Management of localized prostate cancer, risk stratification, and progress

or

‘Shrinking the grey zone’

ESMO Asia, Singapore Dec 19 2015

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Our world has changed over last decade

2005

- Benefits of PSA widely accepted by urological community
- Enthusiasm for chemoprevention
  - PCPT 2003
  - SELECT trial launched (Vit E, Sel)
- Benefit of RP on Pca mortality (SPCG-4, NEJM 2002)
- Menon 1st Robot RP SUO 2003
- Taxotere survival benefit; no other drugs for CRPC improve OS
- 95% of low grade Pca treated radically

2015

- USPSTF Grade D on PSA screening; CTFPHE similar
- Chemoprevention dead
  - FDA denies 5 ARI approval
  - SELECT trial negative, increased Pca Vit D arm
- Minimal impact of RP on OS, CSS in PIVOT (Wilt, NEJM 2012)
- In US: Open RP on life support, ~80% Robotic RP
- Abi/Enza/Cab/Zofigo approved
- MRI transforming field
- Active Surveillance
- Focal therapy

Localized PCa - Treatment Options

Conservative

Active Surveillance

Organ Sparing

Focal Therapy

Radical Therapy

Surgery vs

Radiation + ADT

Active Surveillance for low risk PCa
What has changed recently?
(since Klotz, Choo J Urol 167: 1664, 2002)

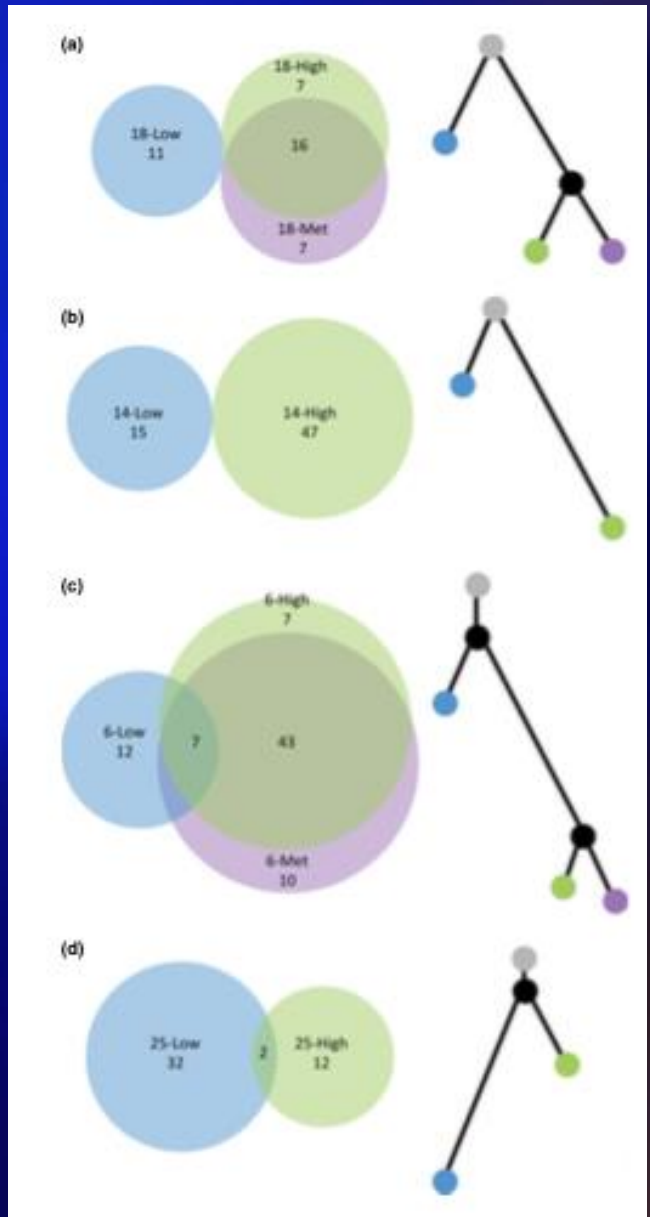
- Greater recognition of overtreatment problem, wide acceptance of surveillance concept
- Better understanding of nature of occult high grade disease
- Predictive value of baseline parameters for metastasis and defining of risk
- Better understanding of flaws of PSA kinetics
- Multiparametric MRI
- New modelling studies
- Longer follow up
- Randomized data on role of 5 ARIs

Gleason 3 lacks hallmarks of cancer

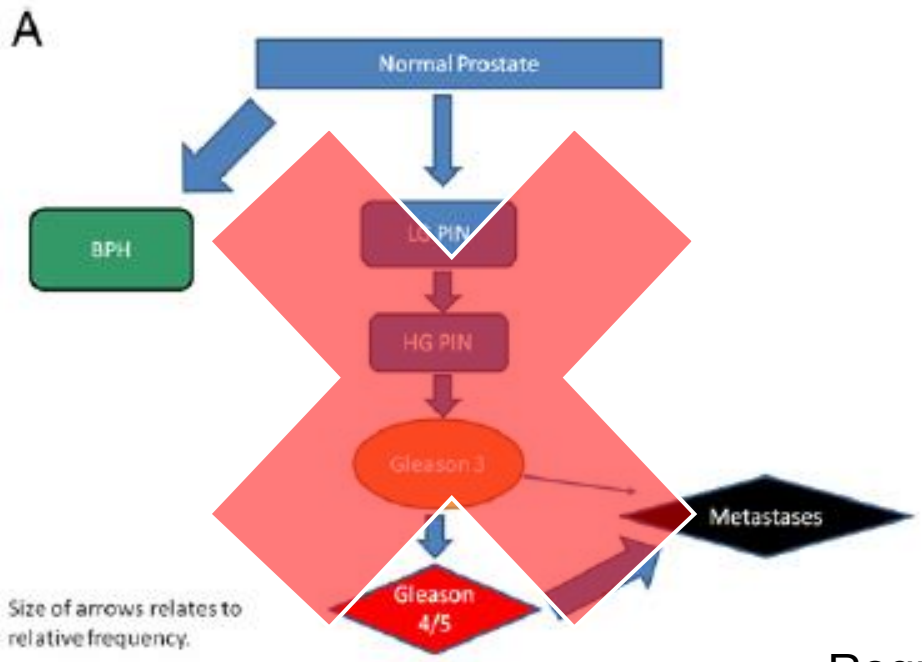
Characteristic/Pathway	Gleason 3	Gleason4
Expression of pro-proliferation embryonic, neuronal, hematopoietic stem cell genes, EGF, EGFR	No	Overexpressed
AKT pathway: MAP2K4, RALA, PHLPP, PML	No	Aberrant
HER2/neu	No	Amplified
Antigrowth signal insensitivity (Cyclin D2, CKDN1β)	Expressed	Absent
Resisting apoptosis: DAD1	Negative	Strong Exp
BCL2	Mostly Neg.	Upregulated
Absence of senescence: TMPRSS2-ERG	ERG normal	Increased
Sustained angiogenesis: VEGF	Low	Increased
Expression of other pro-angiogenic factors	Normal	Increased
Tissue invasion/metastasis markers (CXCR4, others)	Normal	Overexpressed
PTEN loss	36%	> 90%
Clinical evidence of metastasis/mortality	Absent	Present

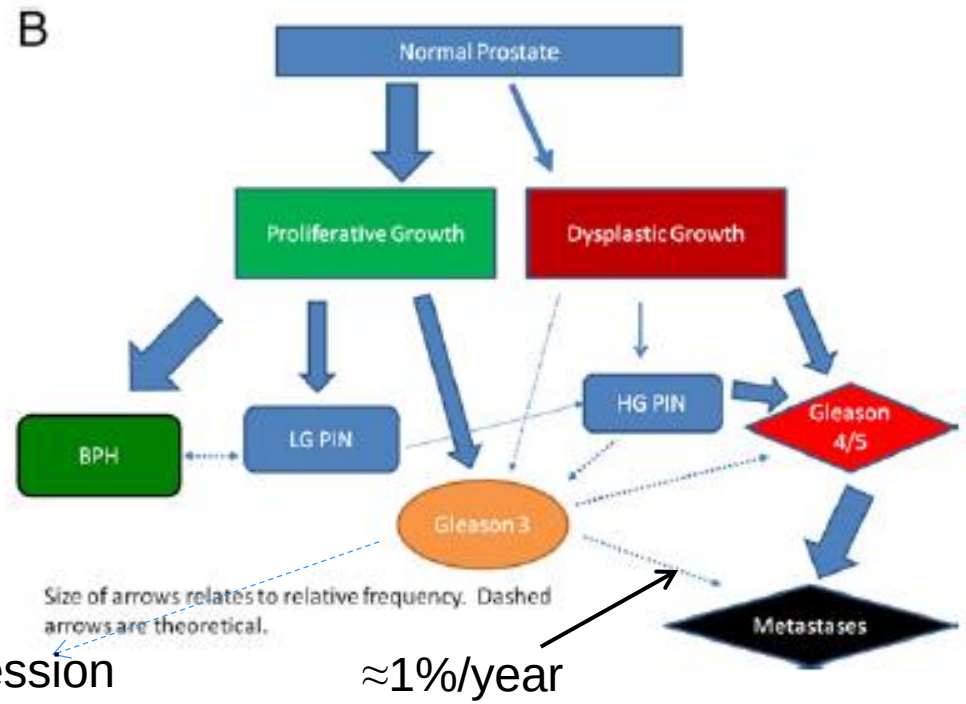
Low-grade prostate cancer diverges early from high grade and metastatic disease . VanderWeele D Cancer Sci.105 (8) 2014

- Phylogenetic trees for 4 cases with deep sequencing of somatic mutations



Linear vs bifurcated models of Pca development (Droller M et al 2012)





There are virtually no well documented cases of pathologically proven Gleason 6 cancers that have metastasized

- 12,000 Gleason 6 cancers treated with RP with 20 year follow up (Eggener S, J Urol 2011)
  - Pca mortality 0.2% at 20 years
  - Re-review of these showed higher grade Ca
- 14,123 cases of pathologic Gleason 6 at RP (Ross HM, Am J Surg Path 2012)
  - 22 with positive nodes (era of limited node dissection)
  - All were upgraded on re-review

Most guidelines differentiate between very low risk and low risk based on cancer volume

If Gleason pattern 3 doesn't metastasize, why does volume of Gleason 3 cancer matter?

Answer: High volume is a marker for the presence of higher grade cancer

Finding the wolf in sheep's clothing: 2 different species of wolf:

1. Misclassification of occult higher grade cancer (25=30%)
2. Biological grade progression over time (~1% per year)

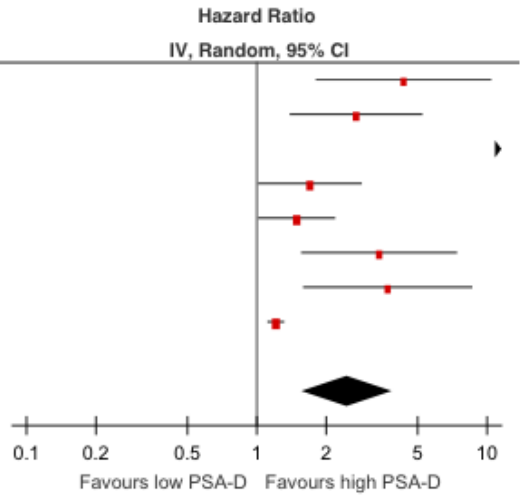
Predicting disease reclassification during AS

PSA Density

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Ross 2012	1.467	0.444	11.1%	4.34 [1.82, 10.35]	2012
Iremashvili 2013	0.993	0.335	13.4%	2.70 [1.40, 5.20]	2013
Wong 2014	6.37	1.557	2.0%	584.06 [27.61, 12353.12]	2014
Andrews 2014	0.531	0.261	15.1%	1.70 [1.02, 2.84]	2014
Barayan 2014	0.399	0.193	16.5%	1.49 [1.02, 2.18]	2014
Oh 2014	1.223	0.394	12.1%	3.40 [1.57, 7.35]	2014
Newcomb 2015	1.3083	0.4277	11.4%	3.70 [1.60, 8.56]	2015
Tosoian 2015	0.1906	0.0394	18.5%	1.21 [1.12, 1.31]	2015
Total (95% CI)			**100.0%**	**2.46 [1.56, 3.88]**	

Heterogeneity: Tau² = 0.29; Chi² = 44.12, df = 7 (P < 0.00001); I² = 84%

Test for overall effect: Z = 3.87 (P = 0.0001)

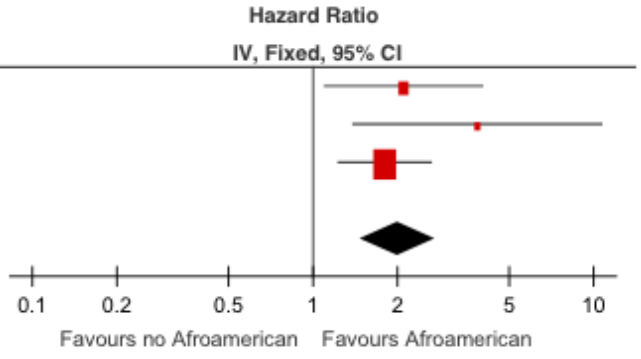


Race

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Iremashvili 2013	0.742	0.33	23.3%	2.10 [1.10, 4.01]	2013
Odom 2014	1.348	0.52	9.4%	3.85 [1.39, 10.67]	2014
Sundi 2015	0.588	0.194	67.3%	1.80 [1.23, 2.63]	2015
Total (95% CI)			**100.0%**	**2.00 [1.47, 2.74]**	

Heterogeneity: Chi² = 1.90, df = 2 (P = 0.39); I² = 0%

Test for overall effect: Z = 4.37 (P < 0.0001)

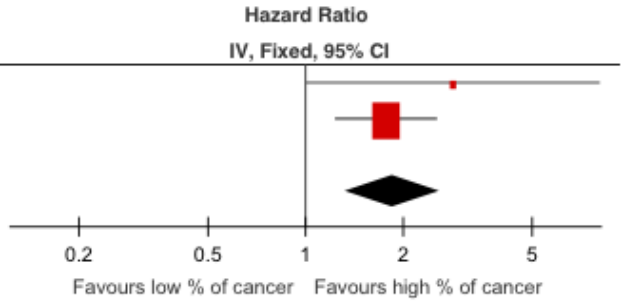


Core involvement

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Russo 2014	1.047	0.529	10.6%	2.85 [1.01, 8.04]	2014
Jo 2015	0.571	0.182	89.4%	1.77 [1.24, 2.53]	2015
Total (95% CI)			**100.0%**	**1.86 [1.33, 2.61]**	

Heterogeneity: Chi² = 0.72, df = 1 (P = 0.39); I² = 0%

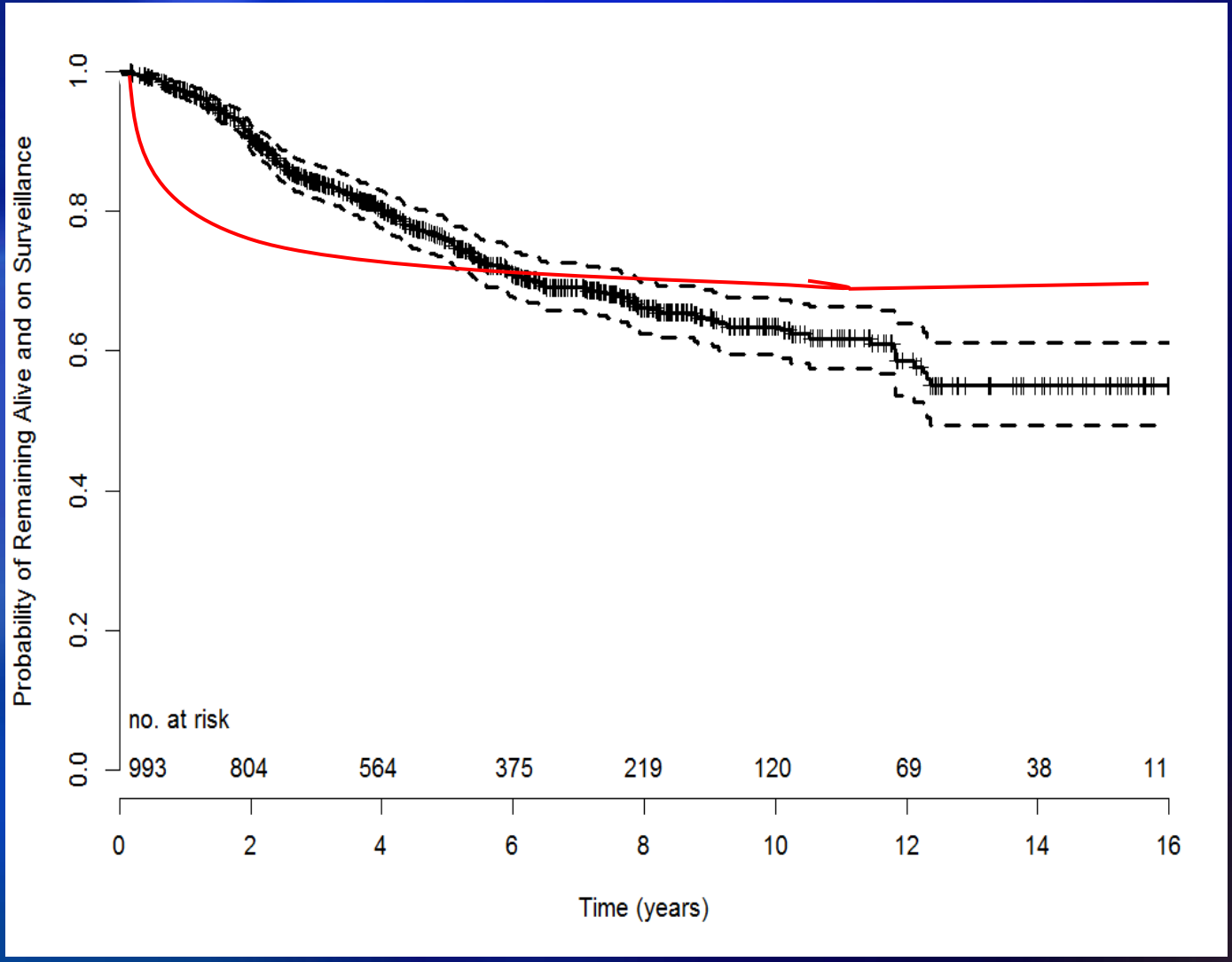
Test for overall effect: Z = 3.61 (P = 0.0003)



Toronto Surveillance Cohort

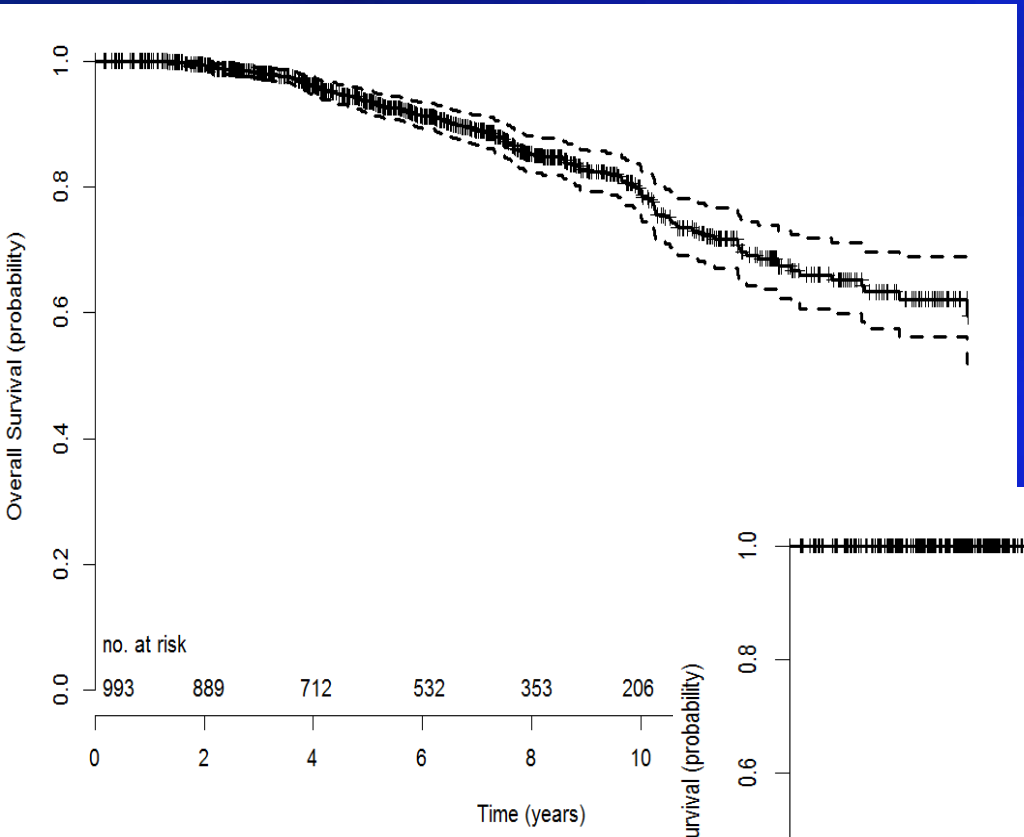
- 993 patients, median f/u of 8.9 years (0.5 – 19.8 years)
- Serial PSA, biopsy (no MRI until 2012)
  - 78% low risk
  - 22% patients intermediate risk (G7 or PSA > 10)
    - 38% of these < 70 years
- Intervention for PSA DT < 3 years (until 2010), upgrading to Gleason 3 + ‘significant’ 4
- 30 patients have developed metastases
  - 15 died of prostate cancer
  - 4 died other causes, 11 alive with mets

Intervention free survival in active surveillance Klotz et al JCO 33(3):272-7 2015

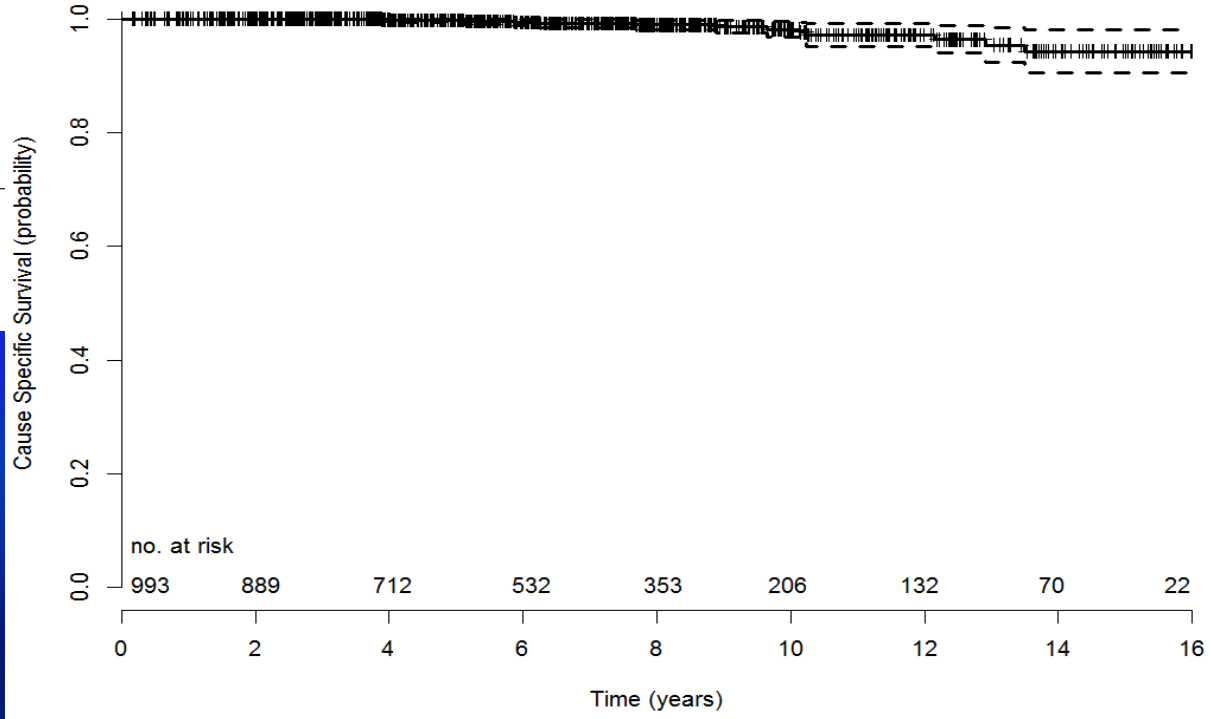


Survival with AS Klotz et al JCO 33(3):272-7 2015

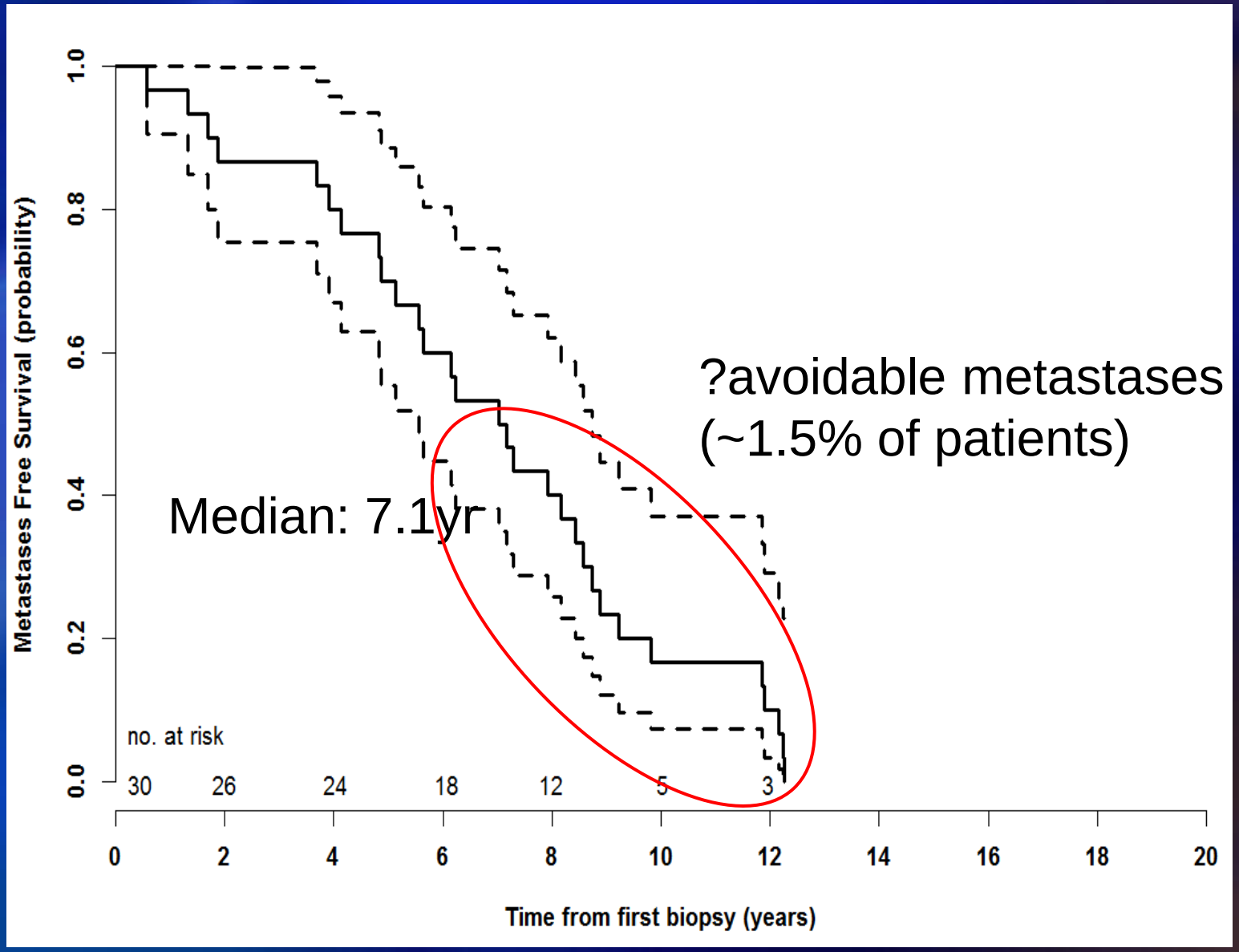
OS



CSS

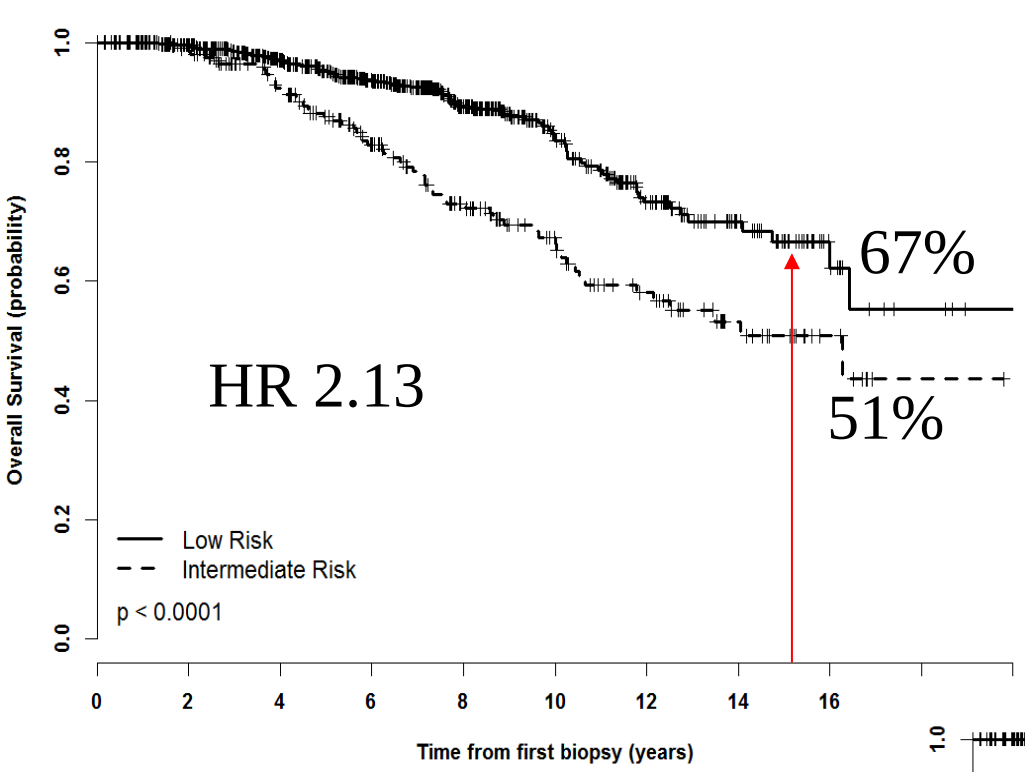


Time to metastasis from first positive biopsy in 30 men managed with initial surveillance

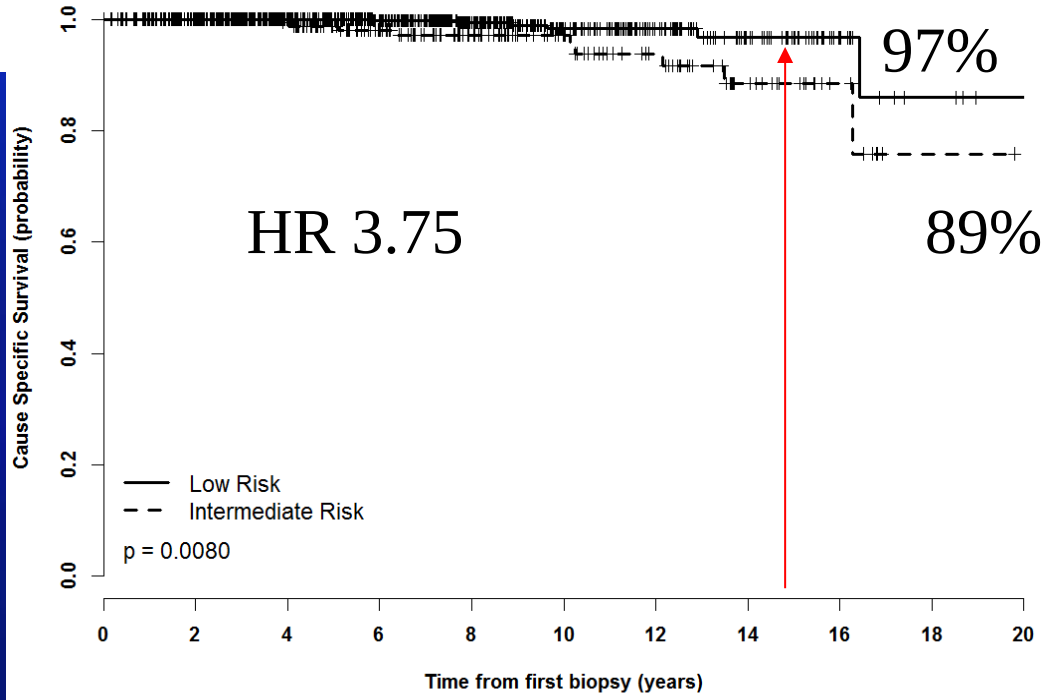


OS and CSS:
Low vs Intermediate risk (Gleason 3+4, PSA >10)

Overall Survival

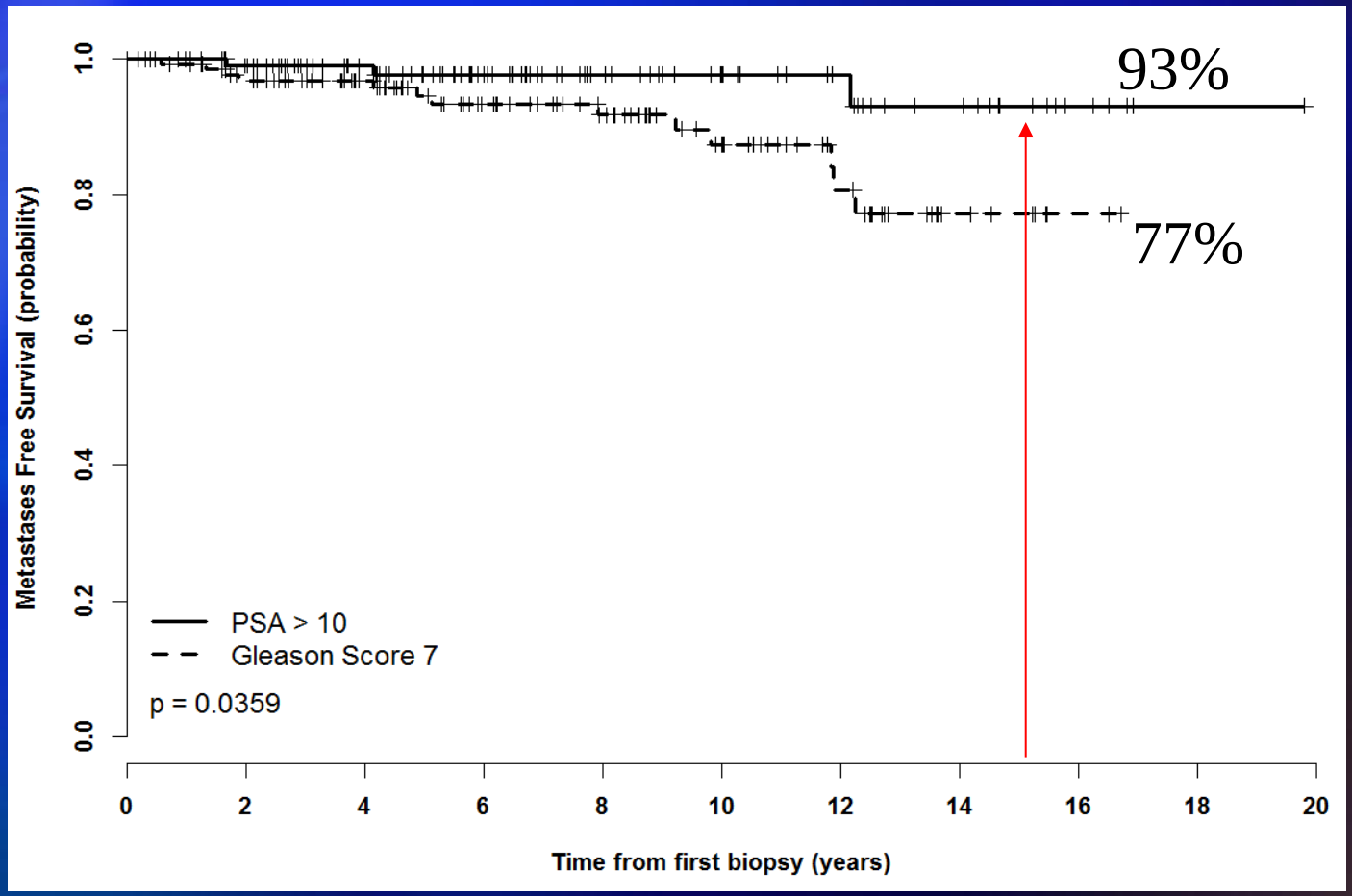


Cause Specific Survival



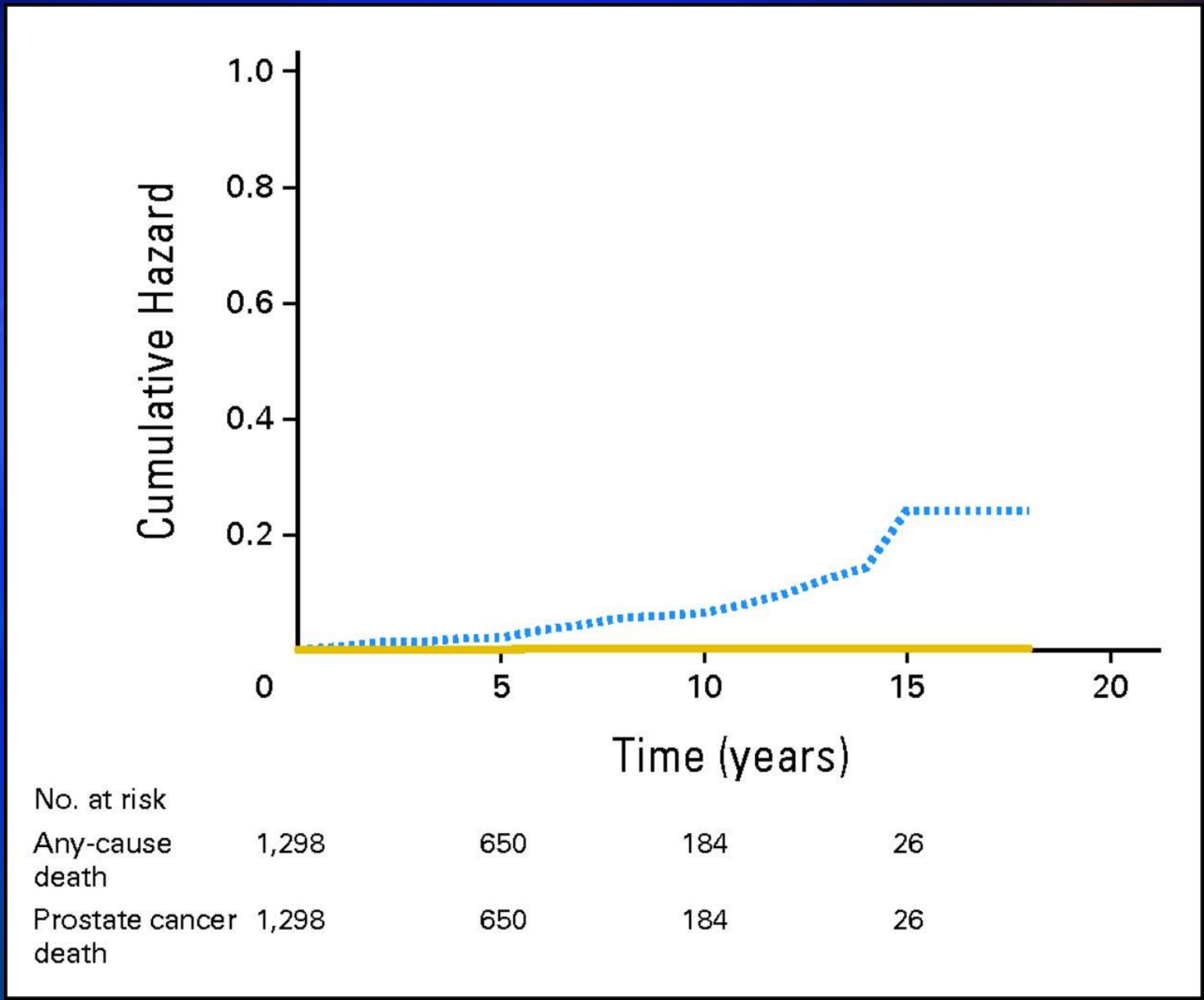
Intermediate risk group: Baseline Gleason score, not PSA, predicted for mets

Baseline PSA >10 vs GS 7, Met free survival



Hopkins AS long term outcome: Overall mortality and Pca mortality Tosoian J, Carter B et al. JCO.2015

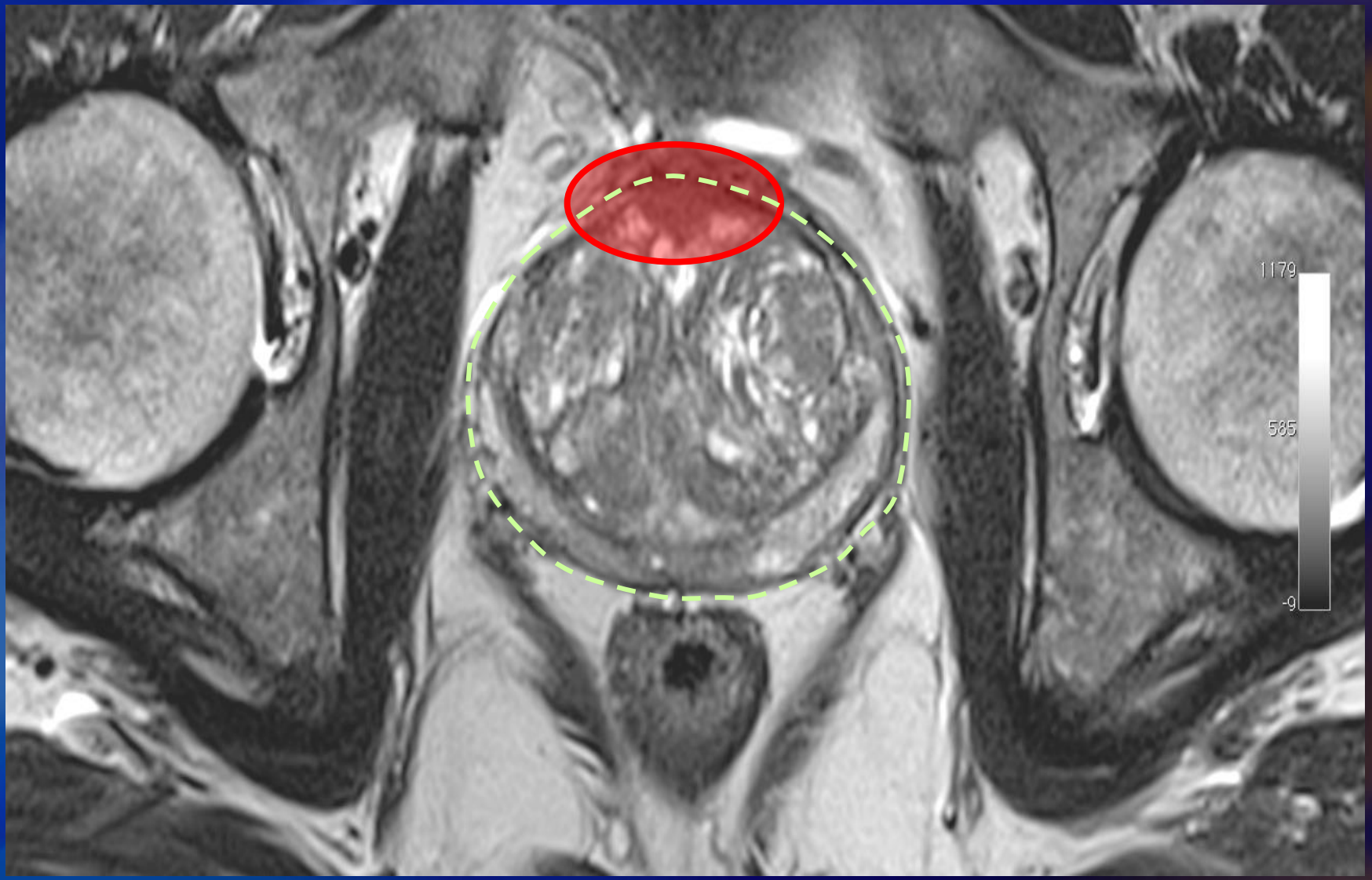
Pca mortality 0.5% at 15 years



Long term outcome of surveillance reflects inclusion criteria and intervention strategy

	Sunnybrook	Johns Hopkins
Eligibility	All Gleason 6, PSA <=15, and selected Gleason 3+4	NCCN low risk (<= 2 pos cores, <50% core involvement, PSAD < 0.15
Intervention	Gleason 4+3	≥ NCCN low risk (volume progression or any Gleason 4)
Proportion of Pca patients eligible	50%	20%
15 year Pca mortality	5% (mostly baseline Gl. 7)	0.5%

MRI targeting: Gleason 3+4 after prior biopsy: 1 pos core 10% Gleason 3+3



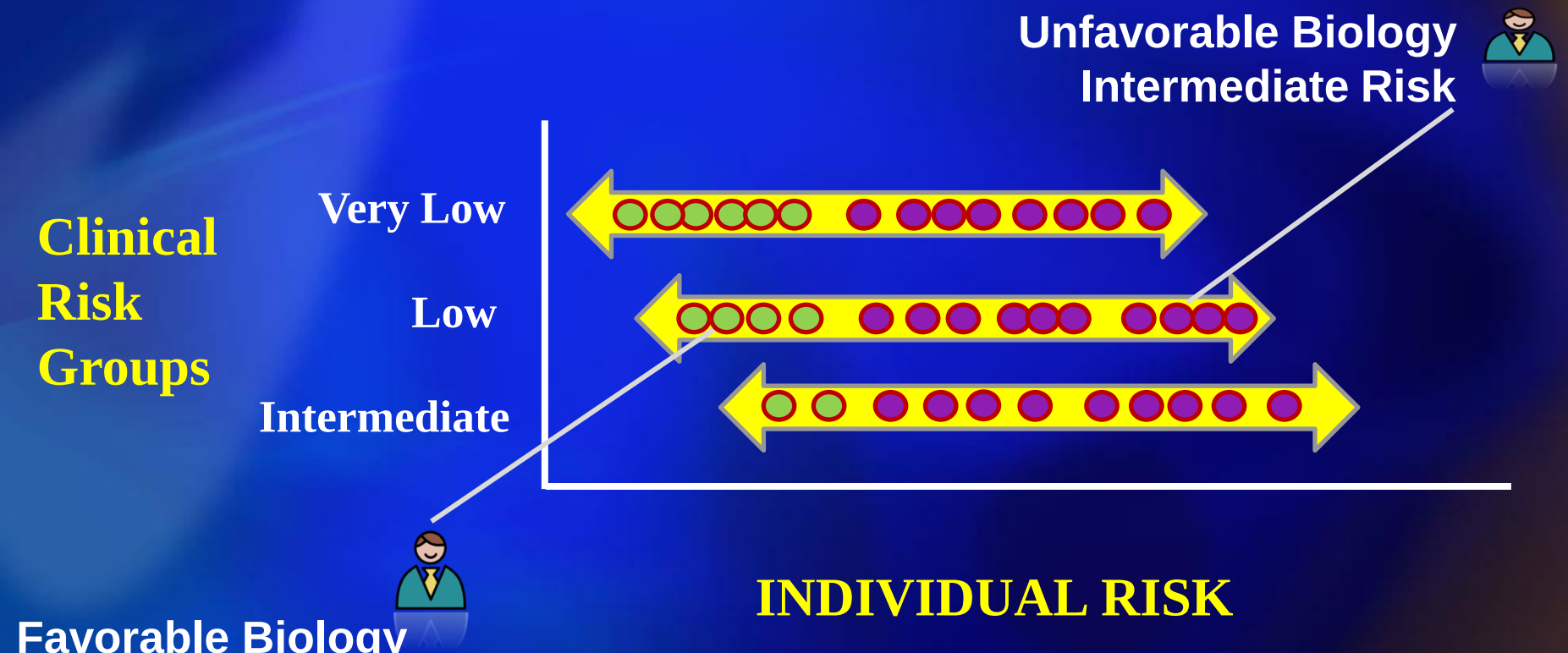
The ‘new’ low risk: Gleason 6 with negative MRI

- Vargas et al J Urol 2012: In men on AS, NPV for clinically significant cancer 97%
- Pannebianco et al Urol Onc 2015: NPV for Gleason ≥4 100%
- Siddiqui et al JAMA 2015:
  - Targeted vs systematic: 30% more high risk cancers (17% vs 12%), 17% fewer low risk (21 vs 26%)
  - Adding systematic to targeted identified additional 10% with cancer, but 83% low risk
  - Number needed to biopsy with systematic in addition to targeted: -For 1 high risk cancer: 200 For 1 intermediate risk cancer: 46

New Biomarkers

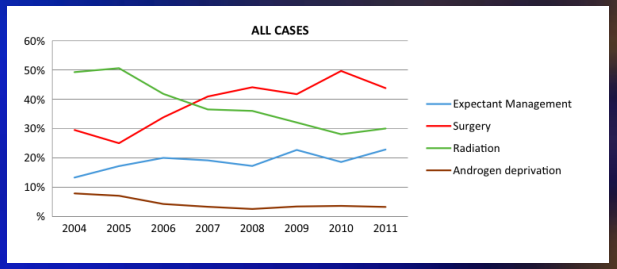
Who to Biopsy	Who to Rebiopsy	Who to Watch or Treat
• PSA • PCA3 • PHI • TMPRSS2-ERG • 4K	• PCA3 • Confirm MDx • PCMT	• OncotypeDX • Prolaris • Promark • Decipher

The Promise of Genomics

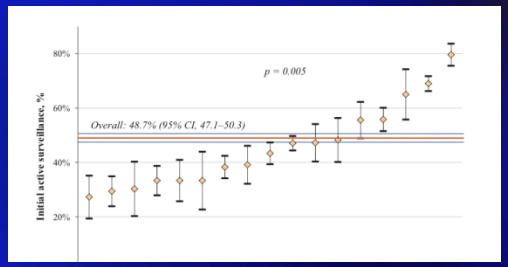


Trends in Active Surveillance: Utilization

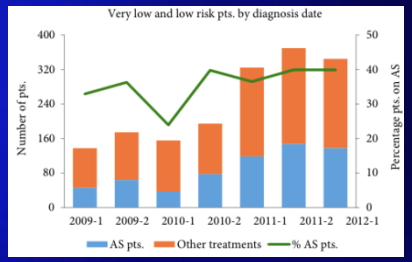
- Ingimarsson JP (New Hampshire) Cancer Causes Control. 2015 Jun;26(6):923-9.



- Womble PR (MUSIC): (Michigan) Eur Urol. 2015 Jan;67(1):44-50

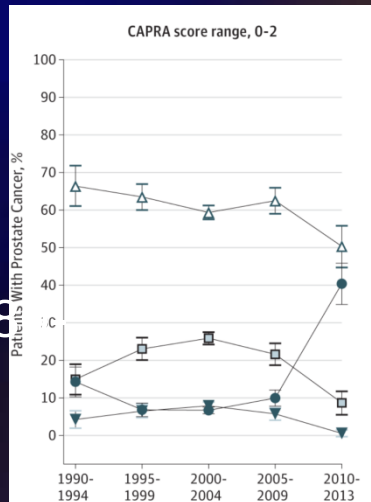


- Weerakoon M (Australia): BJUI 2015: 115 S5, 50-56



- Loeb S (Sweden): AS in 91% VLR and 74% LR, URS 2015

Cooperberg M et al, JAMA. 2015;314(1):82

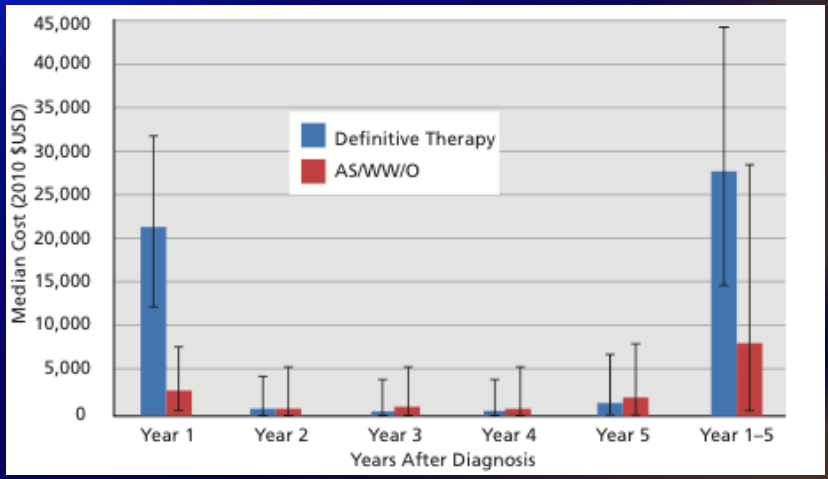


Cost Implications of Overtreatment of Low-Risk Prostate Cancer in the US. Aizer A et al *Natl Compr Canc Netw* 2015;13:61-68

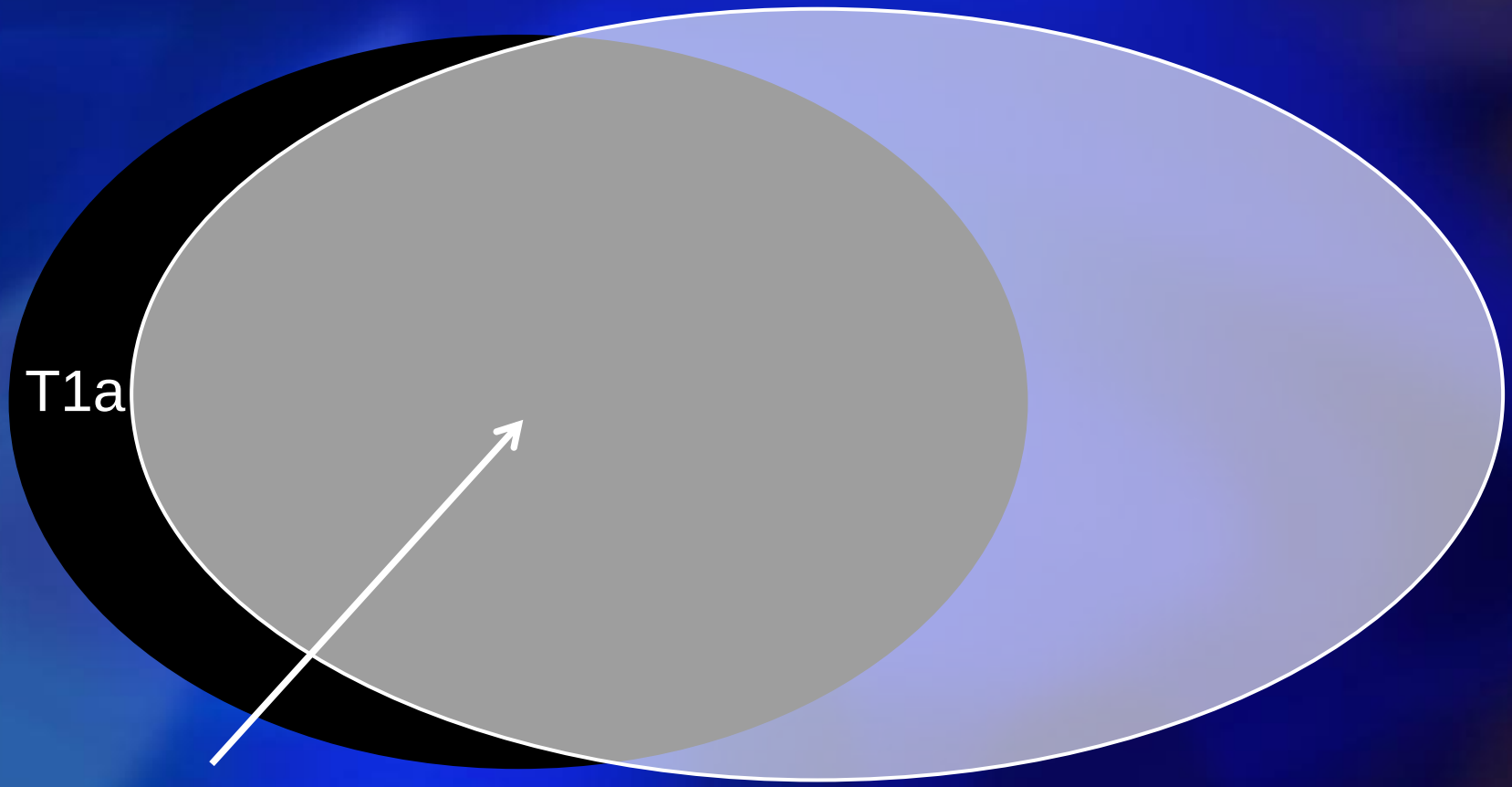
Table 3 Adjusted Median Cost[a] of Each Management Modality for Prostate Cancer

Management Modality	N	Cost[b]	IQR
Radical retropubic/perineal prostatectomy	143	13,868	10,629–21,203
Minimally invasive radical prostatectomy	88	14,157	9849–20,188
Brachytherapy	937	16,883	11,482–28,105
External-beam radiation therapy	145	18,592	13,105–24,713
Image-guided radiation therapy/stereotactic radiation therapy	116	26,930	22,263–36,260
Intensity-modulated radiation therapy	445	29,616	23,664–40,271
Proton therapy	21	42,772	35,214–53,176
Cryotherapy	64	12,516	9816–16,517
AS/WW/O	760	2766	518–7806
Primary androgen deprivation therapy	195	7070	3231–13,409

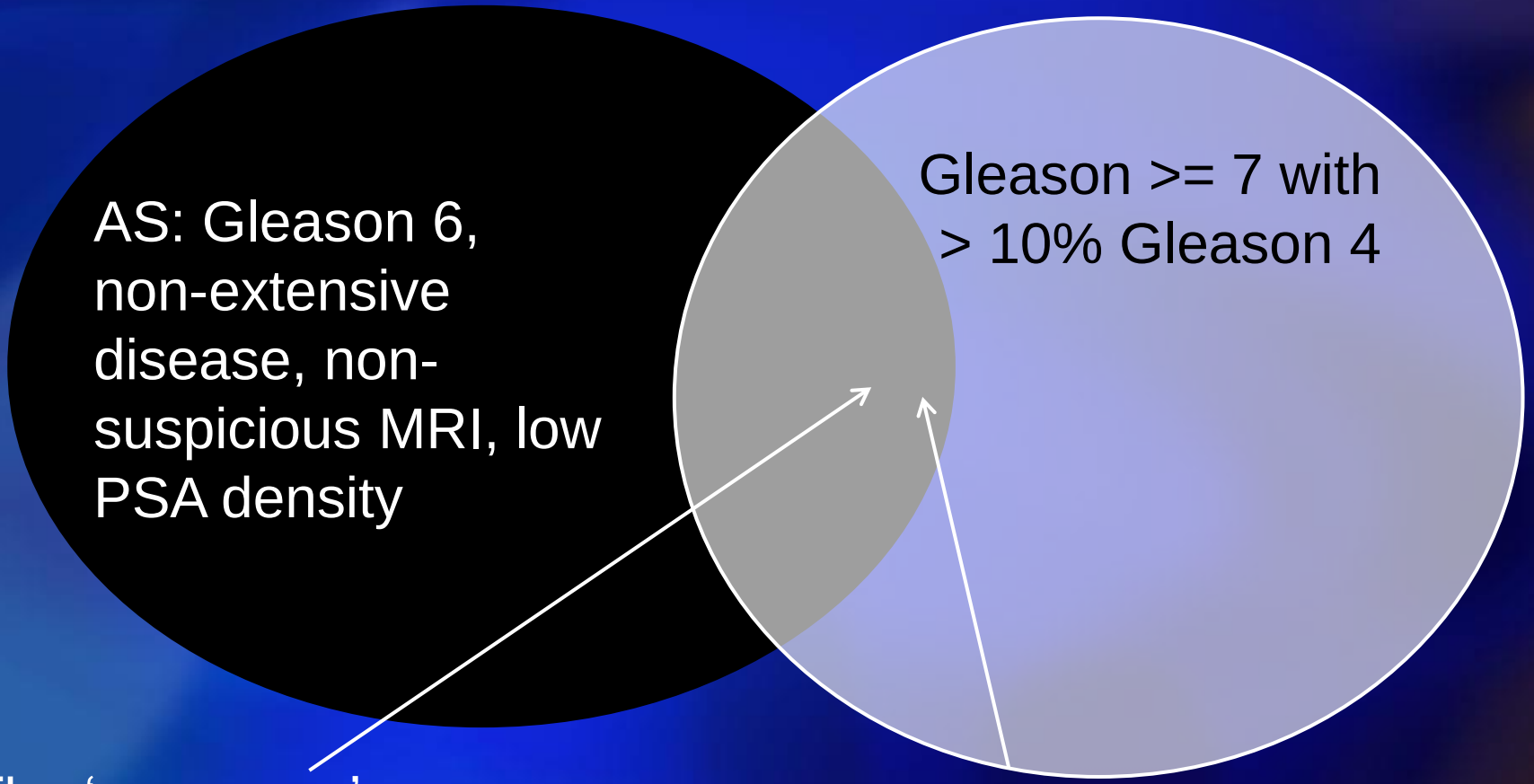
Compared to active surveillance, median additional cost per definitive treatment $18,827 over 5 years. Avoiding treatment of the 80% of men with clinically insignificant prostate cancer would save $1.32 billion per year in US.



PCa: Traditional large grey zone



The new black, white, and grey zones



The ‘grey zone’:

- Extensive Gleason 6
- Gleason 6 in men < 50 yrs
- Gleason 7 with < 10% Gleason 4

- PiRADS 4-5 with low grade cancer on targeted biopsy,
- high PSAD

Localized PCa - Treatment Options

Conservative

Surveillance

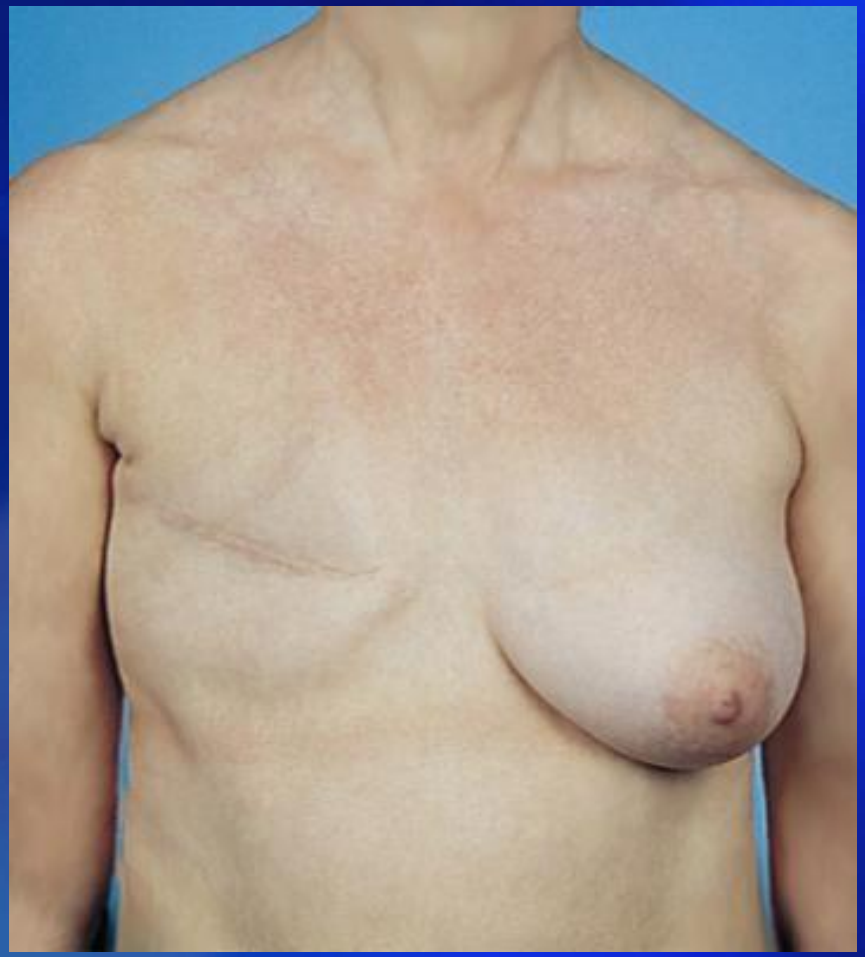
Organ Sparing

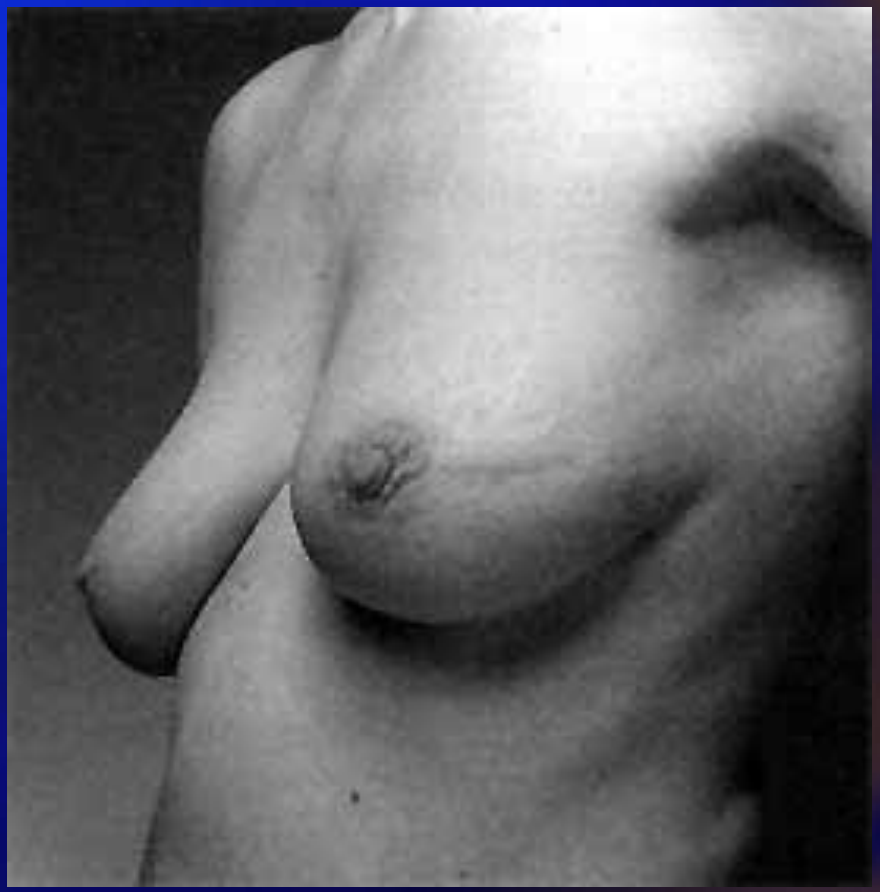
Focal Therapy

Radical Therapy

Surgery

Radiation





Why focal therapy?

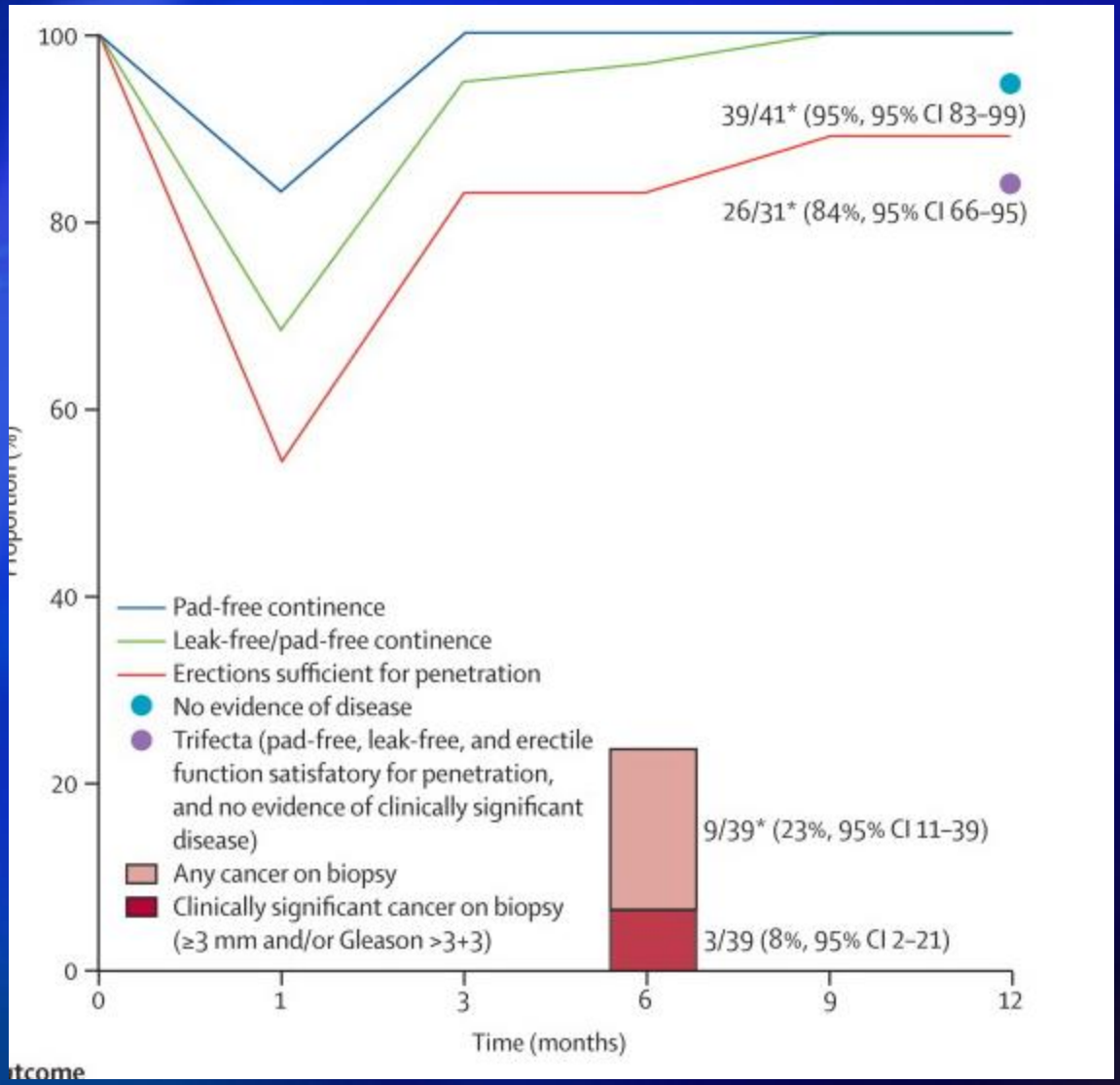
- Little to lose.
- We need to change the paradigm (ie, vs Robot—'pseudo-advance')
- Plenty of tissue to preserve
  - Mean cancer volume 1-2 cc vs prostate volume 40 cc
- Preserving prostate matters (improved functional outcome)
- Diagnostic pathway is changing (MRI replacing biopsy for elevated PSA)
- Our understanding of disease is changing
  - Index lesion concept

Prospective studies of focal therapy with > 50 patients. Klotz L, Emberton M, Nat Rev Clin Oncol 2014

- 9 studies
- Pad free continence 96-100%
- Intact erectile function 58-85%
- bDFS 73-95%
- Repeat treatment in 18-34%
- Radical treatment 5-7%

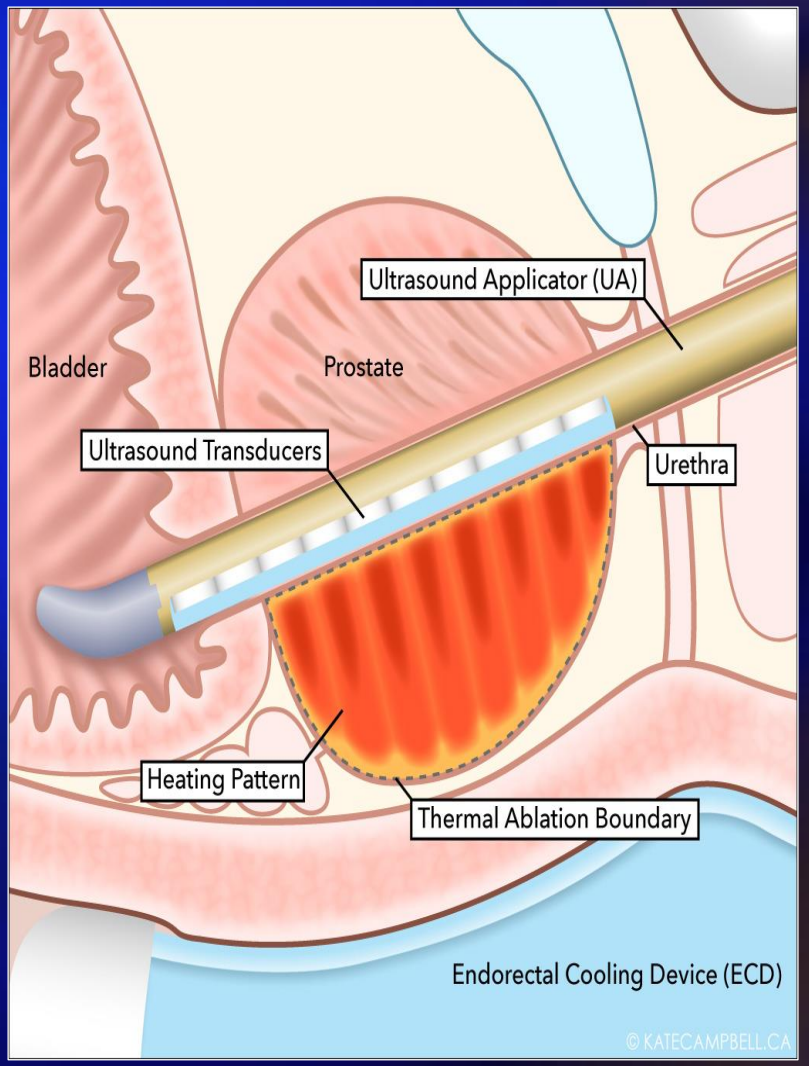
nature REVIEWS CLINICAL ONCOLOGY

Trifecta rate after focal HIFU. Ahmed H, Emberton M et al Lancet Oncology (June 2012), 13 (6), pg. 622-632

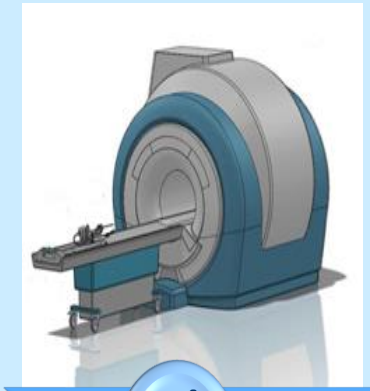


Trans-urethral Ultrasound Ablation of Prostate (TULSA)

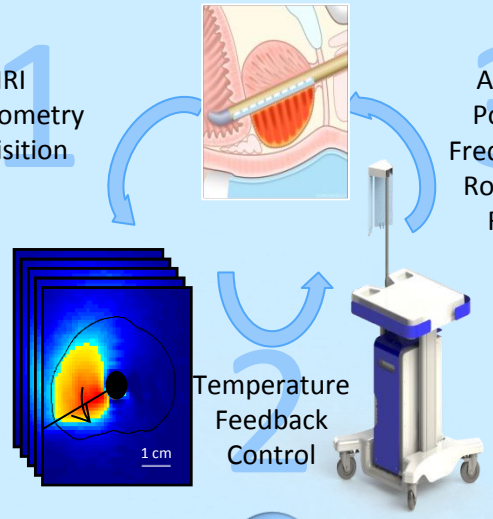
- Directional high-intensity (*not focused!*) U/S energy thermally coagulates prostate
- 3D control of thermal ablation (± 1 mm)
  - Axial: 10 independent US transducer elements
  - Radial: U/S power and frequency control depth of heating
  - Rotational: 1 complete rotation
- MRI-Thermometry Real-Time Feedback Control to shape ablation volume to anatomy
- Water cooled urethra and rectum



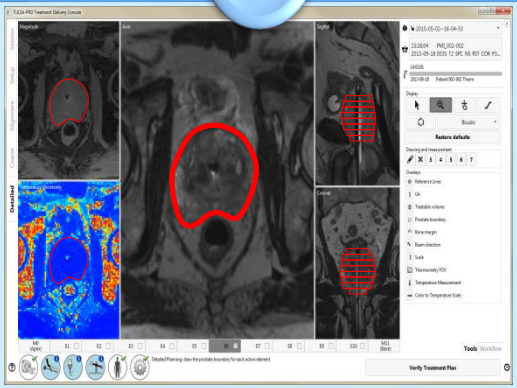
MRI-GUIDANCE



Device Positioning



Planning

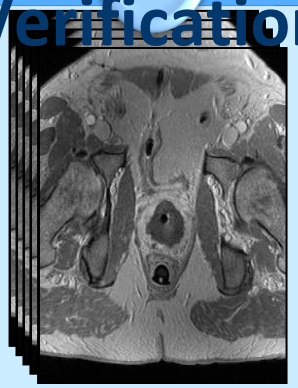


Precise Treatment Planning

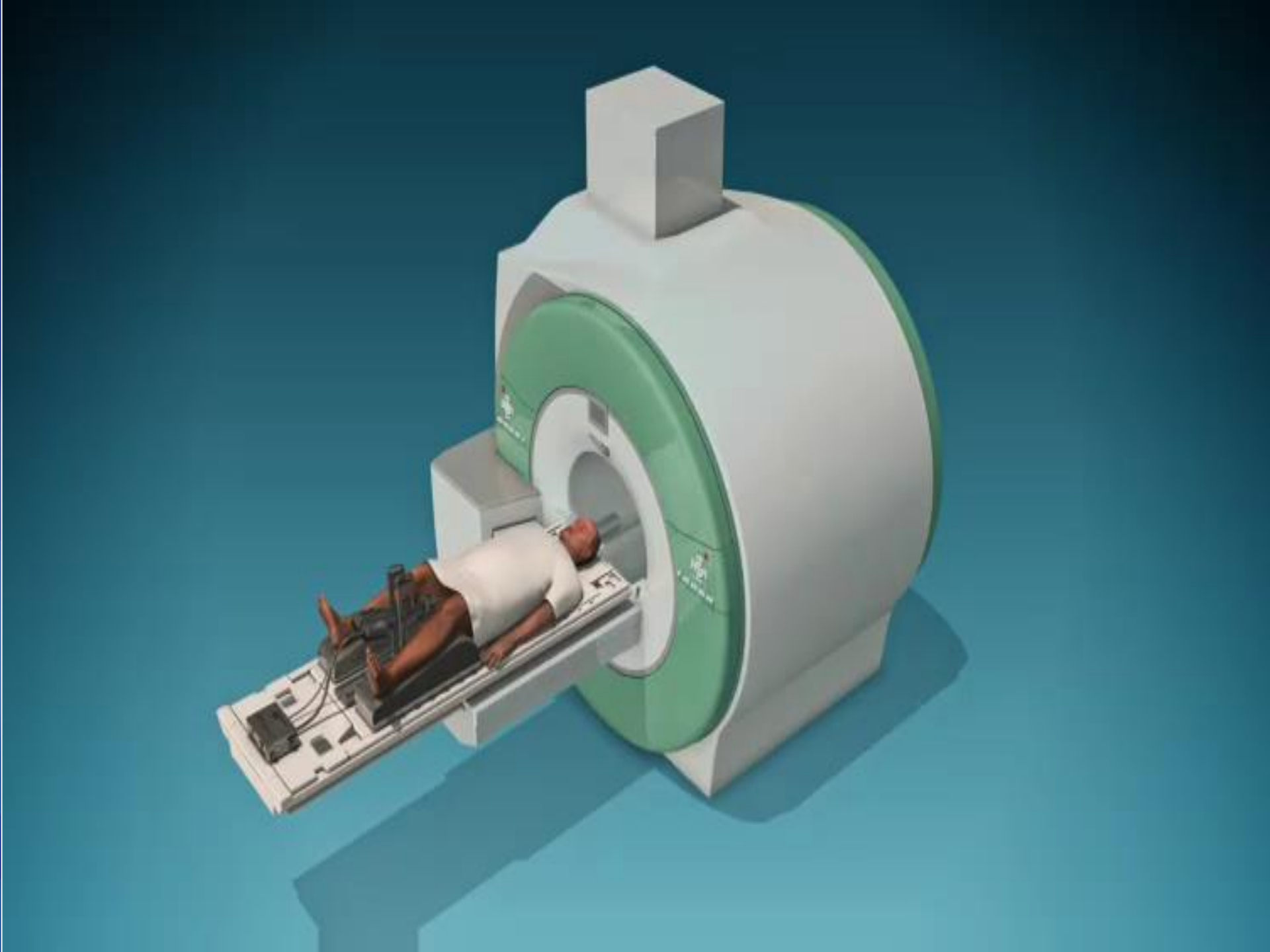
Treatment

40 min

CE-MRI Verification

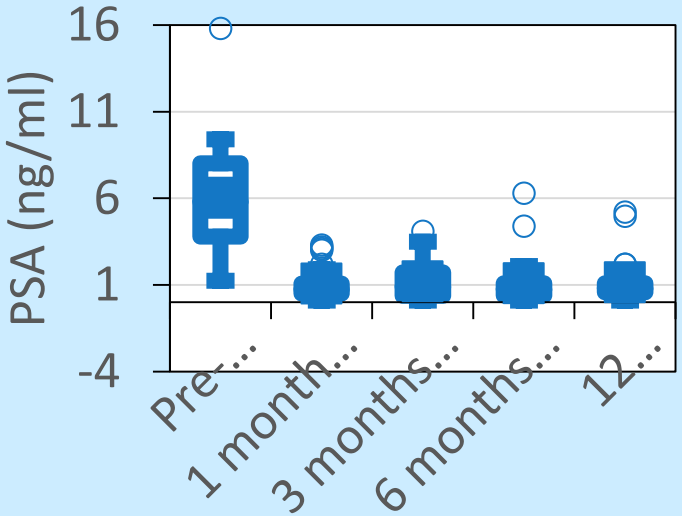


Visualization of Non-Perfused Volume (NPV)

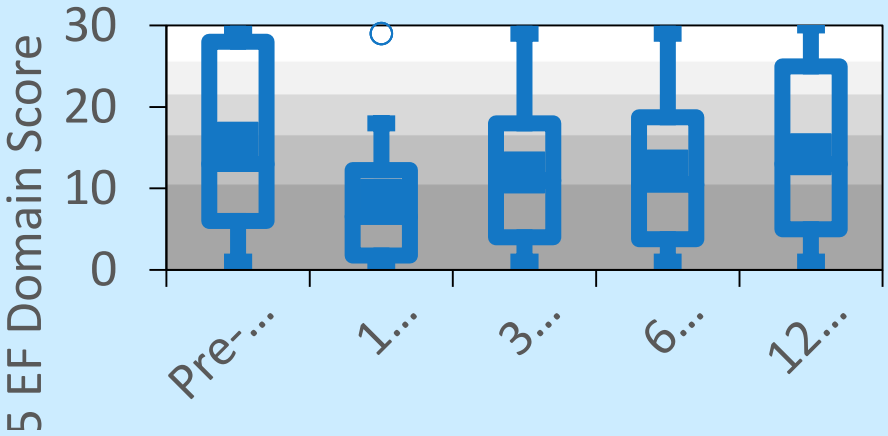


Efficacy of TULSA

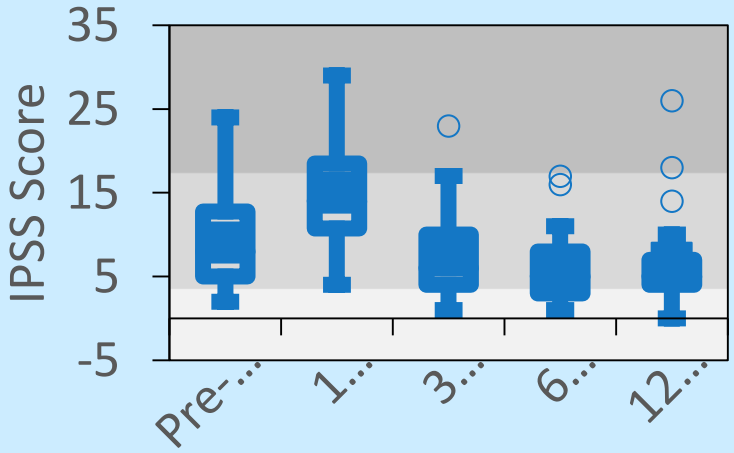
PSA



IIEF-15 Erectile Function Domain



IPSS



Focal therapy: the problems

- Most favorable risk patients don't need any treatment
- Substantial risk of overtreatment; recapitulate RP history
- Risk of undertreatment for those with occult high risk cancer
  - False reaasurance
- MRI: accuracy of defining borders of lesions uncertain
- Need for life long surveillance/biopsy/imaging etc.
- Proof of 'real' efficacy challenging
  - Robust end points require long follow up, large numbers
- Risk of 'snake oil' therapy: Innocuous treatment which has no real benefits

Localized PCa - Treatment Options

Conservative	Organ Sparing	Radical Therapy
Surveillance	Focal Therapy	Surgery
		Radiation

Radical prostatectomy vs radiation: What is the evidence for comparative effectiveness?

Disclaimer

- I am a urologist who does radical prostatectomies.

RP vs radiation for prostate cancer

- Prior randomized trials limited by methodological flaws
- Retrospective studies show similar biochemical recurrence rates
  - But PSA based comparisons problematic: differences in post treatment PSA kinetics, definitions of PSA recurrence, use of ADT with radiation.
- PSA recurrence ≠ clinical metastases or death.
- Clinical guidelines do not address how outcomes compare
  - EAU Heidenreich A Eur Urol. 2014 Jan;65(1):124-37
  - 'Comparative effectiveness of treatments' Wilt TJ et al Ann Intern Med.2008 Mar 18;148(6):435-48

Why re-visit this question?

- Recent advent of propensity adjusted analysis to compare treatments in the absence of a randomized trial
- Dramatic increase in this approach over last decade (>10,000 studies in Pubmed)
- RP vs XRT: 14 independent studies comparing effectiveness adjusting for covariates
- 9 since 2012
- 7 with > 10,000 patients, 2 with > 60,000

References:

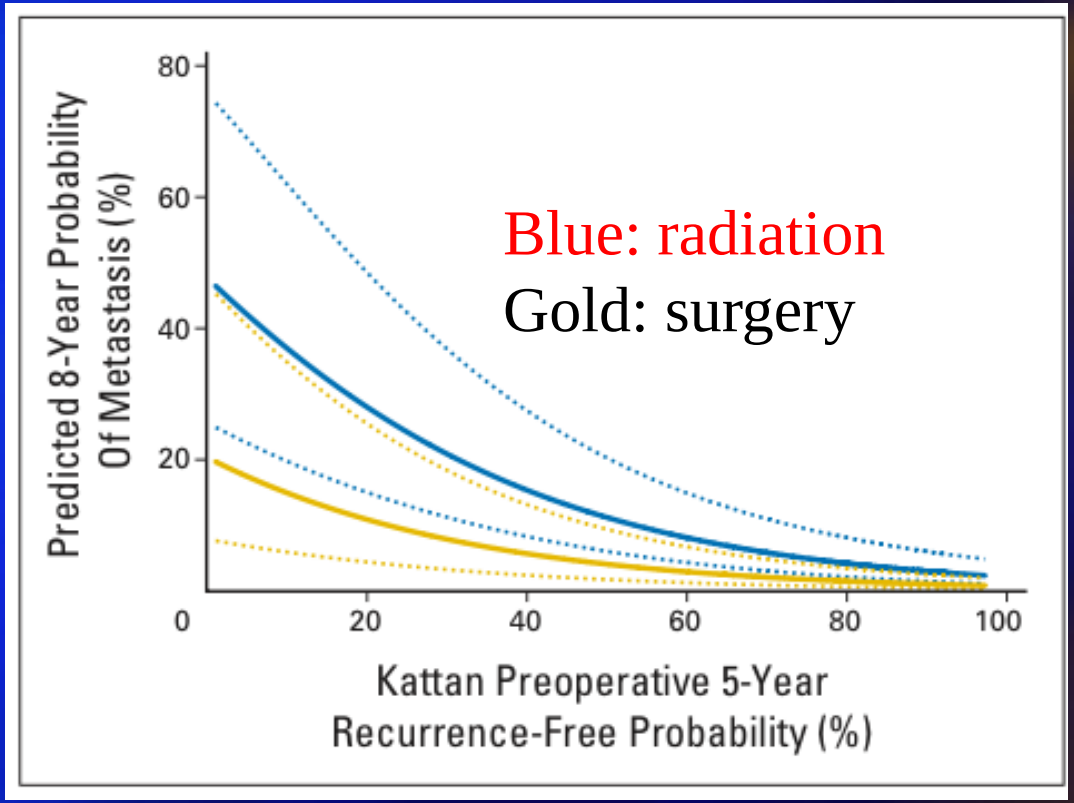
1. Tewari A J Urol 2007 Mar;177(3):911-5.
2. Albertsen PC et al, J Urol. 2007 Mar;177(3):932-6
3. Merglen A Arch Intern Med. 2007 Oct 8;167(18):1944-50.
4. Zelefsky MJ, JCO 2010 Mar 20;28(9):1508-13.
5. Cooperberg M, Cancer 2010 116(22):5226-34
6. Kibel A, J Urol. 2012 Apr;187(4):1259-65.
7. Abdollah F, Int J Urol. 2012 Sep;19(9):836-44;
8. Nepple K, Eur Urol. 2013 Sep;64(3):372-8.
9. Hoffman R, JNCI 2013;105:711-718
10. Shao Y, Lu-Yao G. Eur Urol. 2014 Apr;65(4):693-700.
11. Lee JY, Ann Surg Oncol. 2014 May 20
12. Sooriakumaran P BMJ. 2014 Feb 26;348
13. Dorr M EAU 2014
14. Sun M, Karakiewicz PI BJU Int 2014 113(2):200-8.

RP vs XRT: Summary of mortality results from propensity analyses

			PCM, HR XRT vs RP	OS HR (*P<.05)
Tewari 2007	453	GS >=8	2.10	
Albertsen 2007	1618		2.5	1.7*
Merglen 2007	844	1989-98	2.3	1.5*
Zelefsky 2010	2380		3.0 (Met rate)	
Cooperberg 2010	7538		2.21	1.58*
Kibel A 2012	10,429		XRT vs RP 1.5	XRT vs RP 1.6*
Abdollah 2012	68,665	SEER 1992-05	At 10 yrs, HR 2.8 High risk: 11.5% vs 6.8%	
Nepple 2013	10361		1.66	1.71 EBRT*
Shao 2014	66492	SEER	1.5; 1.4 low, 1.9 high	
Lee 2014	376	High risk	3.2	
Sooriakumuran 2014	34,052		1.76	
Dorr 2014	20,935		1.97	
Sun 2014	66,087	SEER	2.5 (> 10 yr LE)	1.5*
Hoffman 2013	1655	PCOS	3.0	1.66

Probability of metastasis at 8 years, adjusted for case mix. Zelefsky M et al, JCO 2010 Mar 20;28(9):1508-13

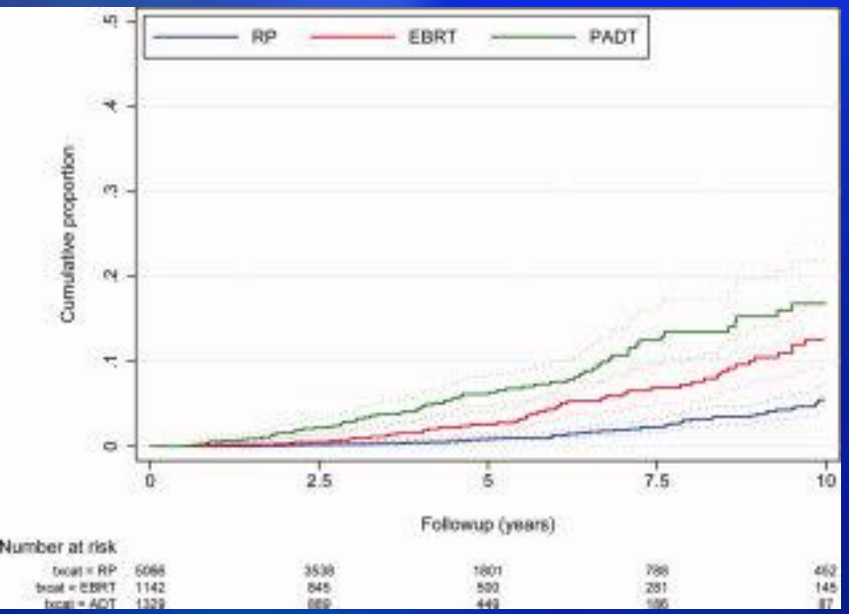
- N=2380 from 2 centres
- 1993-2002



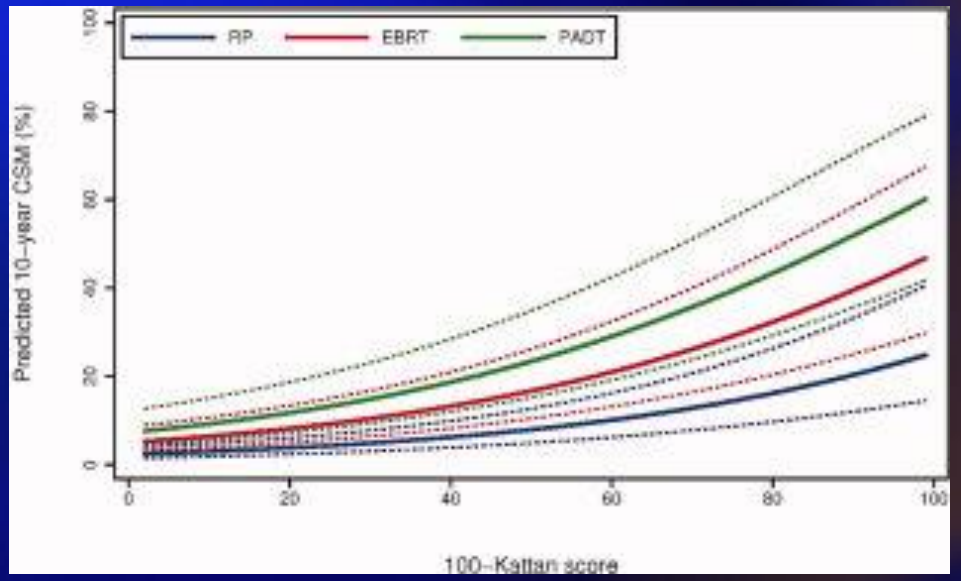
Predictor	HR	95% CI	P
Age at treatment	0.98	0.95-1.02`	.3
NCCN risk high vs int/low	6.37	3.9-10.5	<.0005
Surgery vs XRT	0.35	0.19-0.63	.001

Comparative risk-adjusted mortality outcomes after RP, XRT, and ADT. Cooperberg M et al, Cancer 116(22):5226-34, 2010

- N=7538 (CaPSURE)
- HR 2.21 for CSM (XRT vs RP)
- Increased HR for higher risk disease
- Sensitivity analysis: Robust to 20 Kattan risk points



Unadjusted PCM

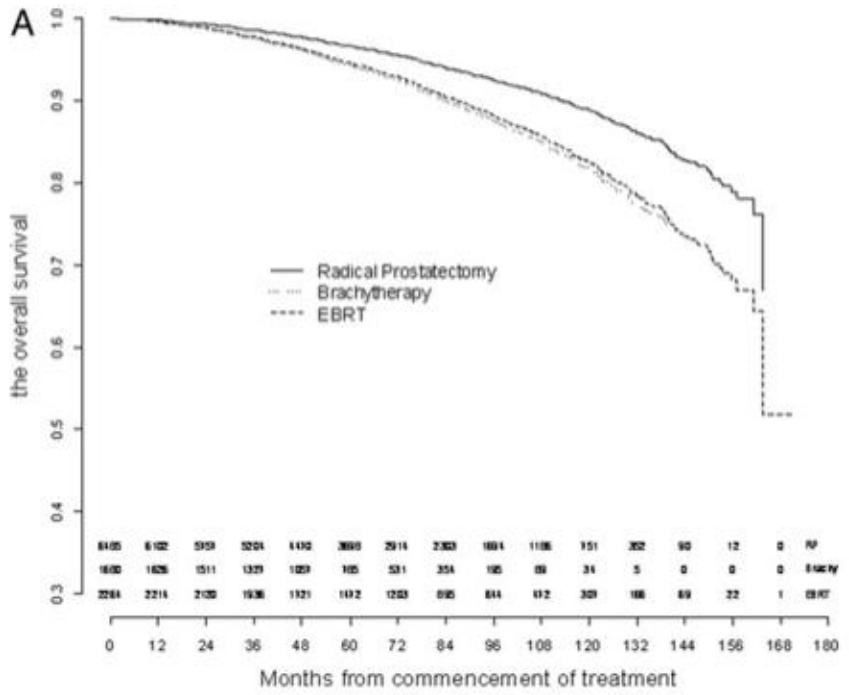


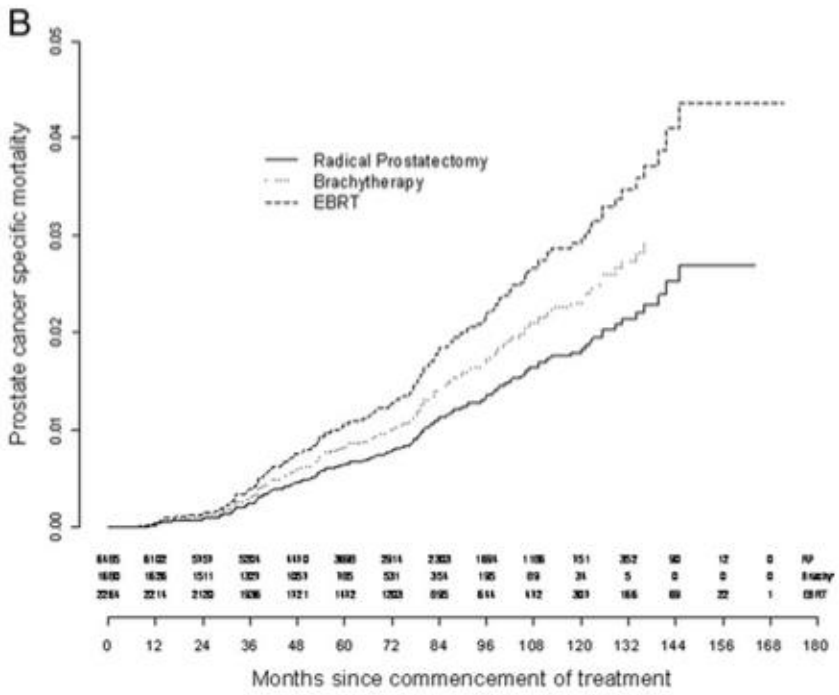
Predicted risk of PCM

Survival Among Men Treated With RP or Radiation Therapy in the PSA Era. Kibel A, J Urol 2012 Apr;187(4):1259-65.

- N=10429

Overall mortality CSM



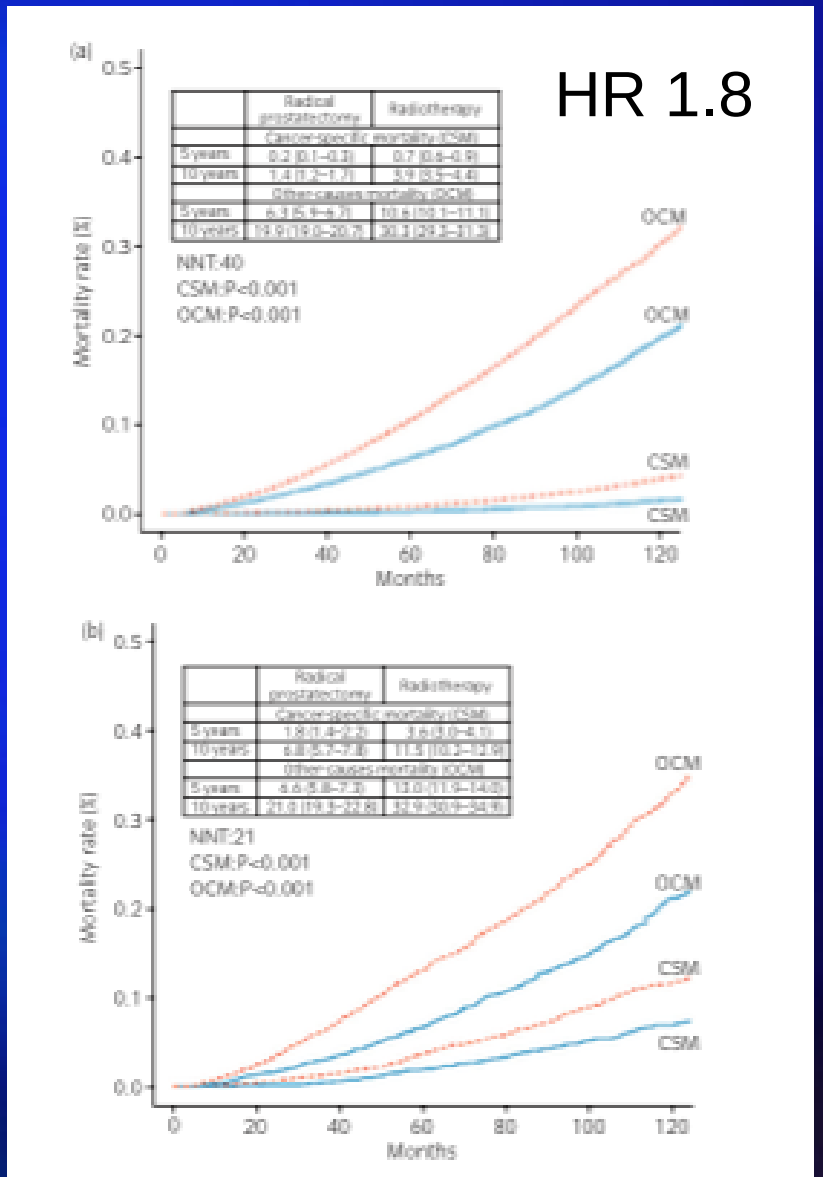


XRT vs RP: 1.5 x CSM, 1.6 x OCM

Comparison of mortality outcomes after RP vs XRT: A population-based analysis . Abdollah F, Int J Urol. 2012 Sep;19(9):836-44;

- N=68,665 (SEER)
- Stratified by Pca risk group, CCI, age

- Effect consistent across all co-morbidity and age groups



HR 1.8

---RP
---XRT

Low-Int risk

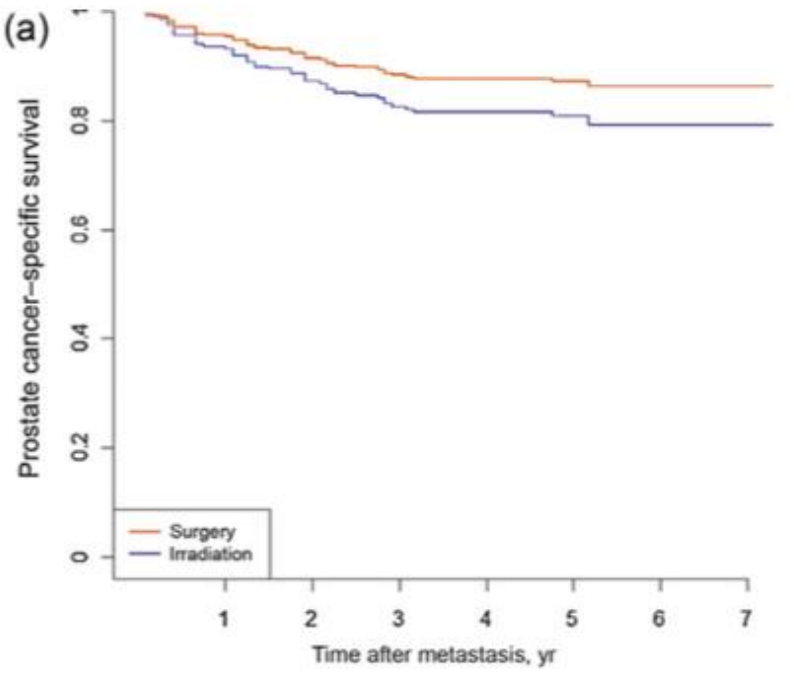
High risk

Cancer-specific Survival After Metastasis Following RP Compared with Radiation: Population-based, Propensity Score–Matched Analysis

Shao Y, Lu-Yao G. Eur Urol. 2014 Apr;65(4):693-700.

N=66492 (SEER)

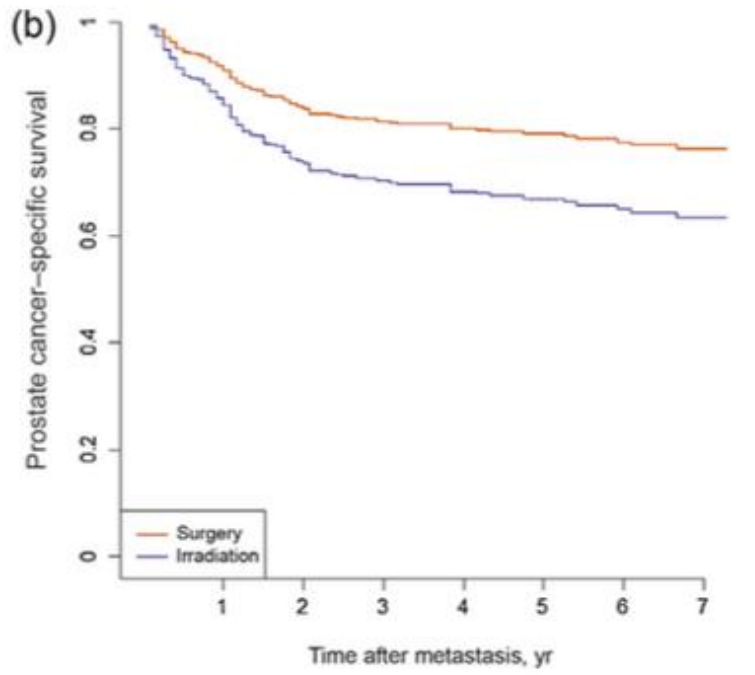
Low risk



Patients at risk, no.

Treatment								
Radical prostatectomy	171	103	64	41	26	16	11	10
Irradiation	171	93	58	37	27	21	12	9

Int-high risk



Patients at risk, no.

Treatment								
Radical prostatectomy	287	186	118	74	44	29	16	10
Irradiation	287	166	84	54	40	29	17	11

But it's not just higher mortality:

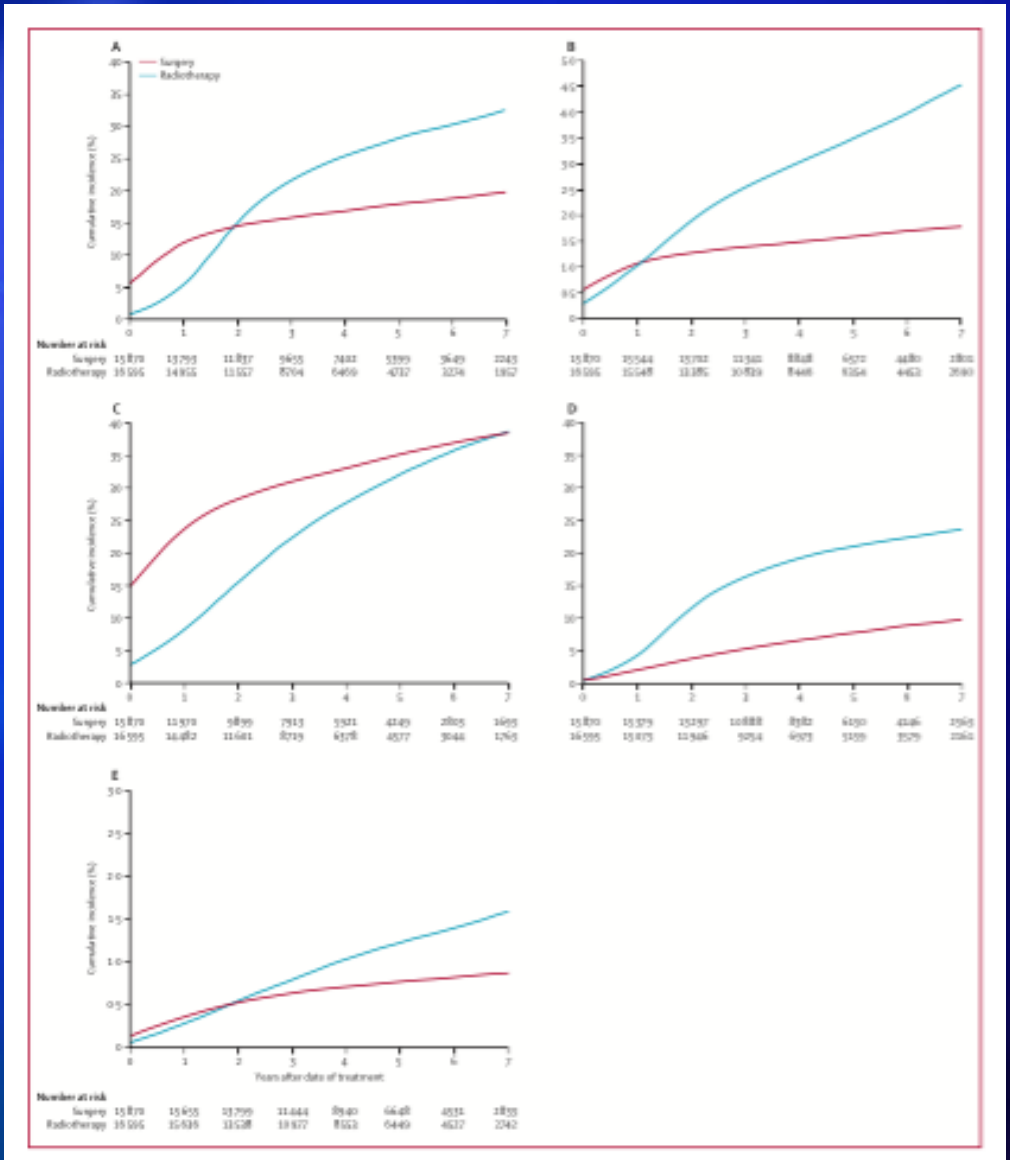
- Long term complications of radiation historically understated
- Population based analyses show long term complication rate with radiation > surgery
- Plus unwanted effects of adjuvant ADT

Incidence of complications other than urinary incontinence or erectile dysfunction after RP or XRT: a population-based cohort study. Nam R et al, Lancet Oncol. 2014 Feb;15(2):223-31

All hospital admissions

Minor GU procedures

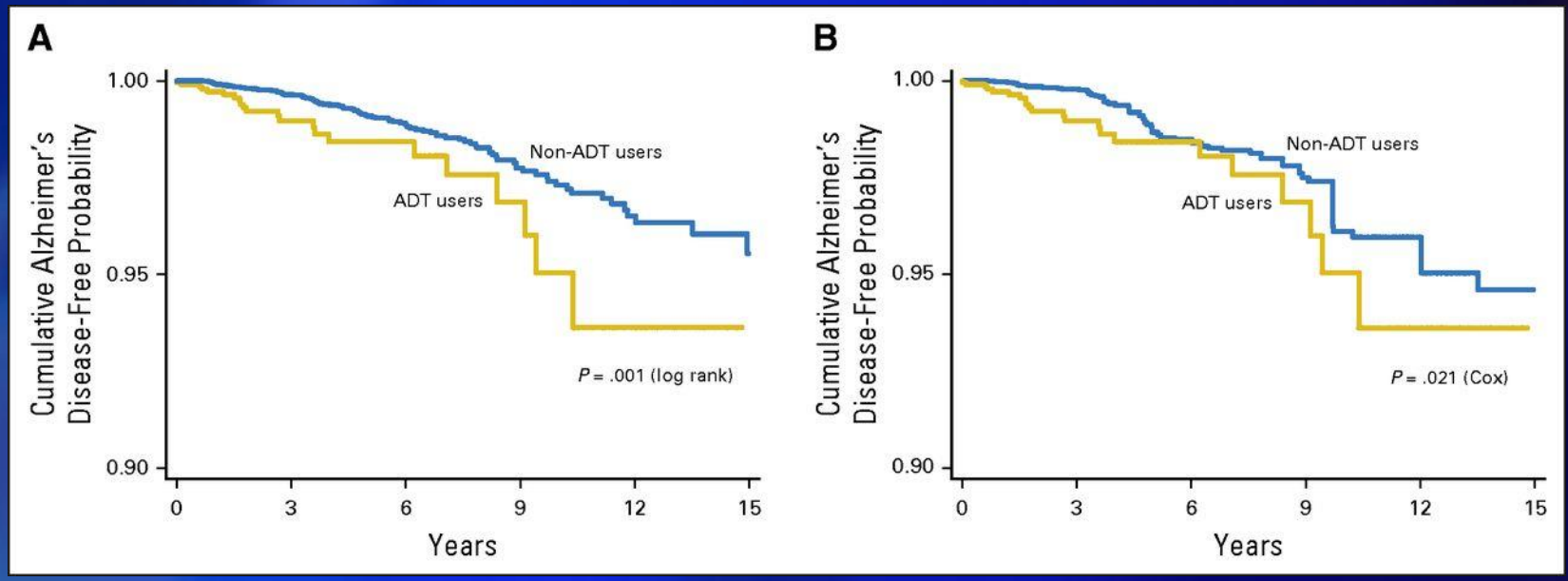
Open surgical procedures



Hospitalization LOS > 1 day

Rectal procedures

Probability of remaining free of Alzheimer's according to ADT use. Nead KT et al. JCO Dec 7 2015



- Any ADT use increased risk of Alzheimer's disease RR 1.9
- > 12 months exposure to ADT increased risk further RR 2.1

Why is surgery better if radiation works so well?

- Prostate cancer mortality difference:
  - Perhaps better local control; but no conclusive evidence for this
  - RP defines extent and grade of disease and allows selection for adjuvant therapy
  - Multi-modality therapy possible with initial resection
- Other cause mortality difference:
  - More ADT use with XRT
  - Second malignancies with XRT
  - ?Other systemic effects of high dose radiation

Analogy to other cancers?

High Risk Prostate Cancer

Radical Prostatectomy

Pathologic Staging and Risk Assessment

Adjuvant Therapy

Radiotherapy

ADT

Chemotherapy

Salvage Therapy

RadiotherapyRadiotherapy

ADT

Chemotherapy

High-Risk Prostate Cancer

Radiotherapy with ADT

NO Pathologic Staging and Risk Assessment

NO REAL Adjuvant Therapy

Continued ADT
Surveillance

NO GOOD Salvage Therapy

Cryo
Brachy
RP
More ADT
Chemotherapy

Conclusions:

- Microfocal Gleason 6 is part of the aging process
  - No metastatic potential
  - Higher volume Gleason 6 a marker for increased risk of higher grade cancer
  - exclude with MRI, biomarkers
- The ‘grey zone’: shrinking
- Presence of Gleason 4 pattern:
  - With AS, 3-4x risk of mets @ 15 years
- Focal therapy: Clear benefit to appropriate patient
  - Defining this population a priority
- Variety of ablative tools available
- No consensus on what is a “success”
- Major academic challenge to sort this out over the next 20 years
- We have a responsibility to reduce overtreatment