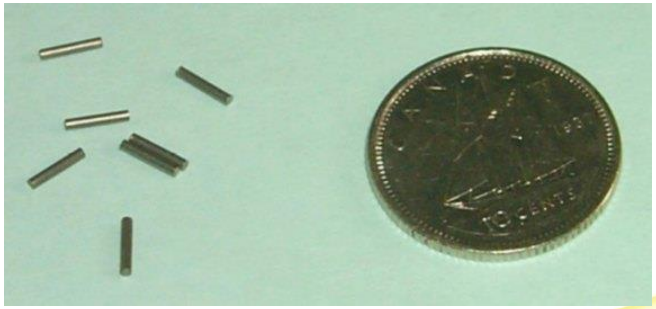
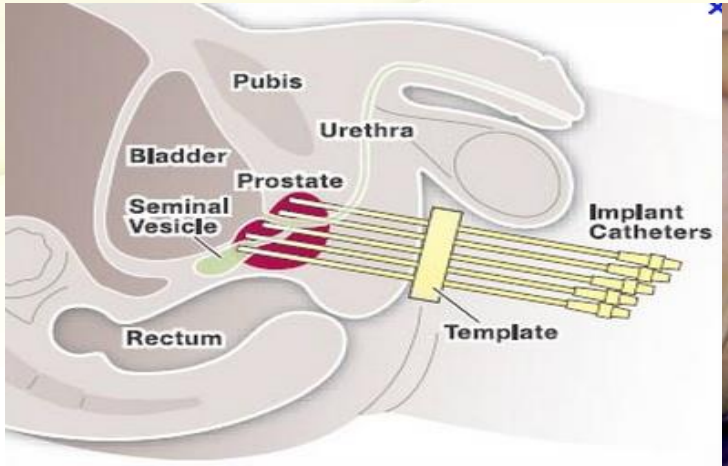
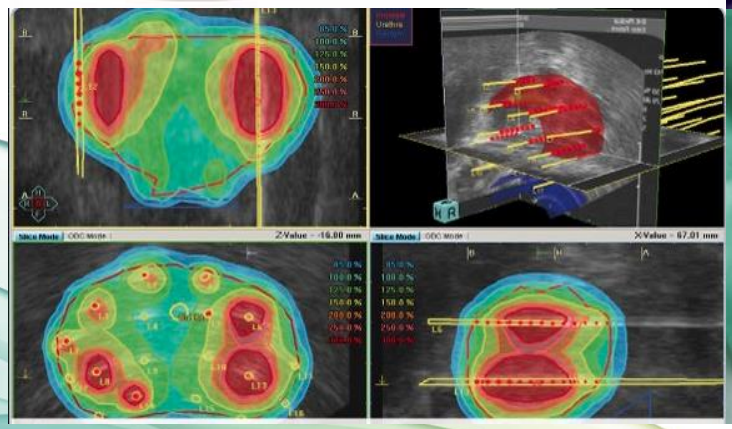
Seed Brachytherapy

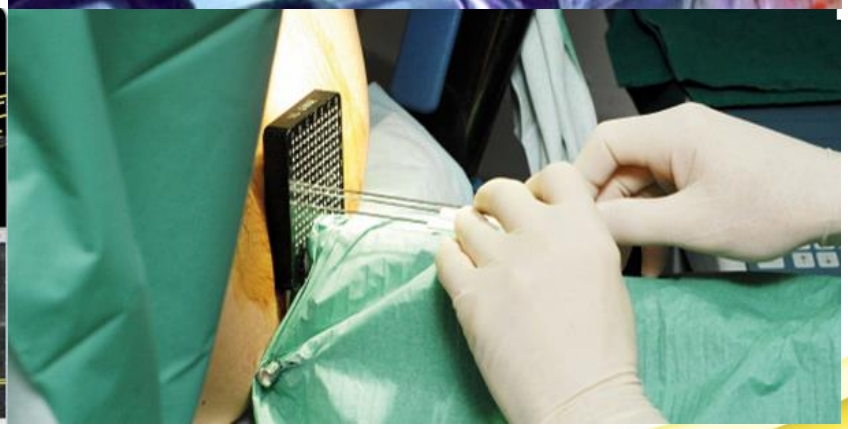




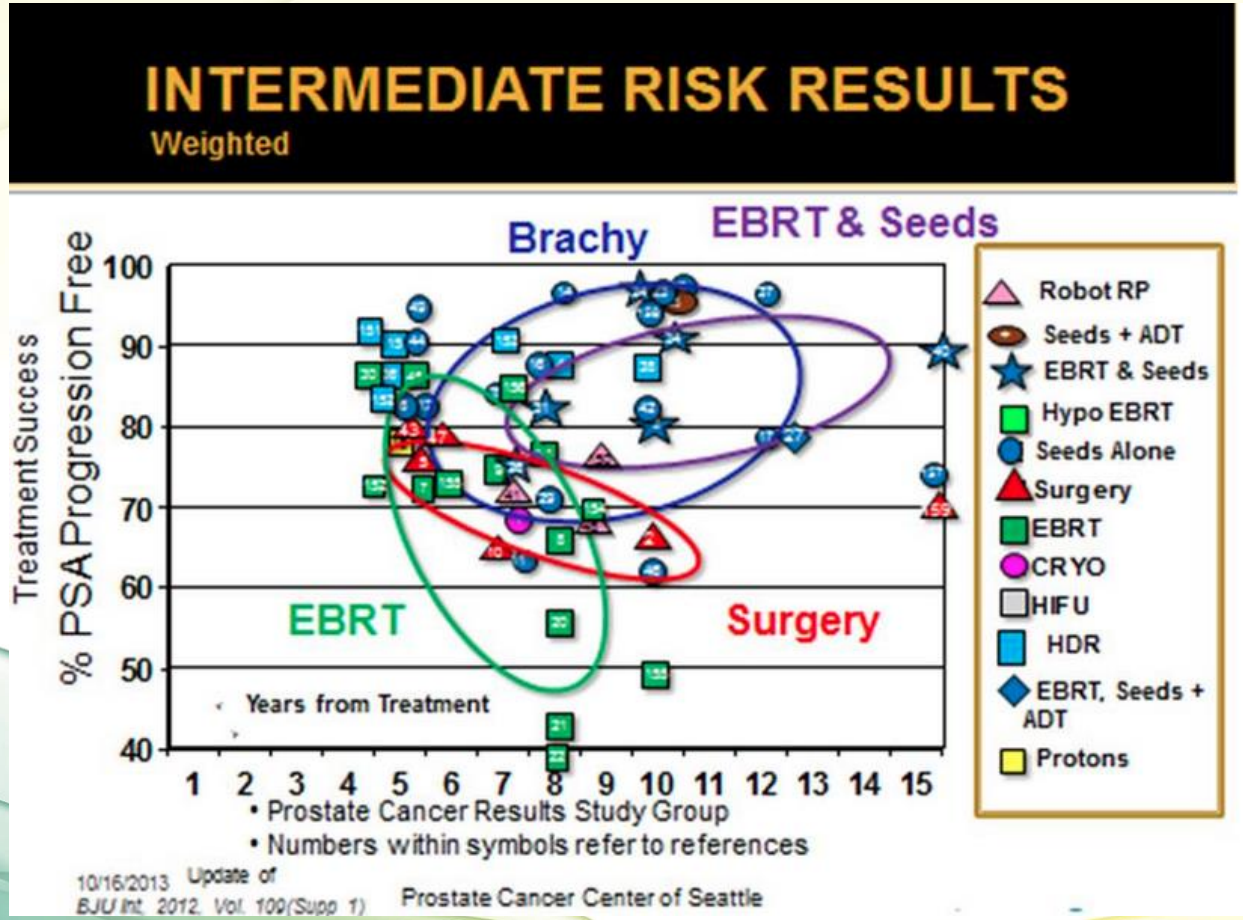
HDR Brachytherapy







Curative Treatment Options!



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COMPASSION is our PASSION

Prostate Cancer Follow-up Guidelines

Recommended Tests	Year 1	Year 2	Year 3+
Medical follow-up care appointment (including medical history and physical examination)	Every 3 months	Every 6 months	Every 12 months
Prostate-specific antigen (PSA) test: •Curative-intent treatment with **surgery** •Curative-intent treatment with **non-surgery** primary therapy	 Every 3 months Every 6 months	 Every 6 months Every 6 months	 Every 12 months Every 12 months

Recommended Tests	Recommendation
Complete blood count (CBC)	• For patients on androgen deprivation therapy (ADT) • Annually to monitor hemoglobin levels
Baseline DEXA scan and calculation of a FRAX score	Assess risk of fracture

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Buyers Remorse

- Followed by Oncology, Urology and Family Medicine
- Patient returns and complains of incontinence, ED
- Happy with recovery otherwise, no unexpected complications
- 2 years later, PSA starts to rise. Images are normal.
- What now?

PSMA

- Prostate Specific Membrane Antigen

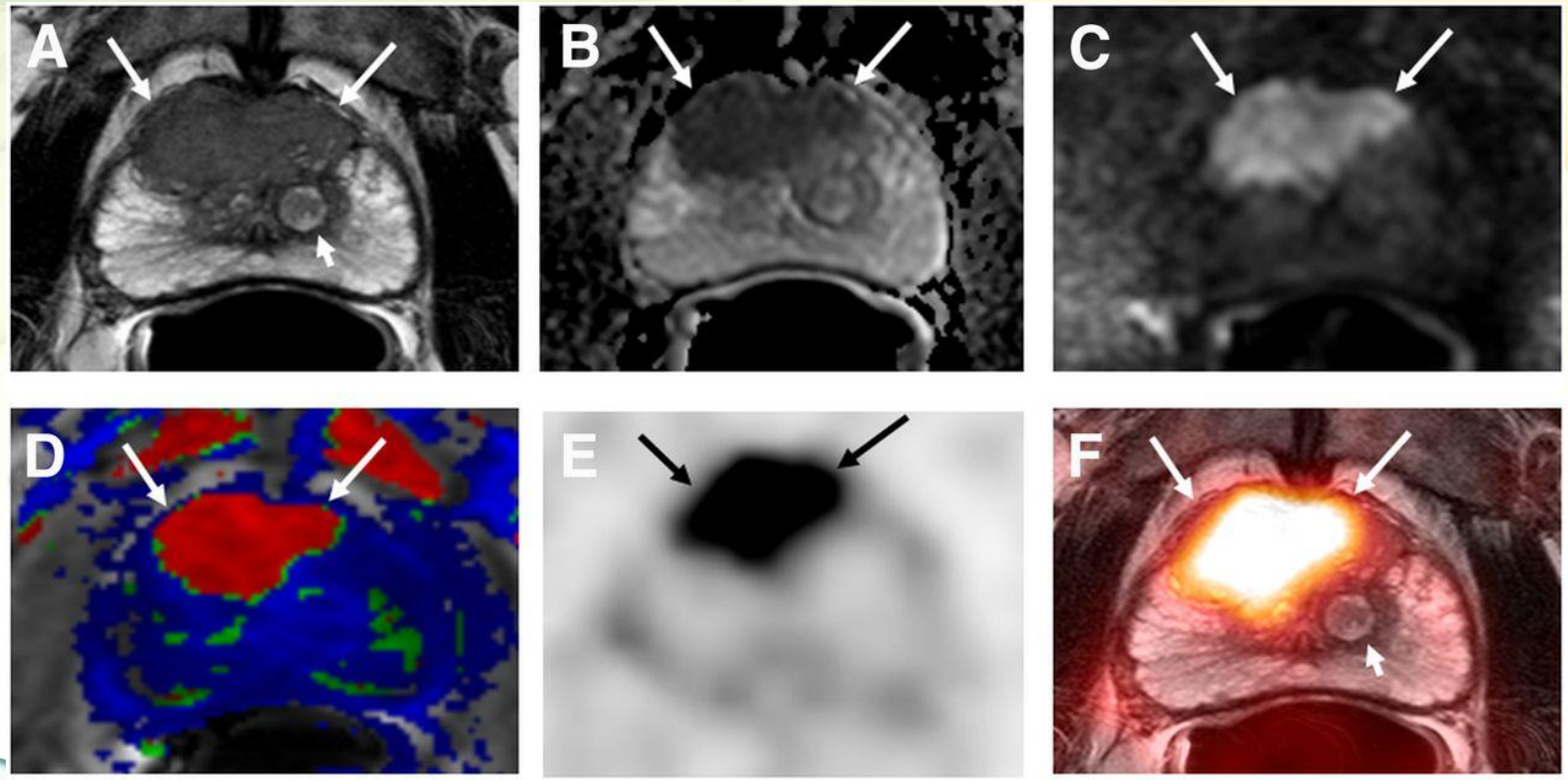
- Excellent target antigen for prostate cancer

- Highly and specifically expressed on the surface of prostate cancer cells at all tumor stages

- Neovasculature of PCa also expresses PSMA

PSMA

- PSMA-11 ligand labelled with ^{18}F or ^{68}Ga
- ^{68}Ga-PSMA-11 or ^{18}F-PSMA ligands
- Low level expression in brain, kidneys, salivary glands and small intestine
- Rises with de-differentiation and in metastatic and hormone refractory cancers



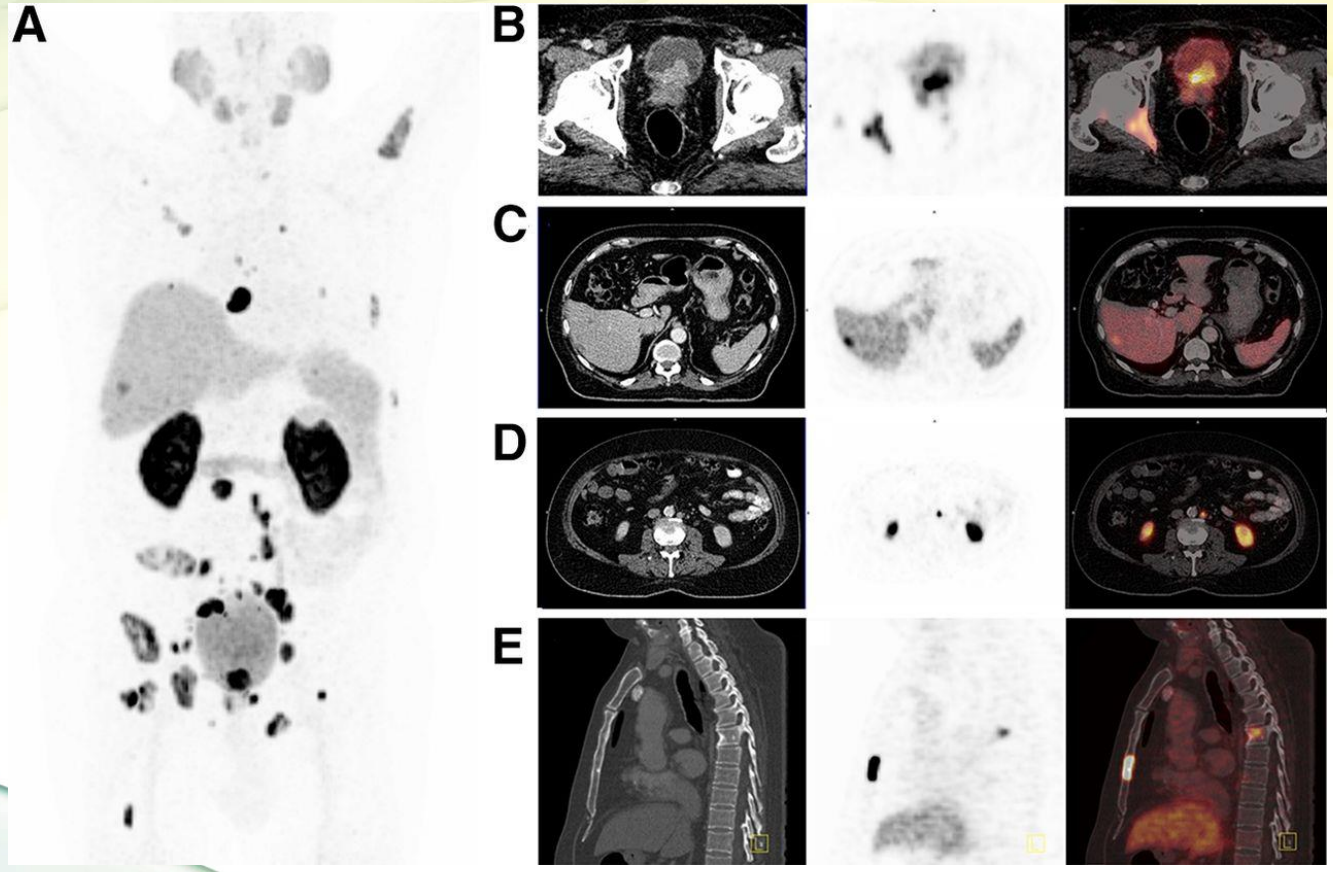
73-y-old man (serum PSA, 38 ng/mL) with history of 2 negative TRUS-guided prostate biopsies. Liza Lindenberg et al. J Nucl Med 2016;57:111S-116S

JNM The Journal of NUCLEAR MEDICINE

Metastatic Disease

RISING PSA POST-THERAPY:

- Oligometastatic disease: resection or stereotactic XRT
- Diffuse mets
- Distribution of mets: low vs. high risk patients
- Response to therapy



68Ga-PSMA I&T PET/CT of patient 1. Martina Weineisen et al. J Nucl Med 2015;56:1169-1176

The Case for Doing Less

- 62 year old, regular visits
- Pmhx: HTN, DDD/Mechanical low back pain
- PSA at baseline 1.2
- PSA 24 months later: 3.2
- Family doc remembers something about PSA velocity being important
- Send to Urology (punts)

The Case for Doing Less?

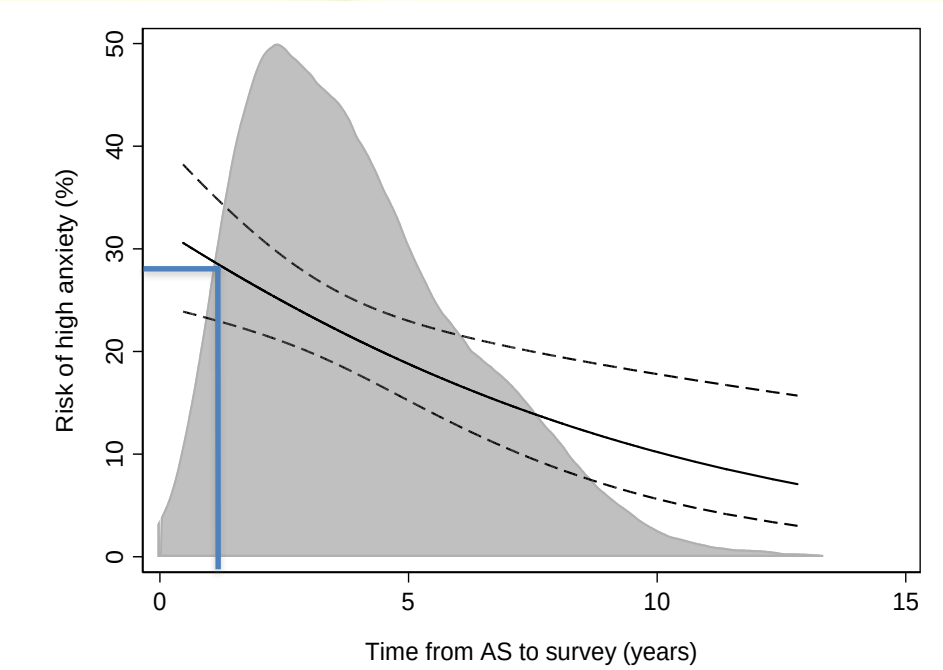
- Urology proceeds to bx
- Gleason score 6
- Imaging/staging has no other concerns
- “Are you telling me you want to do nothing?”
  - I think I need a second opinion?

Active Surveillance (AS)

- Standard of care for Gleason 6 (low risk) PC

- **Deferral of radical therapy - maximize QOL**
  - ~2/3 men will avoid treatment
  - Cancer Specific Survival ~98-100% (Klotz et al, JCO 2015)
  - ~15% may D/C AS because of anxiety

PC Anxiety Decreases Over Time



Risk of reporting cancer specific anxiety **29%** within first year of AS

OR 0.87; 95% CI: 0.79, 0.95; p=0.003

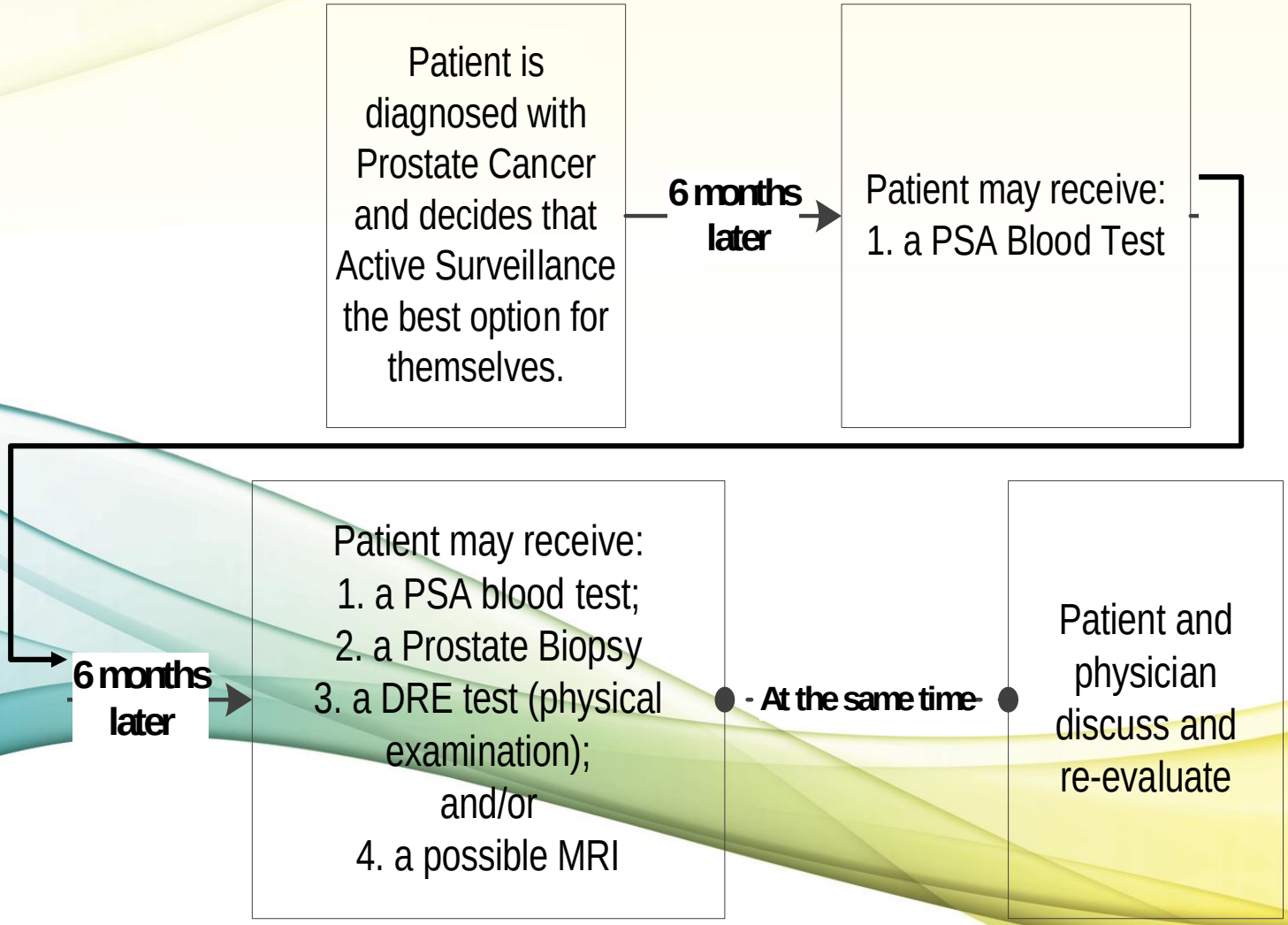
Variable	OR	95% CI	p-value
Age (n=413)	0.98	0.96, 1.01	0.3
Overall Health Score (n=413)	0.83	0.74, 0.93	0.002
Number of Positive Cores on Diagnostic Biopsy (n=399)	1.00	0.83, 1.19	1
Relationship Status (n=412)			
Single	Ref.	.	.
Married	0.69	0.42, 1.13	0.14
Gleason Score on diagnostic biopsy (n=412)			
6	Ref.	.	.
7-8	0.43	0.12, 1.49	0.2
Family History of prostate cancer (n=413)	1.03	0.66, 1.61	0.9
Visit Type (n=372)			
Non-Biopsy	Ref.	.	.
Biopsy	1.26	0.83, 1.92	0.3

Marzouk et al. AUA (2018)

Cancer Care Ontario

Prostate Cancer – Active Surveillance – A Guide for Patients

First Year of Diagnosis:



Tying it all Together

- A common, complex, condition that requires all stakeholders involvement
- Remember the multiple uses of radiation therapy
- There's more to survival than ADT
- If unsure how to navigate, reach out to Urology or Oncology