Active surveillance 2019: From biology to bedside
Sao Paolo, Brazil April 4 2019

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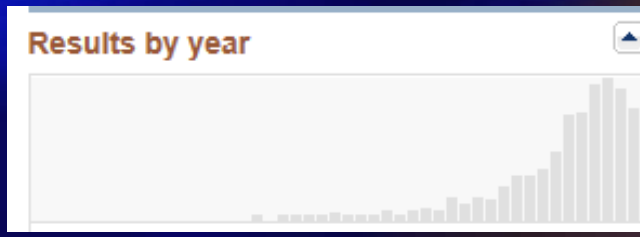
Active Surveillance for low risk PCa
What has changed?
(since Klotz, Choo J Urol 167: 1664, 2002)

- Greater recognition of overtreatment problem, acceptance of concept
- Nature of occult high grade disease
- Predictive value of baseline parameters
- Flaws of PSA kinetics as trigger
- Multiparametric MRI
- Modelling studies
- Multiple mature large registries
- ~3000 publications



What we know

- Molecular genetics
  - Gleason 3--resembles normal cells in most cases
  - Metastatic potential zero.
  - Can invade locally (therefore fulfills criteria of ‘Cancer’)

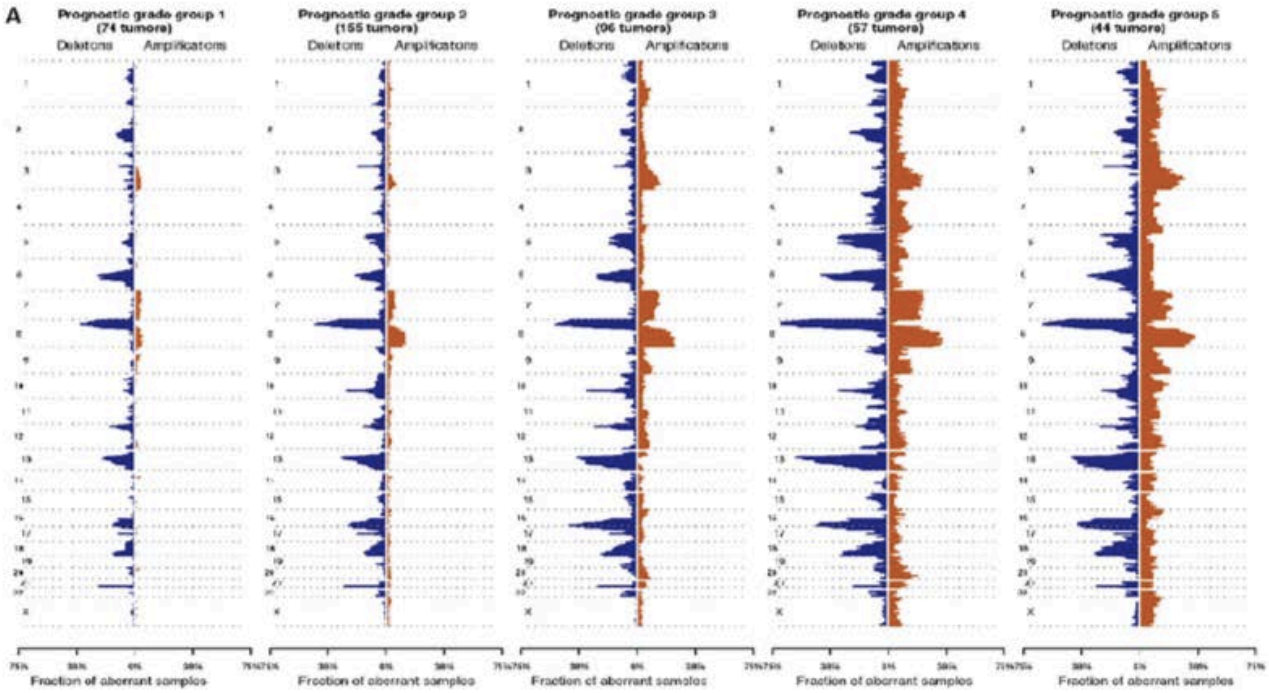
Well documented cases of surgically proven Gleason 6 cancers that have metastasized ~= 0

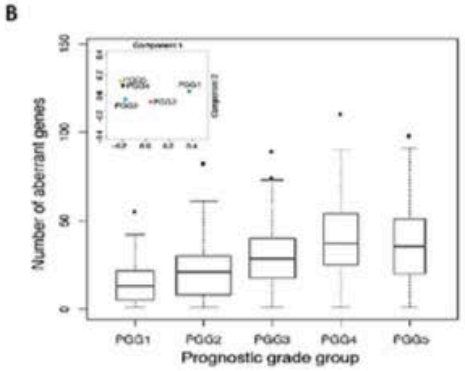
- 12,000 Gleason 6 cancers treated with RP with 20 year follow up (Eggener S, J Urol 2011)
  - Pca mortality 0.2% at 20 years
  - Re-review of these all showed higher grade Ca
- 14,123 cases of pathologic Gleason 6 at RP (Ross HM, Am J Surg Path 2012)
  - 22 with positive nodes (era of limited node dissection)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

The Achilles heels of active surveillance for low risk Pca

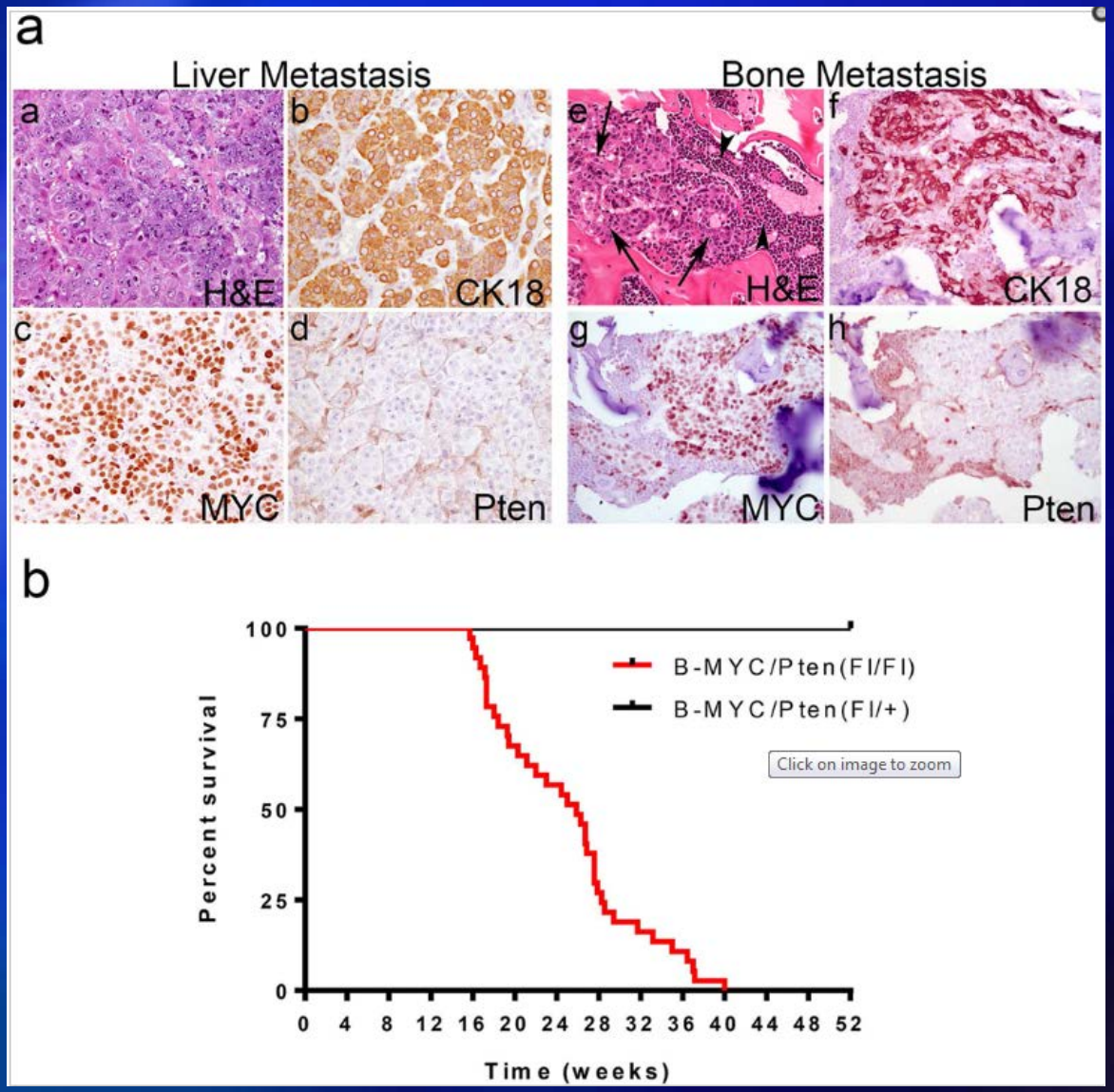
- Common and early: Misattribution of grade (25-30% with systematic biopsies)
  - Less with targeted biopsies
- Uncommon but incremental: Grade progression over time (1-2% per year). Inoue LY, Etzioni R. Stat Med. 2014;33(6):930-9.
  - Usually occurs in a field of extensive GG1
  - In most cases, to Gleason 3+4

Genomic alterations quantitatively, not qualitatively different between grades. Rubin M et al, Eur Urol 2016; 69(4):557-60



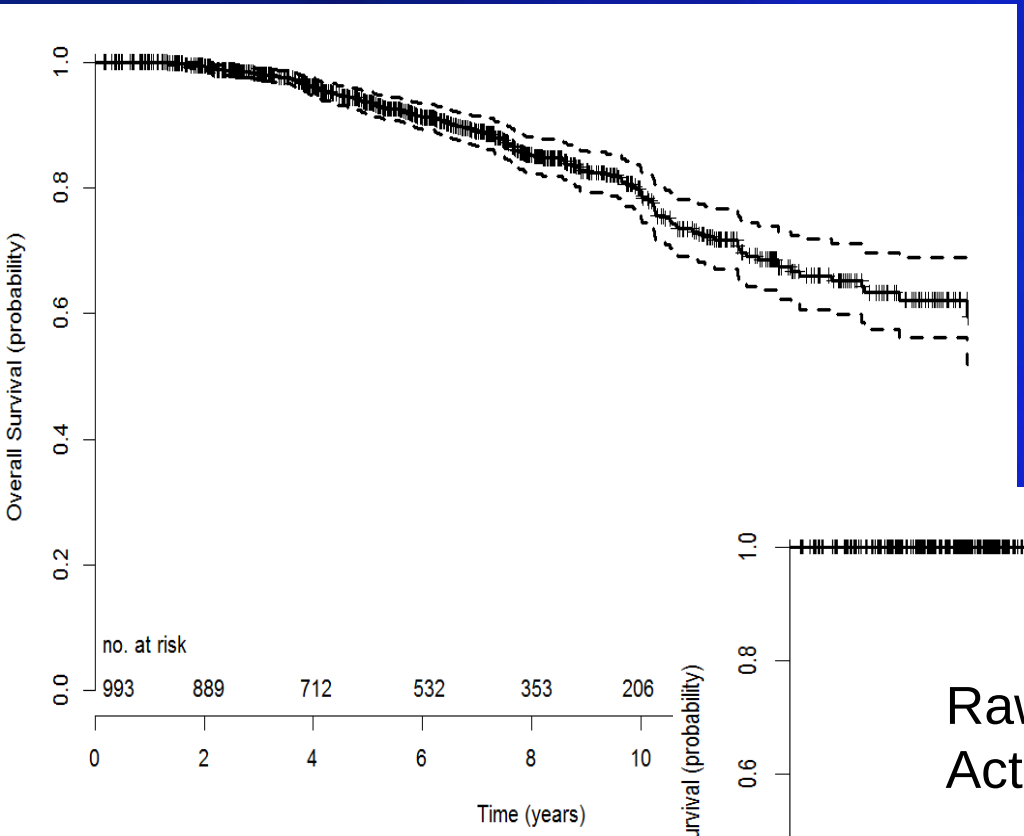


Combined MYC Activation and Pten Loss Create Genomic Instability and Lethal Metastatic Pca . Hubbard GK, Ca Res 2016 Jan 15;76(2):283-92



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

OS



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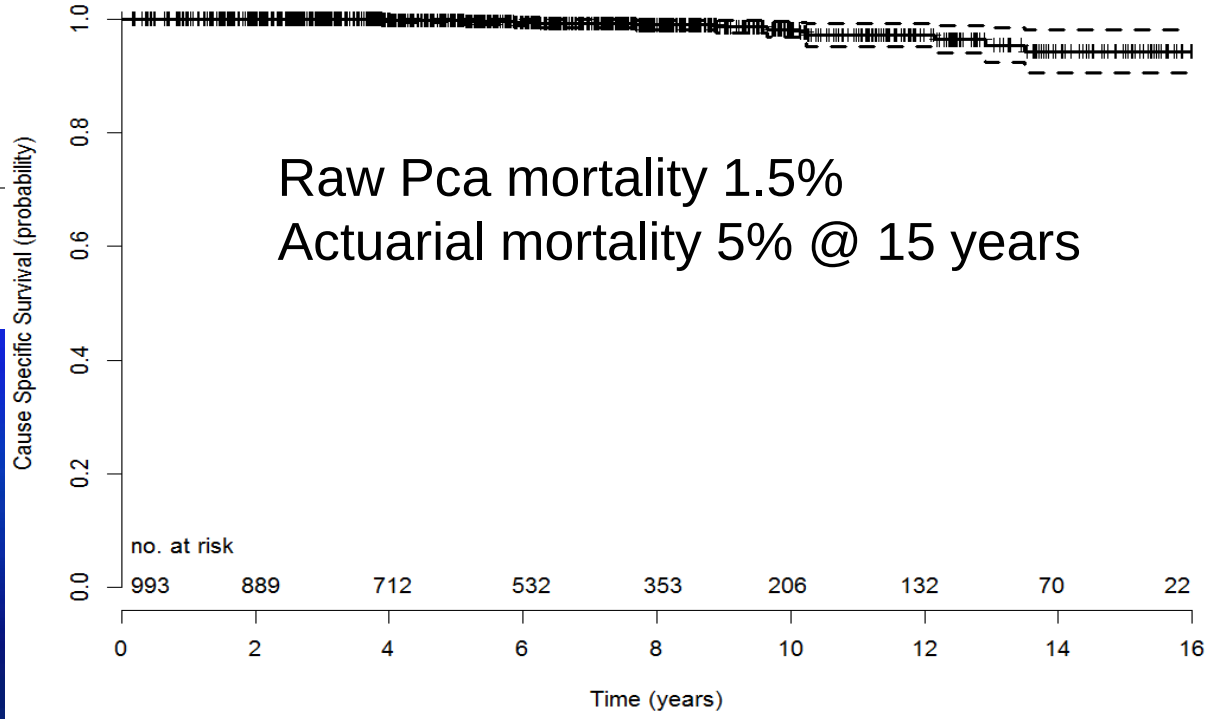
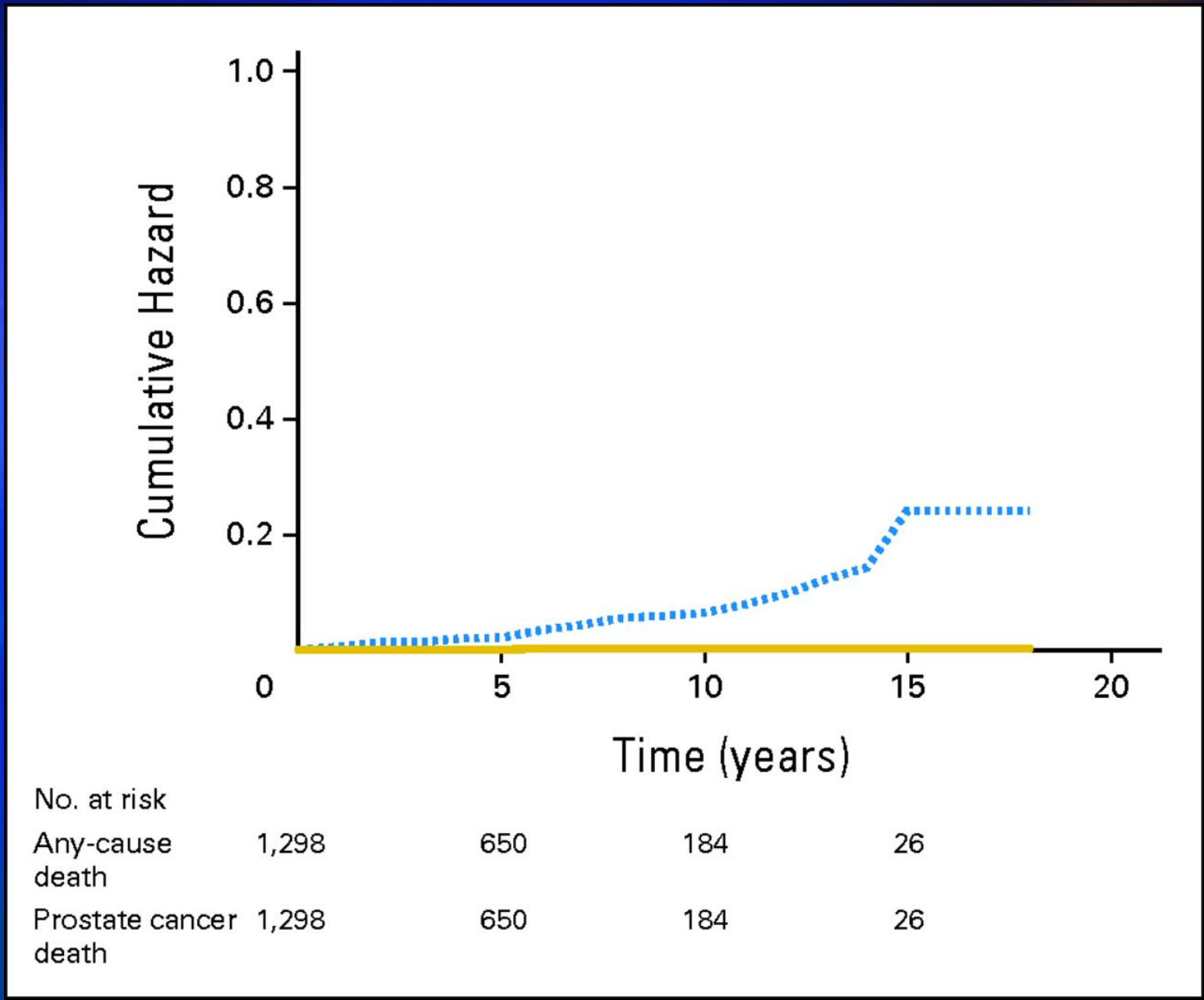


Raw Pca mortality 1.5%

Actuarial mortality 5% @ 15 years

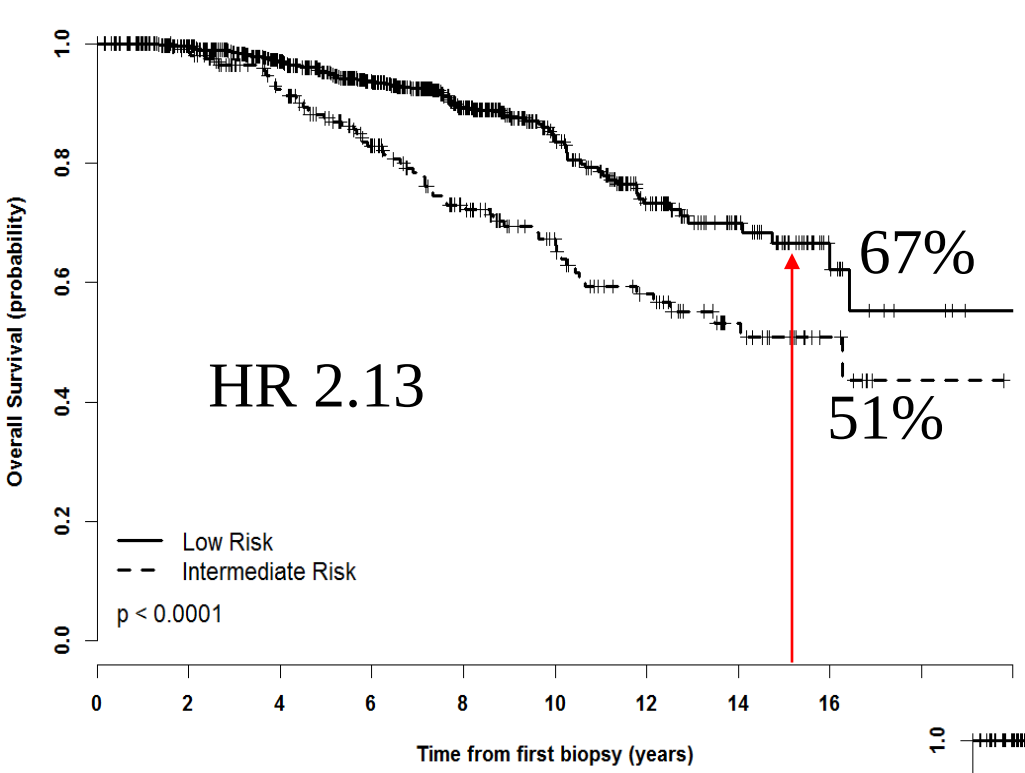
Hopkins AS long term outcome: Overall mortality and Pca mortality Tosoian J, Carter B et al. JCO.2015

Pca mortality 0.5% at 15 years



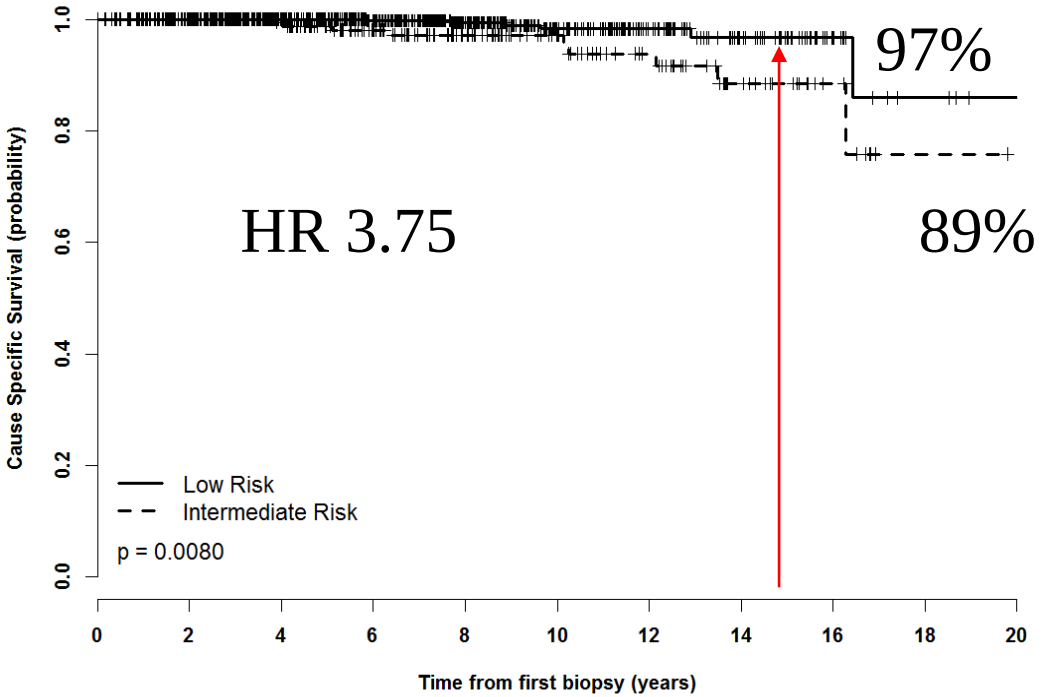
Low vs Intermediate risk (Gleason 3+4, PSA >10)

Yamamoto T, Klotz L. J Urol 195(5):1409-14, 2016



Overall Survival

Cause Specific Survival

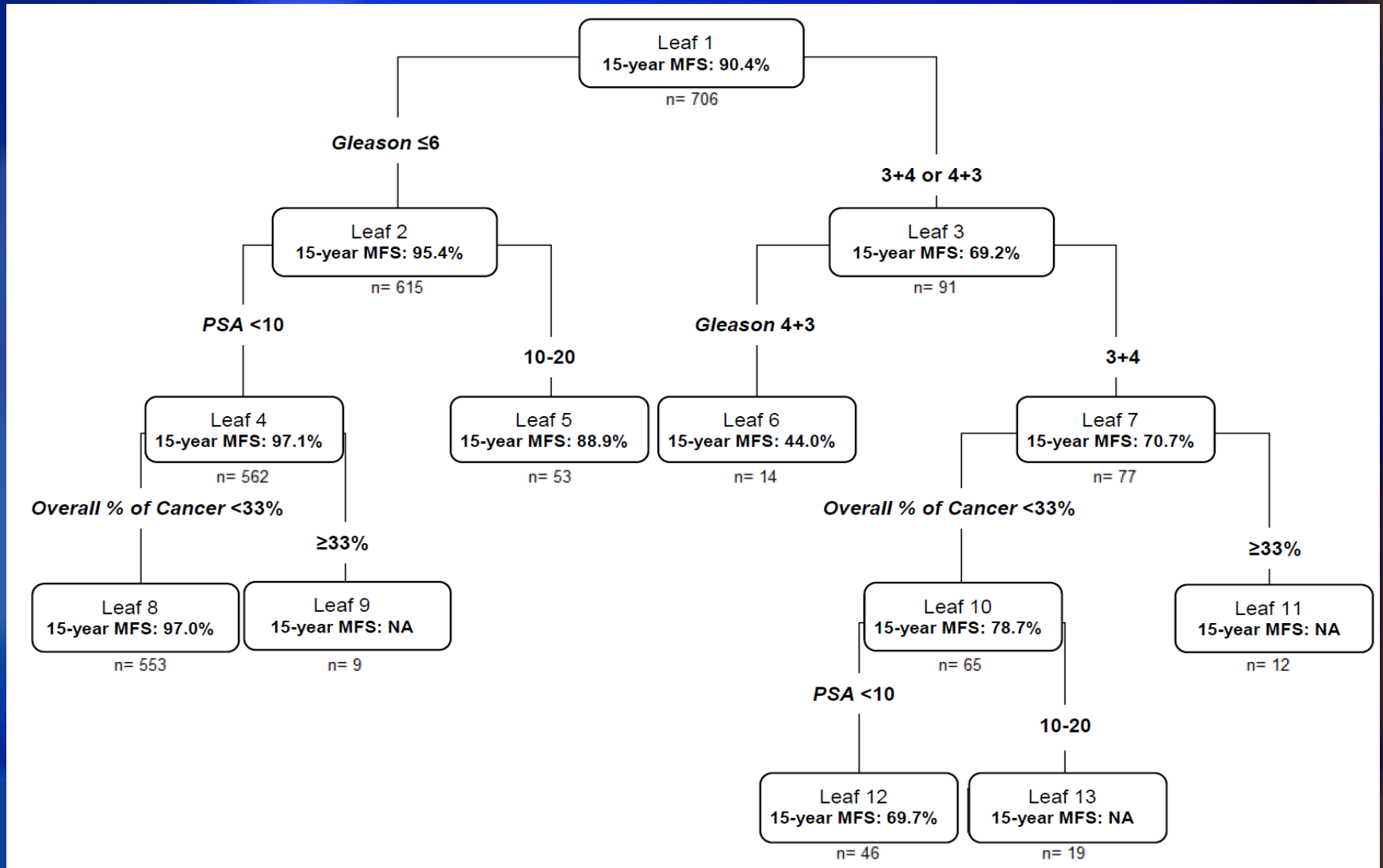


Metastasis rate with low vs intermediate risk on AS

Yamamoto T, Klotz L. J Urol 195(5):1409-14, 2016

- 1400 men on AS, 22% intermediate risk
- Low risk vs Intermediate risk:
  - OS 67% vs 51% @ 15 years, HR 2.13
  - CSS 97% vs 89%, HR 3.75

Recursive partitioning analysis: Metastasis free survival by risk group. Musunuru H, Klotz L et al. J Urol 196(6): 1651 (2016)

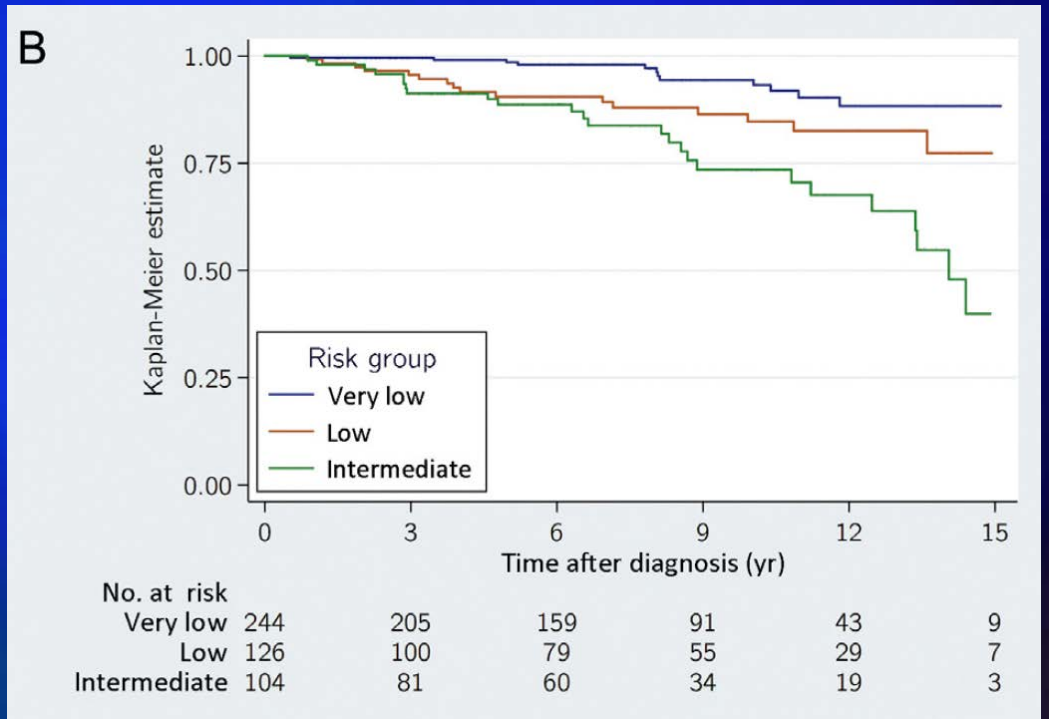


Active Surveillance in the Göteborg Prostate Cancer Screening Trial.

Godtman RA, Eur Urol. 2016 Nov;70(5):760-766.

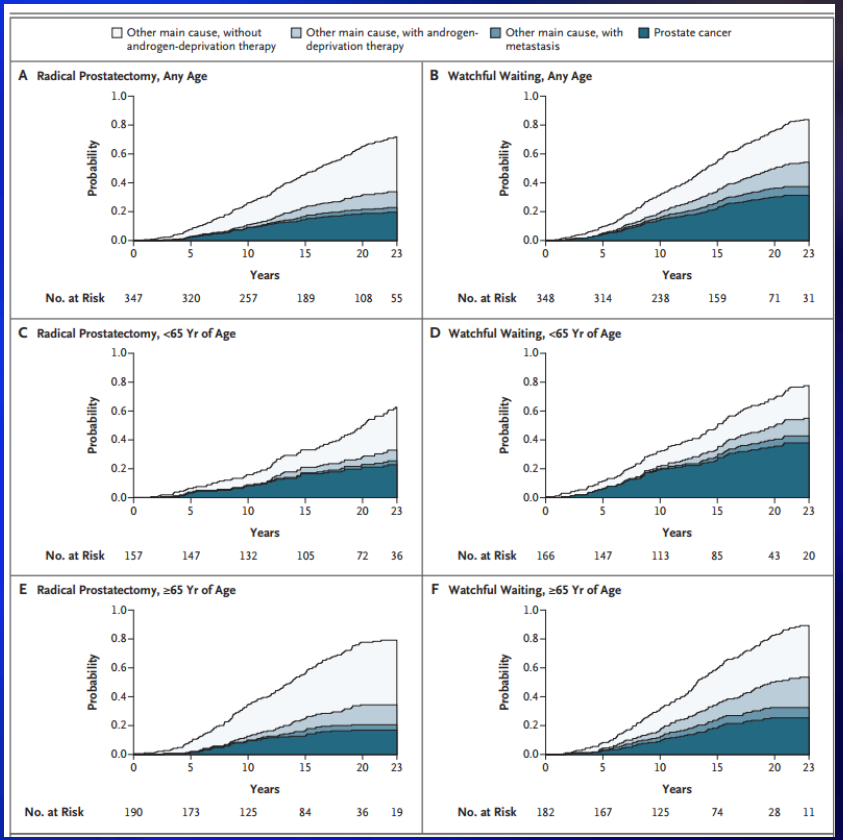
- N=474
- 104 Intermediate Risk; these accounted for 83% of the CSM
- 80% of the Int. risk were GG2
- HR for ‘failure’ for IR vs VLR: 4.8

Failure free survival



Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up.

Bill-Axelson A, N Engl J Med. 2018 Dec 13;379(24):2319-2329.



RP: No benefit for Gleason 3+4

End Point and Risk Factor	No. of Men	No. of Events	Relative Risk with Adjustment for Age Group (95% CI)*	Relative Risk with Adjustment for Age Group and Additional Factors (95% CI)†
Gleason score of prostatectomy specimen				
3–6	88	3	Reference	Reference
3+4	87	5	1.91 (0.46–7.99)	0.99 (0.23–4.33)
4+3	70	21	11.78 (3.51–39.55)	5.73 (1.59–20.67)
8 or 9	38	19	20.06 (5.93–67.91)	10.63 (3.03–37.30)

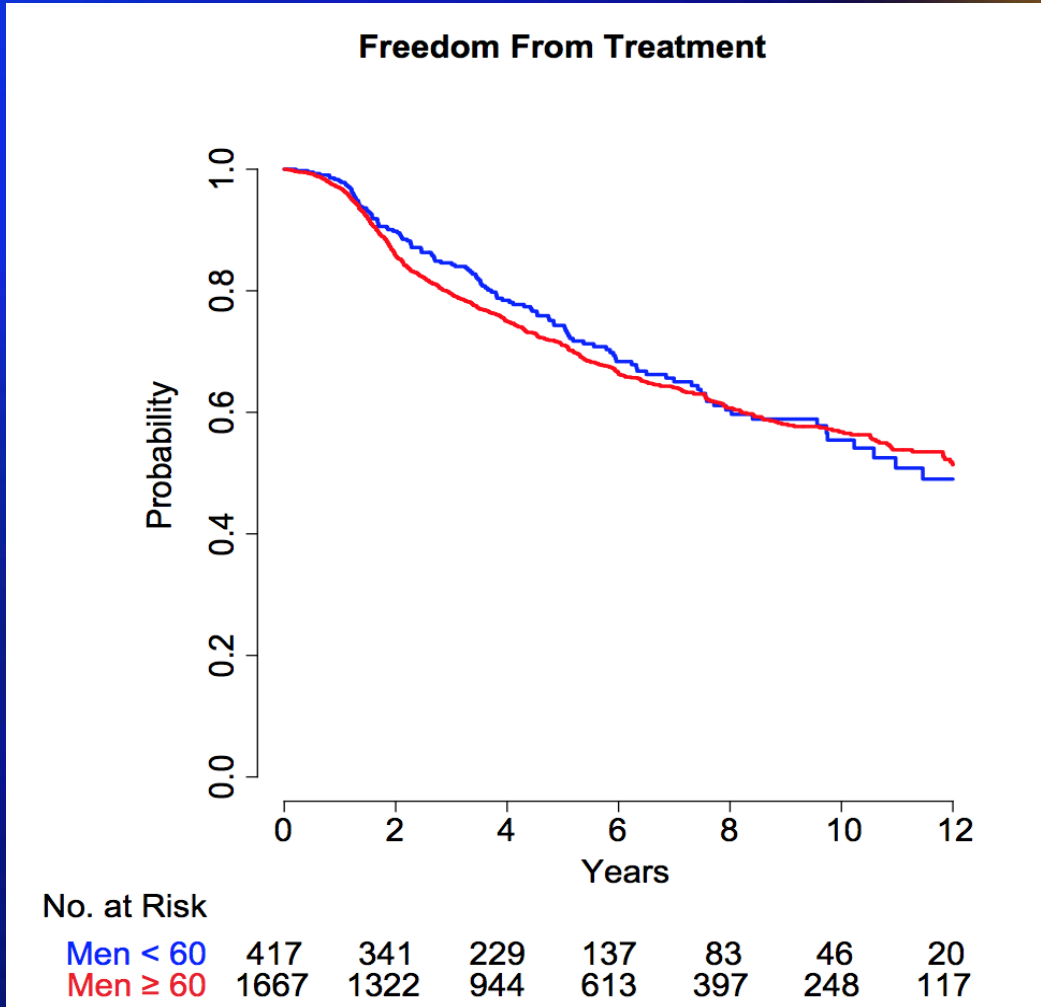
Long term outcome of surveillance reflects inclusion criteria and intervention strategy

	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%	15-20%
15 year Pca mortality	5% (mostly baseline Gl. 7)	0.5%

Is AS safe for young men (< 60 yrs)? Salari K, Klotz L et al AUA 2018

- 417 men < 60 yrs and 1667 ≥60 yrs on AS
- Median follow-up 6.2 years
- No difference in:
  - Treatment rates (74% *vs*. 71%)
  - MFS (99.7% *vs*. 99.0%),
  - CSS (100% *vs*. 99.7%).

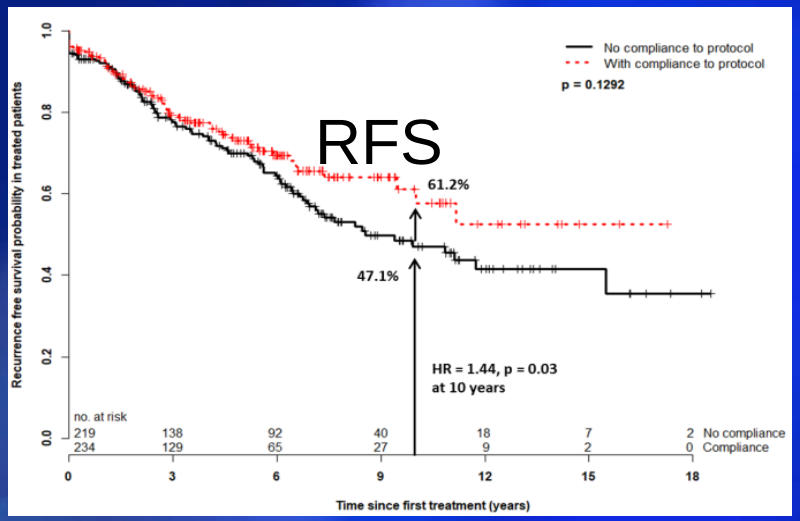
- Caveat: No 30 year follow up!

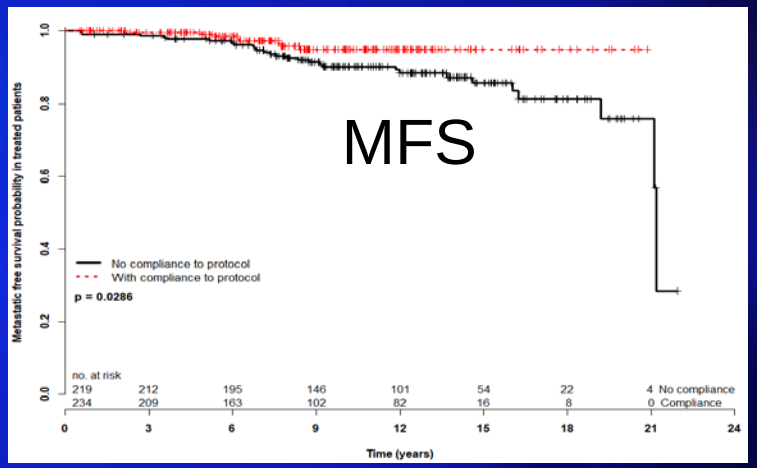


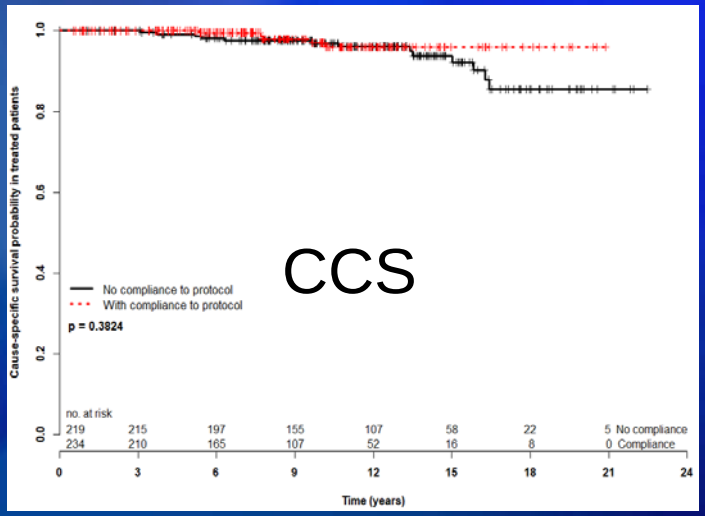
AS patients treated for Pca—characteristics and outcome
Klotz L, Loblaw A, submitted for publication

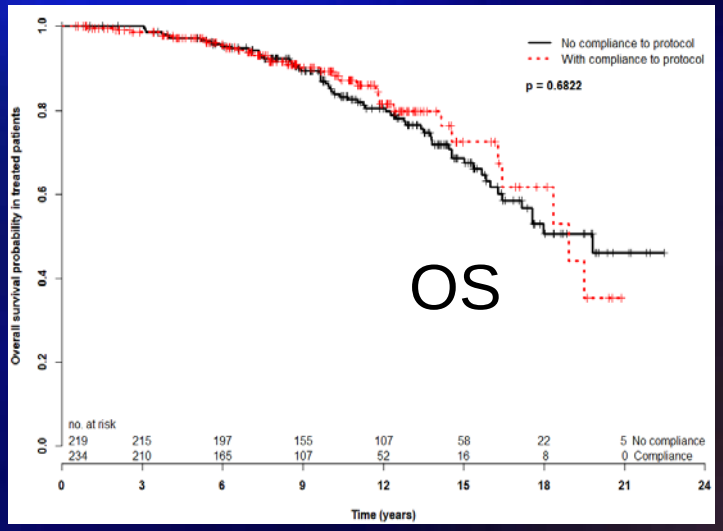
Characteristic	Non-compliant to protocol (n = 219)	Compliant to protocol (n = 234)	p-value
Median age, yr (IQR)	69 (64 – 73)	66 (60 – 70)	**< 0.001**
Treatment received, (%)			**0.021**
Radical prostatectomy	58 (26%)	84 (35%)	
Radiotherapy	127 (58%)	113 (48%)	
HIFU	7 (3%)	22 (9%)	
Failed subsequent treatment, n (%)	89 (41%)	61 (26%)	**0.001**
Developed metastases, n (%)	**28 (13%)**	**8 (3%)**	**< 0.001**
Died of PCa, n (%)	**13 (6%)**	**5 (2%)**	**0.053**
All deaths, n (%)	**60 (27%)**	**32 (14%)**	**< 0.001**

Oncologic outcomes by biopsy protocol compliance, Sunnybrook cohort

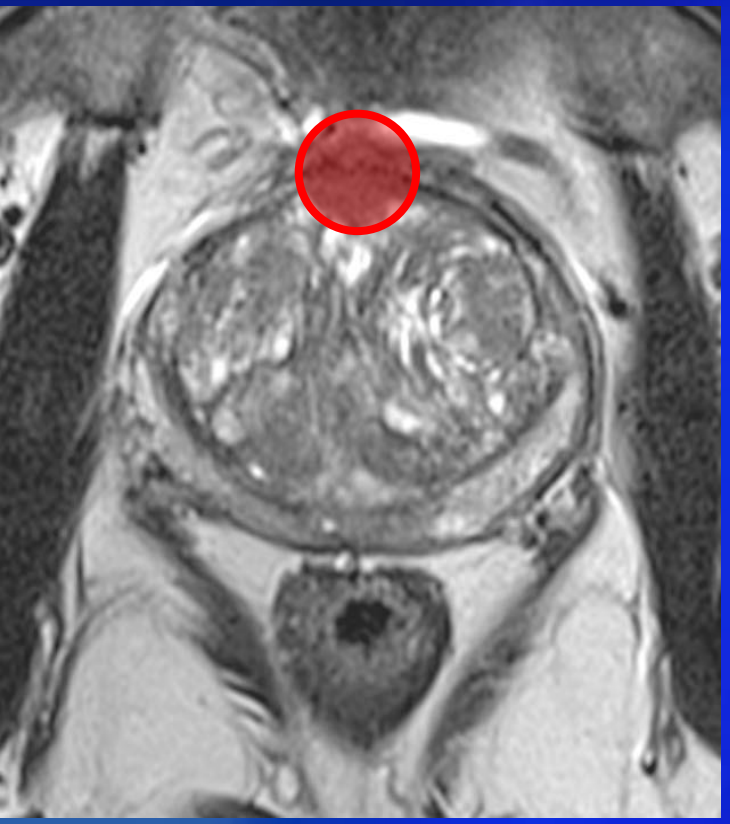


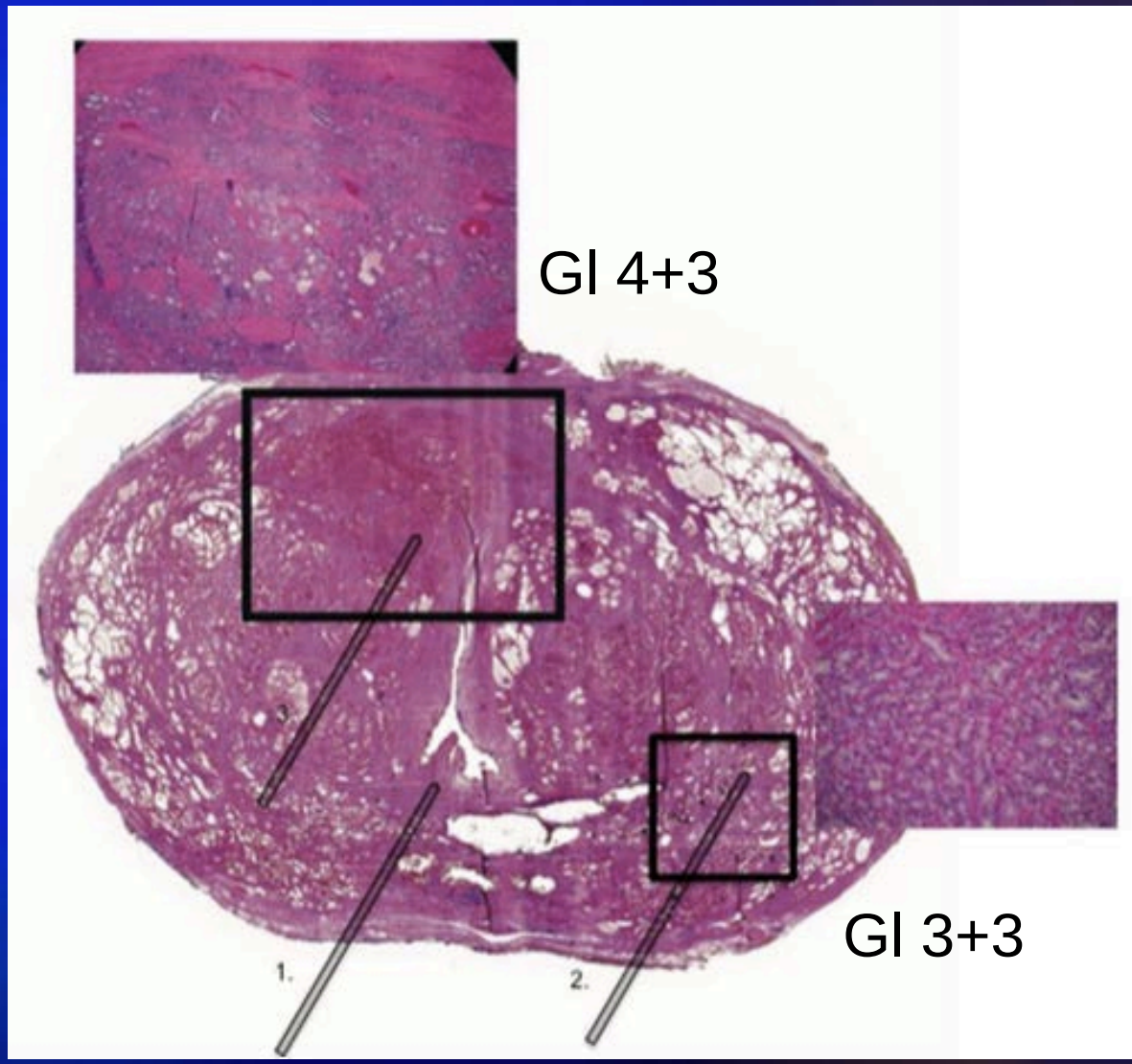






MRI targeting: Gleason 4+3 after prior biopsy showed 1 pos core 10% Gleason 3+3





How well does MRI detect and rule out clinically significant cancer?

Study	Year	N	Ca Dx rate %	Accuracy %	Sens %	Spec %	PPV %	NPV %
Abd-Alazeez	2014	129	55	44	94	23	34	89
Chamie	2014	115	100	72	96	46	66	92
Sonn	2013	105	34	50	NR	NR	NR	NR
Abd-Alazeez	2014	54	63	53	76	42	38	79
Arumainayagam	2013	64	84	72-82	58-73	71-84	49-63	84-89
Kasivisvanathan	2013	182	79	57	79	87	93	79
Hoeks	2012	265	41	35	NR	NR	NR	NR
Rais-Bahrami	2013	538	59	NR	94	28	38	91
Rouse	2011	114	60	86	95	84	68	98
Thompson	2014	150	61	33	96	50	50	96
Pannebianco	2015	1140	80	97	86	94	99	100
Ahmed Promis	2017	740	53	60	88	45	65	76
Klotz	2018	273	23	50	93	27	30	0.86
Systematic Reviews	De Rooij, AJR 2014 Mowatt, HTA 2013				74	88		**0.85**

Randomized MRI studies: Systematic bx vs MRI and targeted bx

All studies: Median PSA ~6, median age ~64,

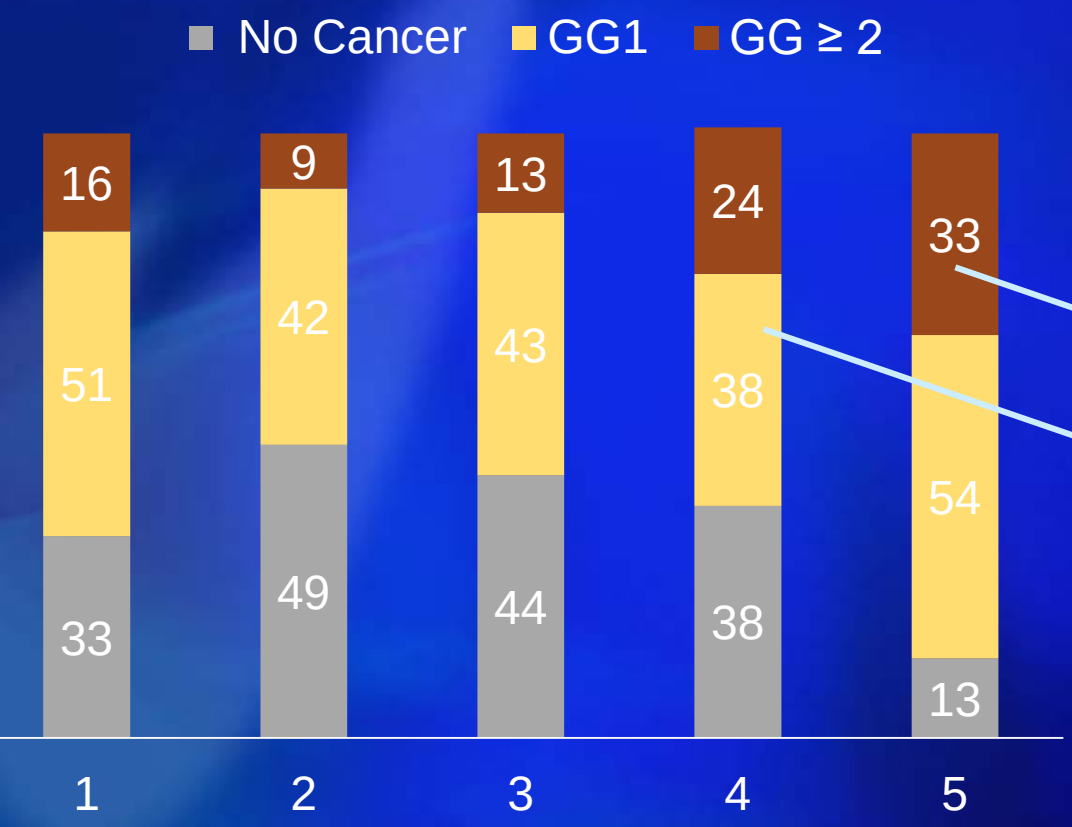
Study	N	Cohort	Biopsies avoided	Clin significant Ca missed if only targeted Bx	GG ≥ 2 Targ vs system-atic	GG 1 Targ vs system-atic	Median # cores/pt.
Precision NEJM 2018 Kasivisanathan	500	↑ PSA	28%		+ 12%	- 13% (9% vs 22%)	4 vs 12
MRI-First Lancet Onc 2018 Rouviere	251	↑ PSA	20%	11%	+ 2% (NS)	-14% (6% vs 20%)	3 vs 12
4M Eur Urol 2018 Van der Leest	626	↑ PSA	49%	4%	+ 2%	-11% (14% vs 25%)	3 vs 12
ASIST Euro Urol 2018 Klotz	275	Active Surv. (Confirm. Bx)	N/A (Syst vs Targ + Syst)	14%	-2%	-4%	N/A (median 2 targeted vs 12 systematic)

NPV of MRI: Meta-analysis from EAU Guidelines Panel. Moldovan PC Eur Urol. 2017 Aug;72(2):250-266.

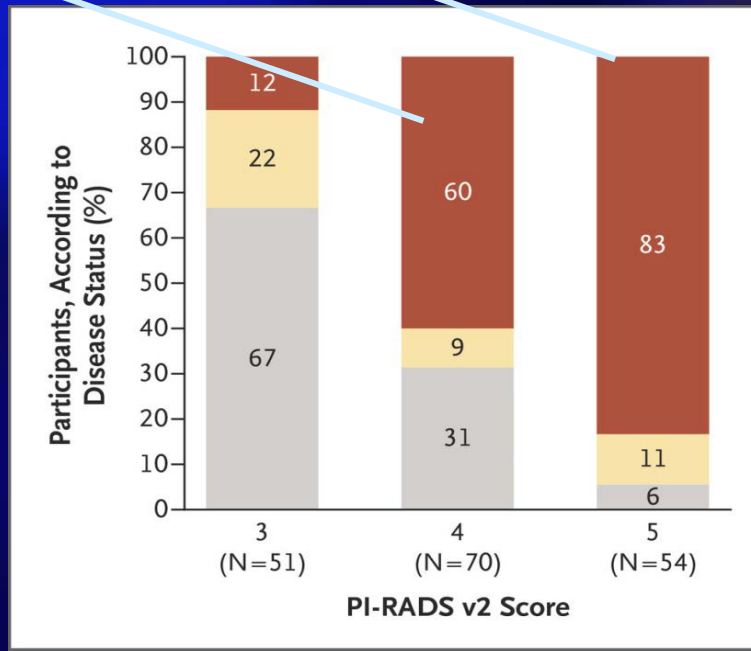
Can biopsy be avoided if MRI negative?

- NPV of MRI a function of underlying risk
  - For 30% risk of Pca, NPV 88%
  - For 60% risk, NPV 67%
- Most studies included all cancers, only one reported Gleason ≥ 7 (NPV 88%)

Percentages with No Cancer, Clinically Insignificant, and Clinically Significant Cancer by Likert score



Precision study NEJM 2018
(Note: definition of CS Ca non- identical)



Radiology

ORIGINAL RESEARCH • GENITOURINARY IMAGING

Value of Increasing Biopsy Cores per Target with Cognitive MRI-targeted Transrectal US Prostate Biopsy

Radiology 2019; 00:1–7

Michelle Zhang, MD, FRCP(C) • Laurent Milot, MD • Farzad Khalvati, PhD • Linda Sugar, MD, FRCP(C) • Michelle Downes, MD, FRCP(C) • Sarah M. Baig, MBBS • Laurence Klotz, MD, FRCS(C) • Masoom A. Haider, MD, FRCP(C)

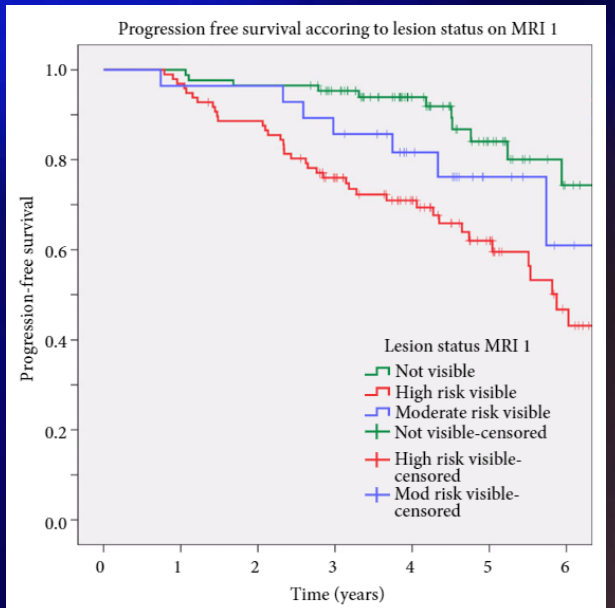
Maximum GG	1 core	3 cores	5 cores
GG ≥ 1	43%	52%	55%
GG ≥ 2	26%	33%	35%
GG ≥ 3	14%	16%	18%

Upgrade	From 1 to 3 cores	From 3 to 5 cores
GG 0 to GG ≥ 1	8%	3%
GG ≦ 1 to GG ≥ 2	6%	2.4%
GG ≦ 2 to GG ≥ 3	2.4%	1.5%
Any upgrade	13%	6%

MRI-based active surveillance: PSA dynamics and serial MRI scans allow omission of F/U biopsies. Gallagher KM, BJU Int. 2019 Mar;123(3):429-438.

- 1/56 patients (1.8%) with negative MRI who underwent confirmatory systematic biopsy had upgrading to ≥ GG2.
- Men with suspicious MRI had high risk of subsequent progression: 19/76 (25.0%) vs 9/84 (10.7%) for patients with negative MRI, despite negative confirmatory biopsies and favorable PSA dynamics.

- Men with low-risk Gleason 3 +3 prostate cancer on active surveillance can forgo biopsies in favour of MRI and PSA monitoring with selective re-biopsy

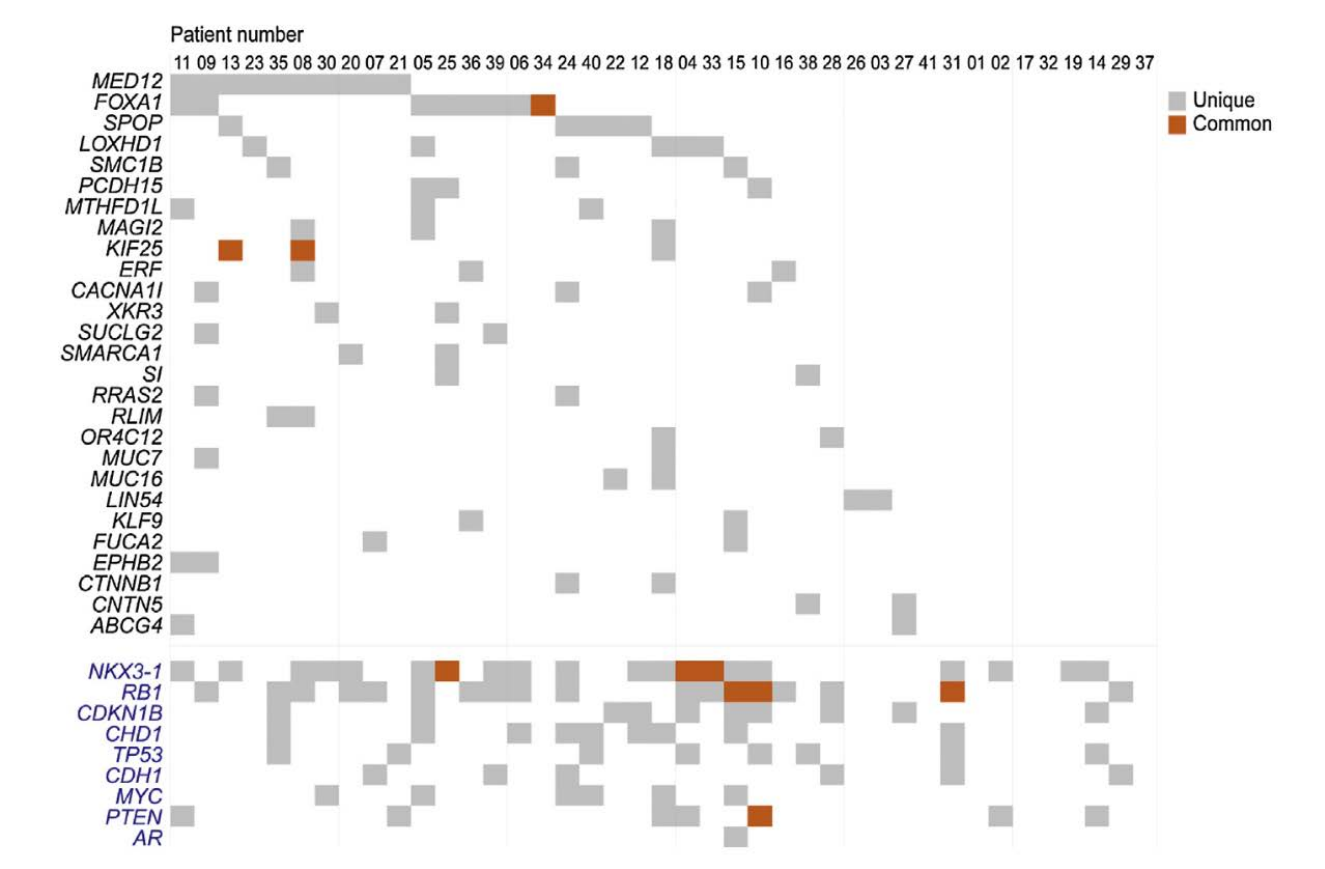


Currently available tissue-based tests for Pca

Test	*Platform*	*Molecular basis*	*Marketed use*	*CMS approved use*	*Clinical scenario*
Ki-67	IHC	Proliferation	NA	No	Active surveillance
Prolaris	RT-PCR	Proliferation	Pre and post Rx decision making	Yes, decision making for surveillance	Active surveillance
PTEN	IHC/FISH	PTEN	NA	No	Active surveillance
ProMark	Quantitative proteomics	Proteins related to PCa adverse pathology and outcomes	Pre-Tx decision making	No	Active surveillance
OncotypeDX Prostate	RT-PCR	Transcripts ~ adverse pathology and outcomes	Pre-Tx decision making	No	Active surveillance
Decipher	RNA MicroArray	Transcripts predictive of PCa metastasis	Post-Tx decision making	Yes, post RP	Adjuvant radiation

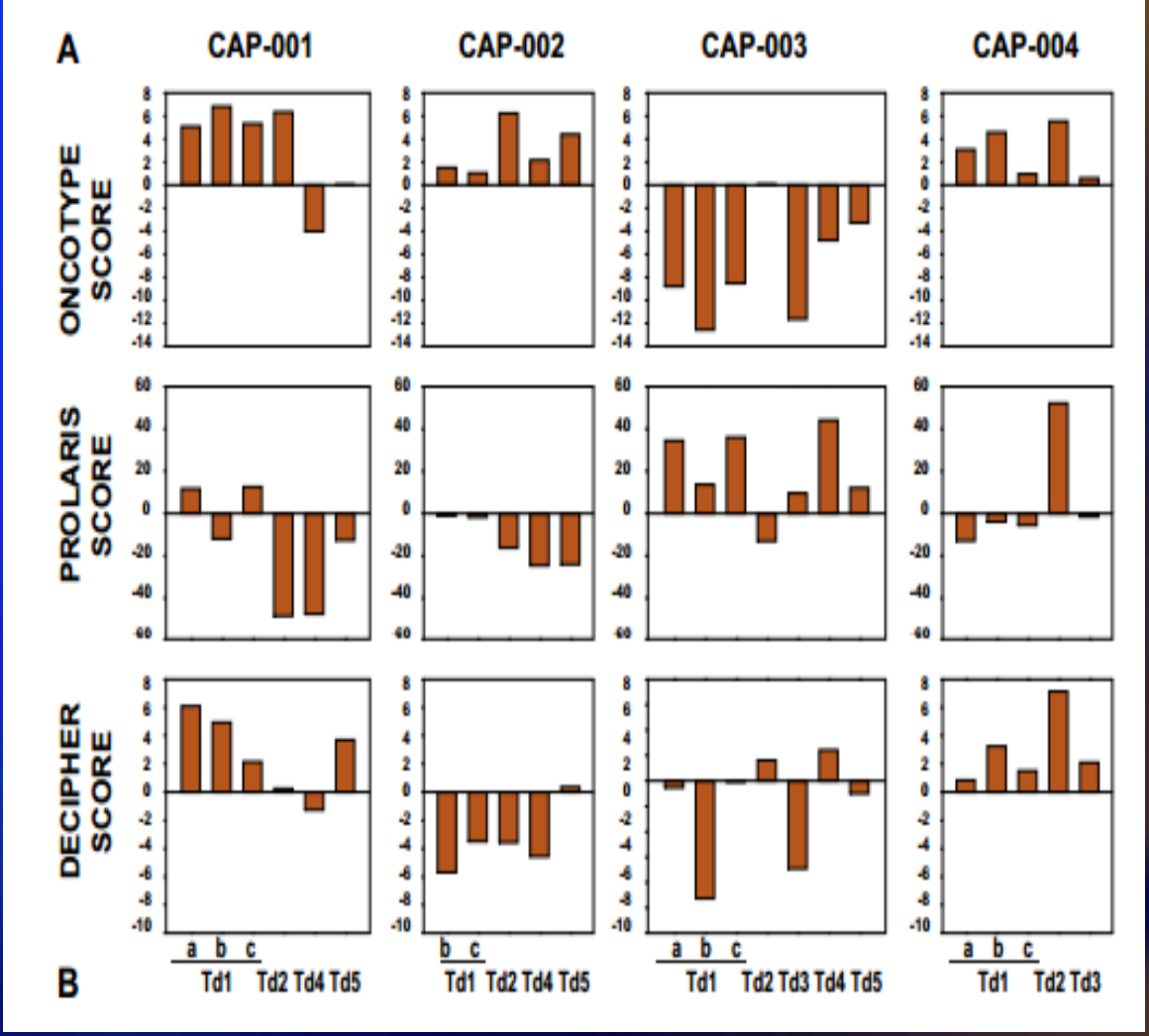
Multifocal Primary Prostate Cancer Exhibits High Degree of Genomic Heterogeneity Løvf M, Eur Urol. 2018 Sep 1.

- High-coverage whole-exome sequencing of 153 samples
- two to three distinct tumor foci and one non-cancerous area
- Grey: unique mutation/alteration
- Orange: common mutation
- N=41 patients



Intratumoral andi intertumoral genomic heterogeneity of multifocal localized Pca impacts molecular classifications and genomic prognosticators. Wei L, Eur Urol. 2016 Jul 20.

Whole-exome sequencing, single-nucleotide polymorphism arrays, and RNA sequencing in 4 representative patients.

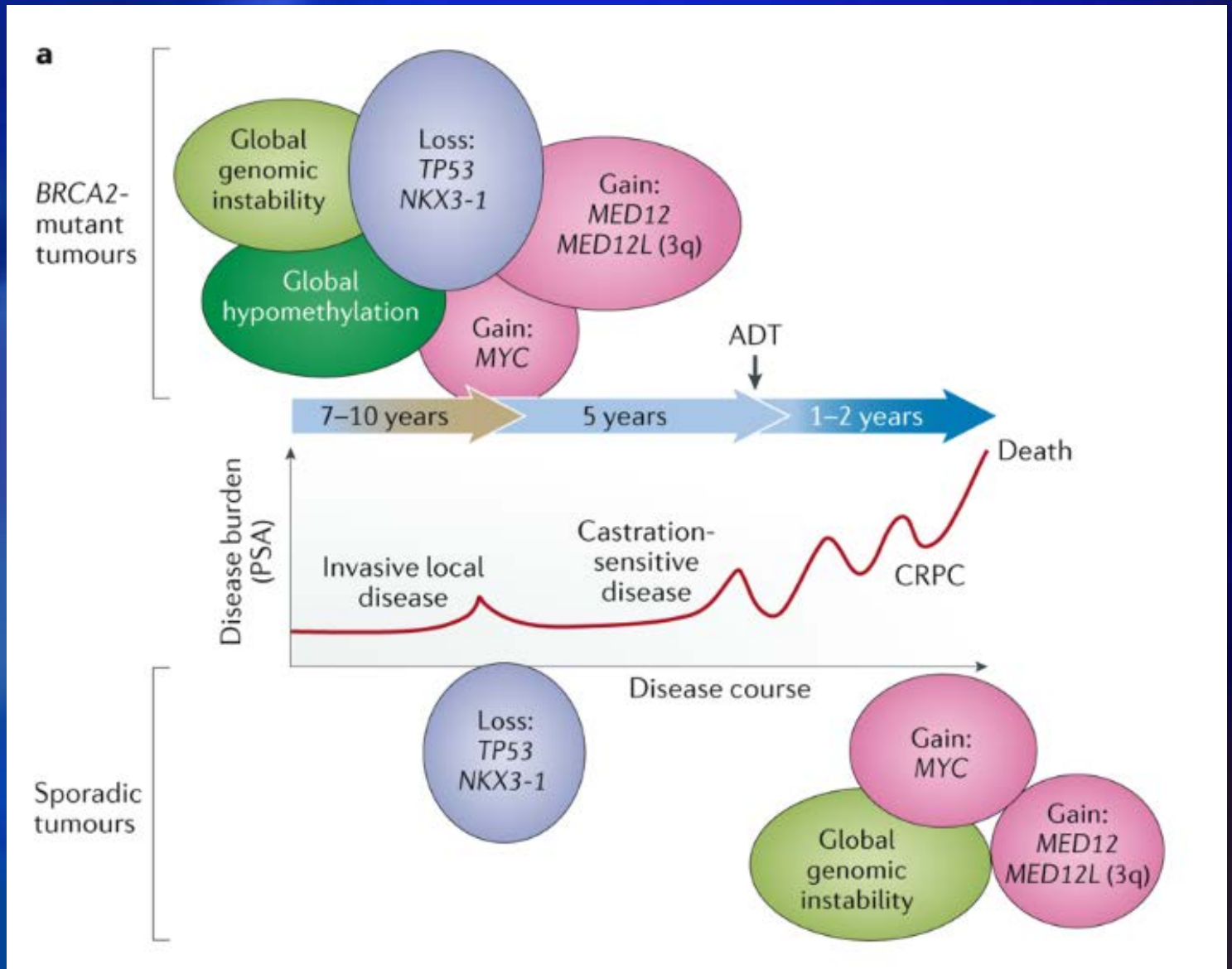


Genetic biomarkers and risk: Bayesian problem

- You have a patient with GG1 and favorable features.
- He has a 1-3% 15 year probability of metastasis
- You apply a molecular diagnostic test
- Risk of false positive likely significantly greater than benefit of test
- Or: 2 cores of Gleason 4+3 with a negative test—would you counsel conservative treatment?

We need the right test in the right patient with risk in the ‘sweet spot’.

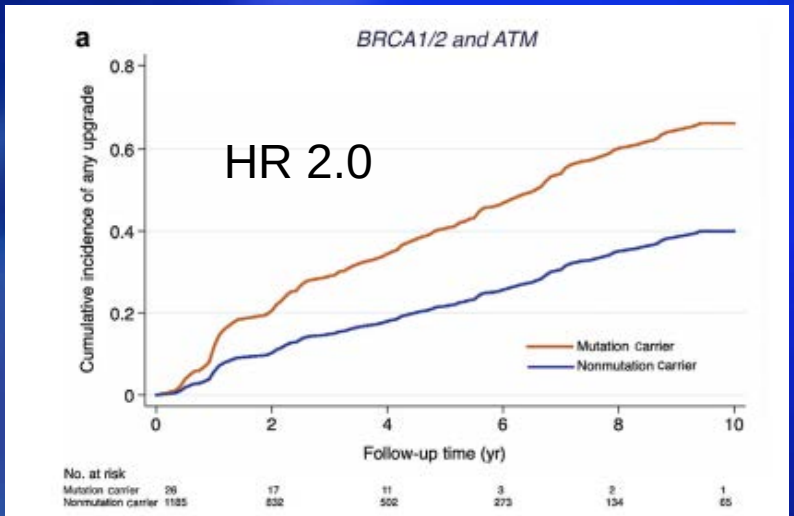
The influence of *BRCA2* mutation on localized prostate cancer. Taylor A, Bristow R, Risbridger G, Nature Reviews Urology Feb 2019

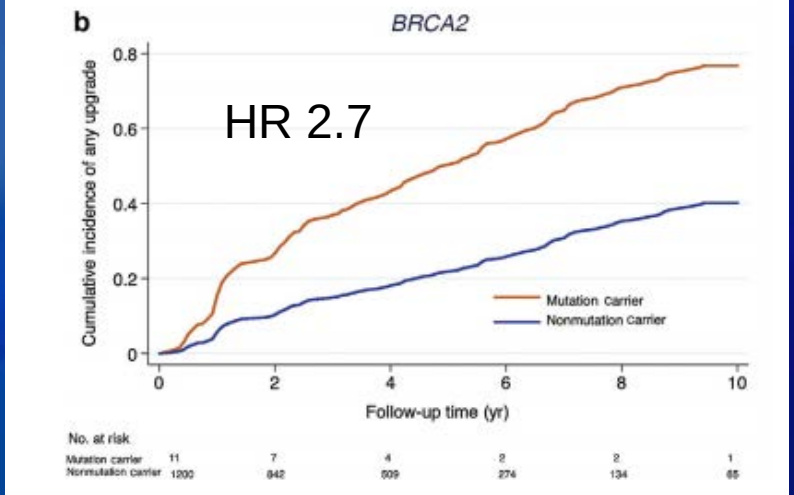


Germline Mutations in ATM and BRCA1/2 Are Associated with Grade Reclassification in Men on Active Surveillance **Carter** HB, Eur Urol. 2018 Oct 8

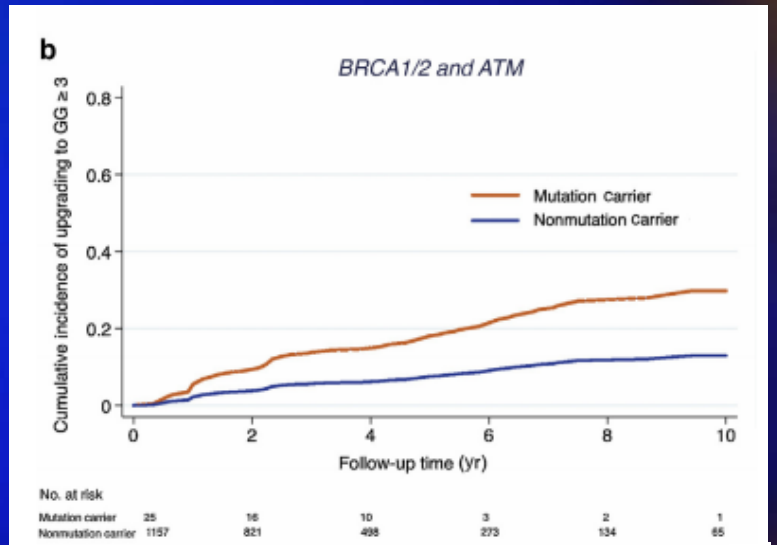
- 1211 men on active surveillance
- 26 with DNA repair germline mutations (BRCA1/2, ATM)

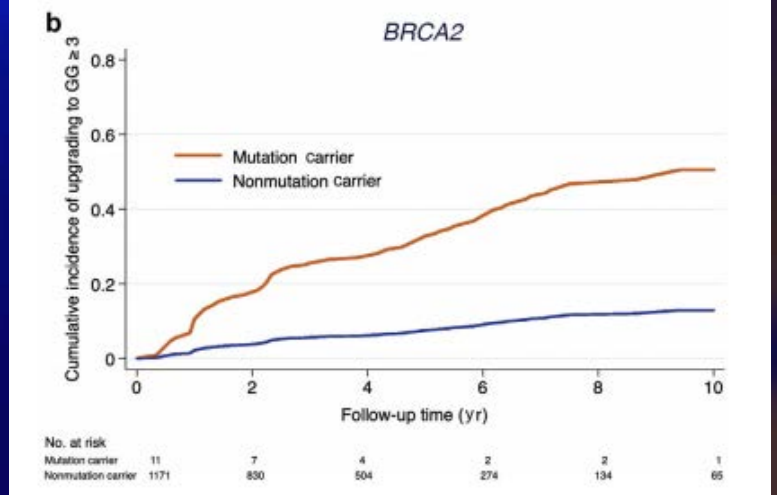
Any upgrading



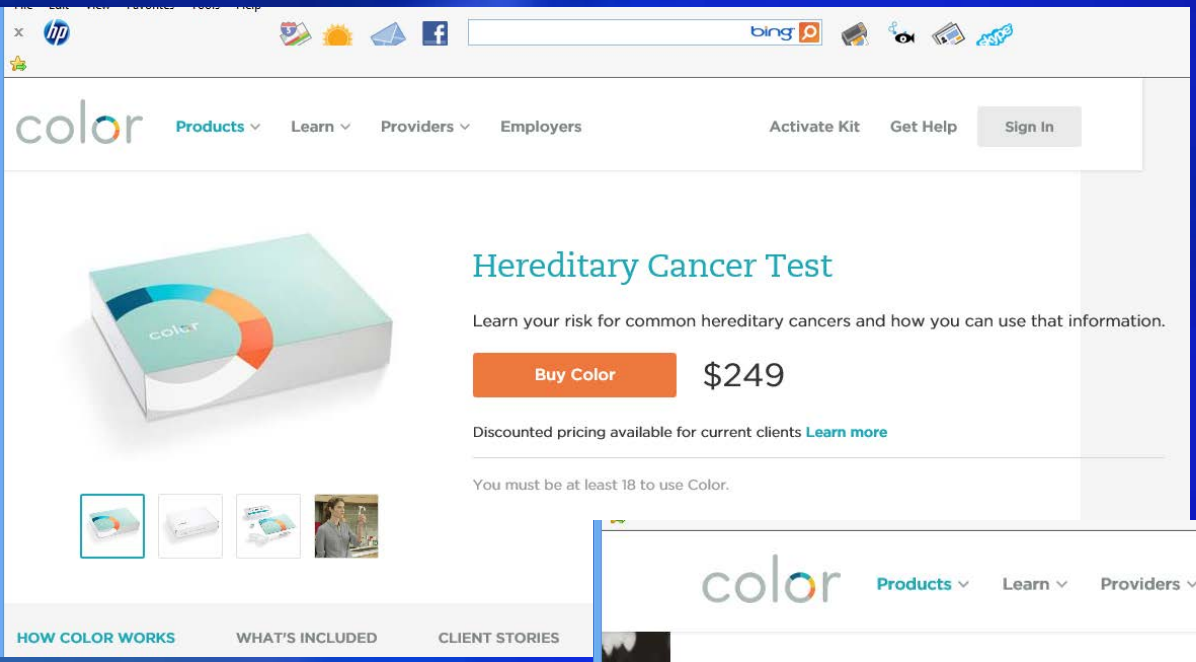


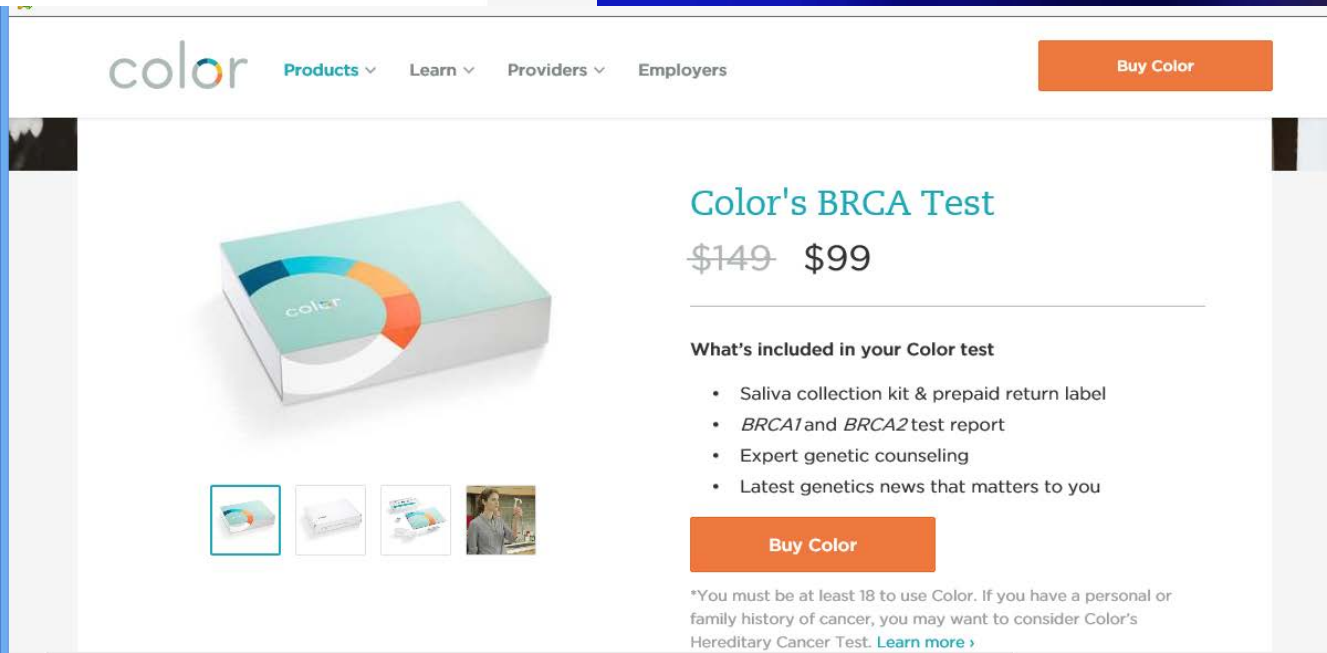
Upgrading to ≥ GG3





Color.com genetic testing for inherited DNA repair defects





Low risk cancers that are candidates for active surveillance

Type of Cancer	Median age	Sex	Definitive Treatment option	Risks of Treating	AS option	Specialty	Stage of Adoption
Prostate	66	100 % ♂	RP or XRT	ED, incontinence, proctitis	PSA, MRI, biopsy	Urologist	Widely adopted
Thyroid	51	75% ♀	Total thyroidec-tomy +/- LND +/- I^{125}	Change in voice and hypoCa^{++}	Neck U/S and serum Thyro-globulin	Endocri-nologist	In trials
DCIS Breast	62	98% ♀	Mastectomy/ lumpectomy + XRT	Lymph-oedema, other	Mammo-graphy	Varies	In discus-sions
Kidney Ca	65	60% ♂	Nephrectomy/ Partial Nx	CRF, ↑ BP	U/S/CT/ biopsy	Urologist	Increas-ing

Comparison of guidelines: US, Canada, UK, Europe

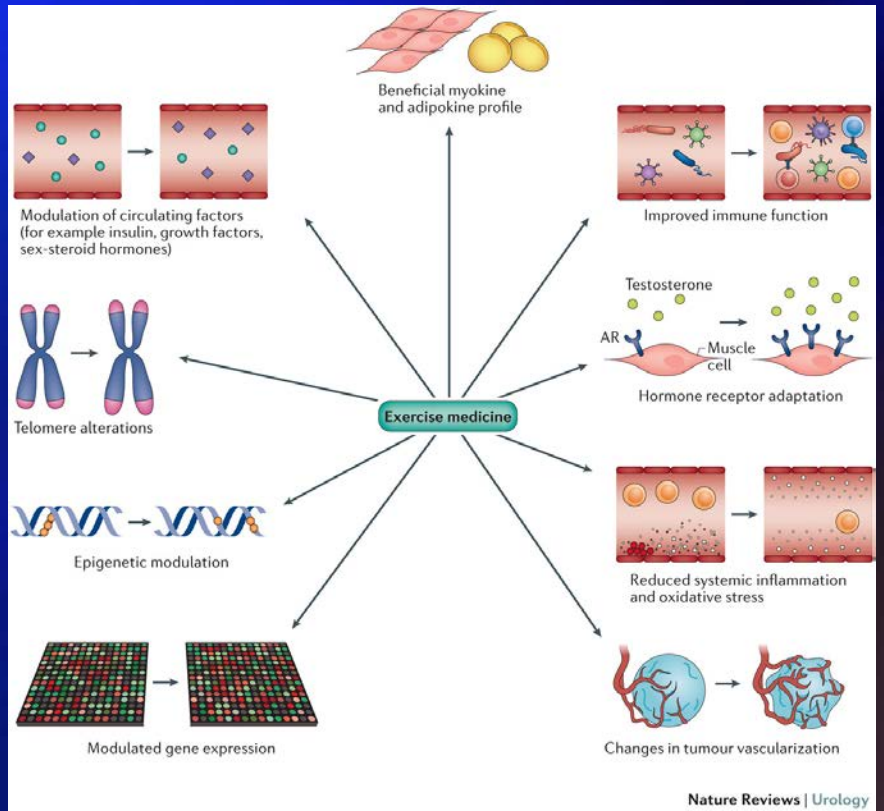
	Low risk Pca	Intermediate risk	F/U: PSA, DRE, Biopsy	Other tests (MRI, biomarkers)	5 ARI
Cancer Care Ontario CUAJ 2015	AS preferred manage-ment	Active treatment; AS for selected pts	PSA q 3-6 mo DRE q 1 yr Systematic bx within 6-12 mo, then q 3-5 yrs	MRI when clinical and path findings discordant	**May have a role**
ASCO JCO 2016	Same	Same	Same	Other tests remain investigational	**No clear role**
AUA 2017	Same	Selected patients	Same	Same	
NICE 2016	Same	Radical treatment for 'disease progression'[2]	PSA q 3-4 months, monitor kinetics, otherwise same	MRI at enrollment	
EAU 2018	Same, esp. if < 20 yr L.E.	Selected patients	Same as CCO	MRI recommended (esp prior to confirm bx)	N/A

Can we prevent 'failure' by innocuous interventions?

- Why:
  - Patients like to feel they are 'doing something'
  - Most proposed interventions have other health benefits
  - Opportunity to improve diet, lifestyle
  - Perhaps reduce biological progression

Simple heart/prostate healthy advice for patients on AS

- Stop smoking
- Regular exercise
- Dietary modification: weight management, moderate red meat intake, increase fruits/vegetables



Galvão, D. A. *et al.* Enhancing active surveillance of prostate cancer: the potential of exercise medicine *Nat. Rev. Urol.* 2016

For men who want to be very proactive

- Vit D 1000-1500 IU/day (especially northern countries)
- Low dose statin (eg, Atorvastatin 10 mgday)
- Metformin 500-850 mg/day

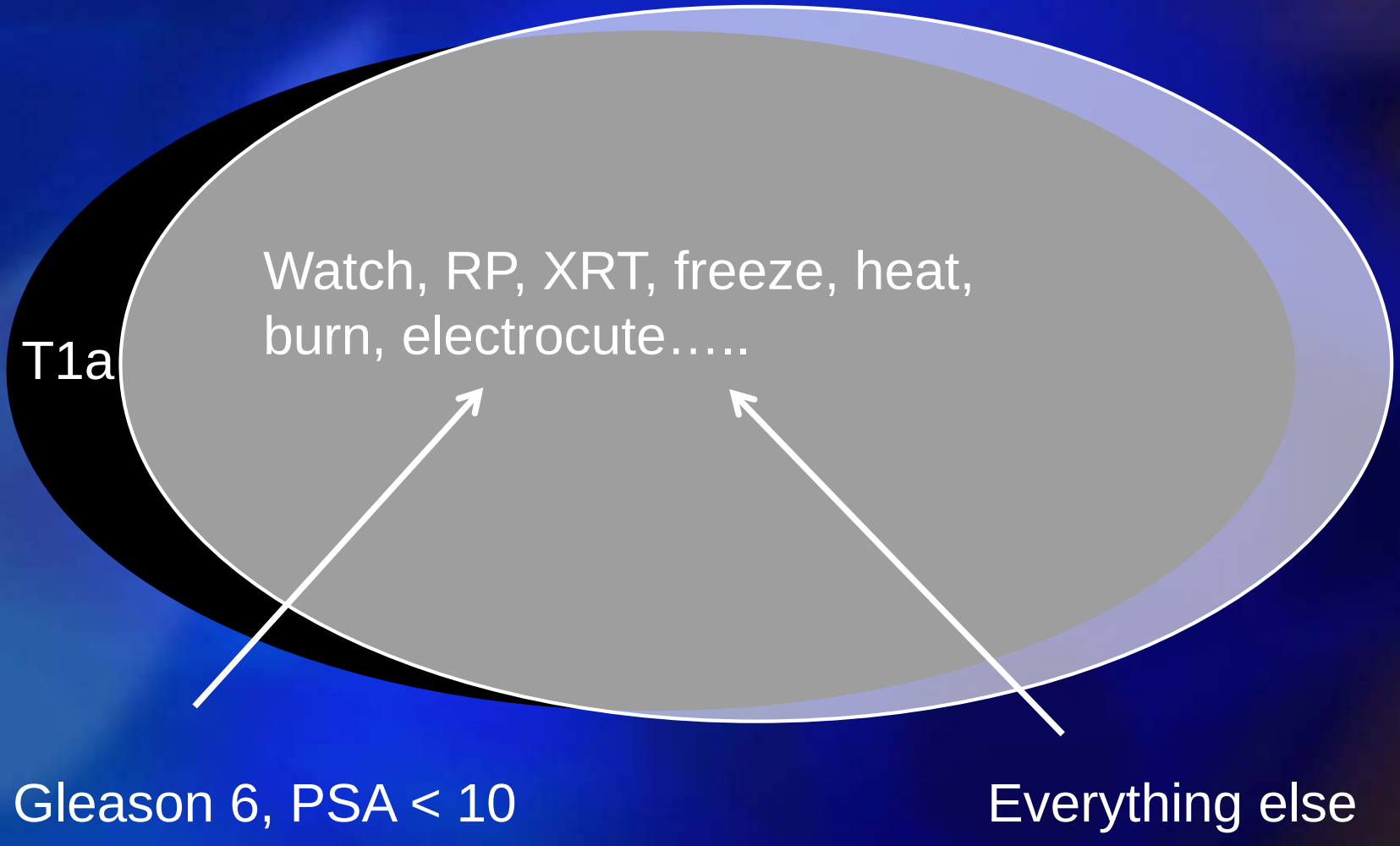
Which intermediate risk patients can be managed with surveillance?

- Gleason 3 + ≦ 5% pattern 4 (artifactual upgrading common in this group)
- Low volume GG 2 with negative MRI and/or favorable genetic biomarker score
- Caveat: We have no data on the long term outcome of favorable Gleason 3+4 managed with AS incorporating serial MRI/biomarkers

AS current management protocol

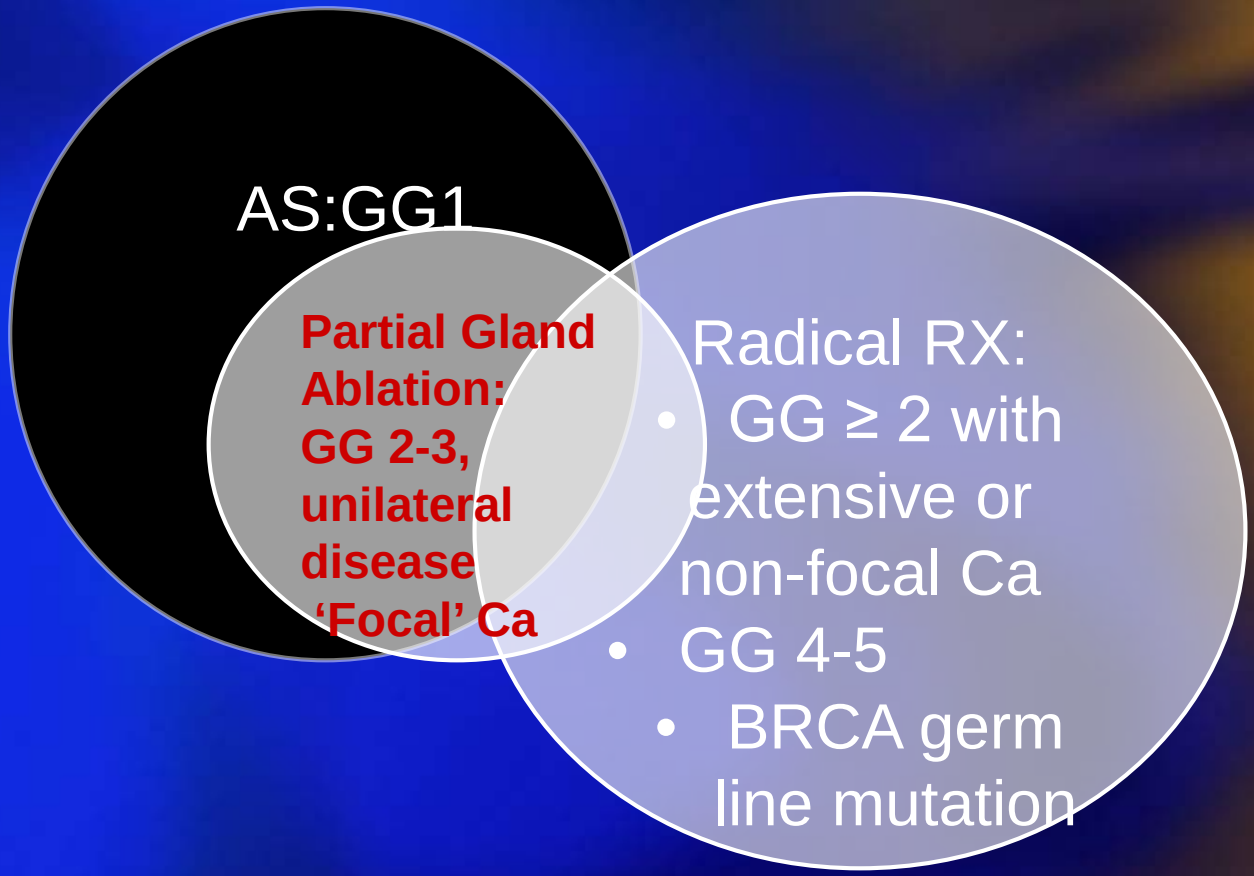
- Initial diagnosis based on 12 core biopsy +/- targeted
- MRI within first year (> 3 months after biopsy)
- PSA q 6 months
  - DRE: 1/yr but little value
- Confirmatory biopsy within 1 year
  - With microfocal disease, low PSA density and negative MRI, defer to year 3 (Etzioni R et al 2019)
- MRI q 2-3 years, targeted biopsy if any change/ROI
- Repeat systematic biopsy q 4-5 years if stable
- Intervention for grade progression (clinical judgment)

PCa: Traditional massive grey zone



Surveillance, focal, and radical therapy:

The new black, white, and grey zones



AS vs Rx: Grey zone 1

- Extensive GG1 in young men
- High PSAD
- PiRads 5 lesion with GG1
- Adverse genetic biomarker score GG1
- GG2 with < 10% Gleason 4
- Favorable genetic score with GG2

PGA vs radical Rx--Grey zone 2

- Small solitary focus of GG 4
- Limited non-focal (ie, 2 small lesions)

Conclusions: Active surveillance

- Active surveillance a robust strategy for many cancers with an indolent phenotype
- Opportunity to reduce morbidity, cost, and enhance appeal of early detection
- Requires patient and physician (and payer) buy-in
- Surveillance must be ACTIVE
- Congruent with emerging era of molecular medicine
- Opportunity for concurrent health maintenance interventions