Active surveillance: From Biology to Bedside

Who is Going to Fail?

What is the main reason low risk patients fail?

1. GG1/Gleason 3+3 metastasizes (uncommon but may occur)
2. Misattribution of concurrent higher grade cancer (present, but missed on biopsy)
3. Gleason 3+3 dedifferentiates over time to higher grade cancer which metastasizes
4. All of the above

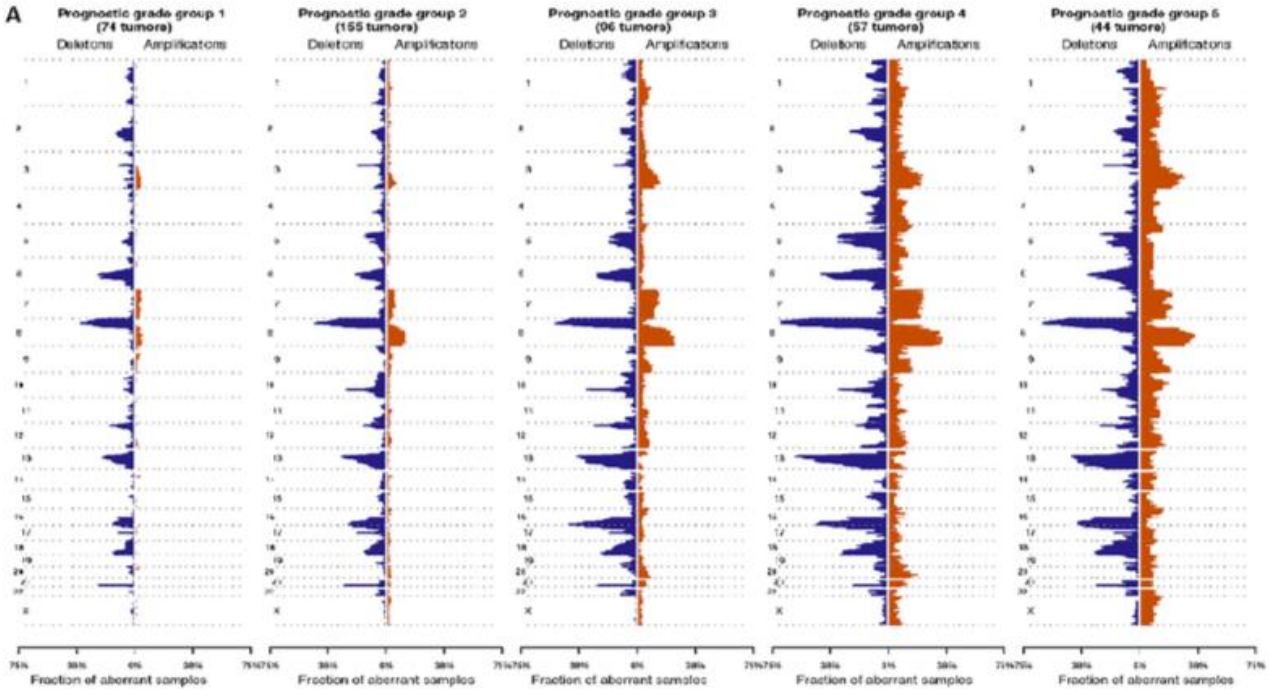
2018: What we know

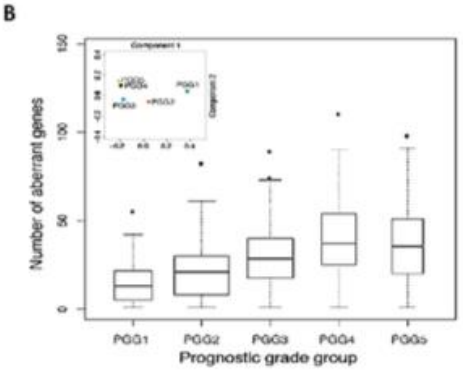
- Gleason 3:
  - Molecular genetics resembles normal cells in most cases
  - Metastatic potential ~ zero.
- Vs Gleason 4: molecular hallmarks of cancer
- ‘Achilles Heel’ of active surveillance strategies relates to pathologic miss of co-existent higher grade cancer
- True biological grade progression is uncommon
- Pre-histologic adverse genetic alterations exist
- MRI and molecular biomarkers enhance diagnostic accuracy and are complementary

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

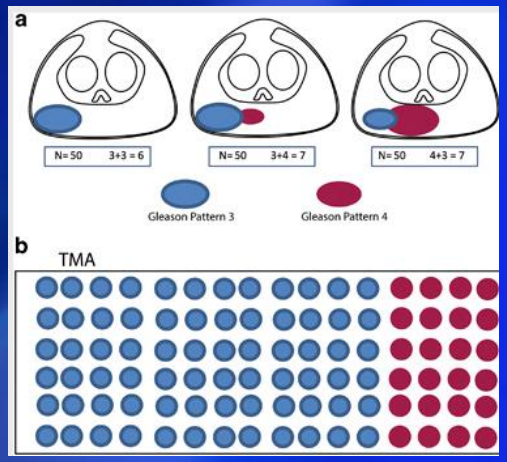
- Misclassification of occult higher grade cancer (25-30%)
- Biological grade progression over time (1-2% per year) Inoue LY, Etzioni R. Stat Med. 2014;33(6):930-9.

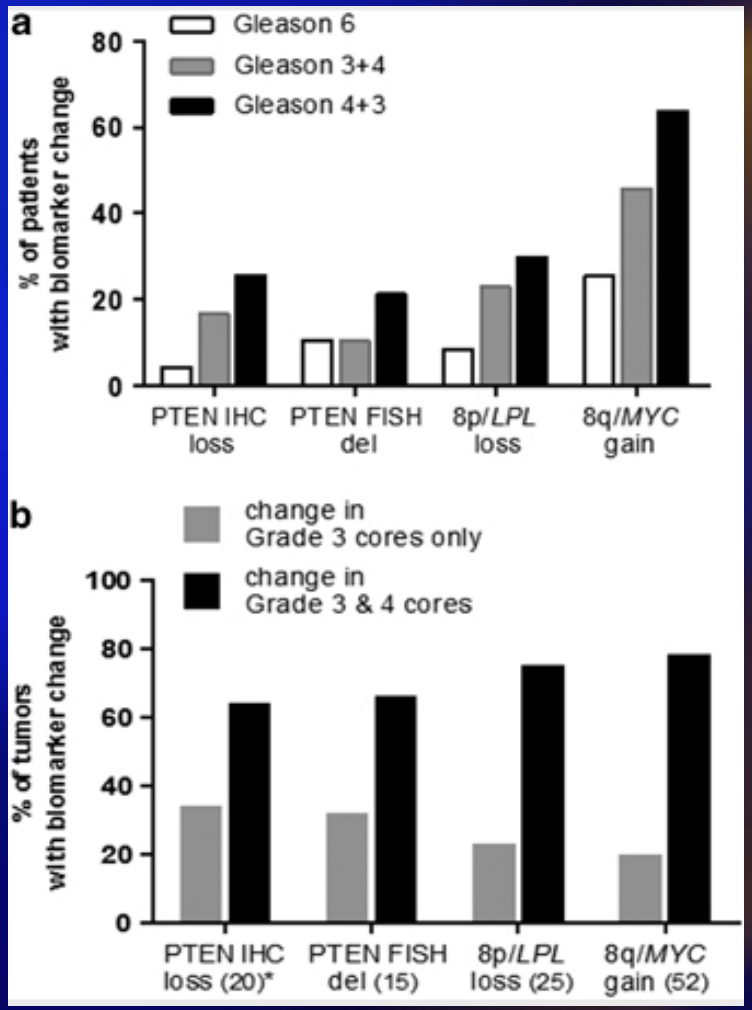
Genomic alterations quantitatively, not qualitatively different between grades. Rubin M et al, Eur Urol 2016; 69(4):557-60





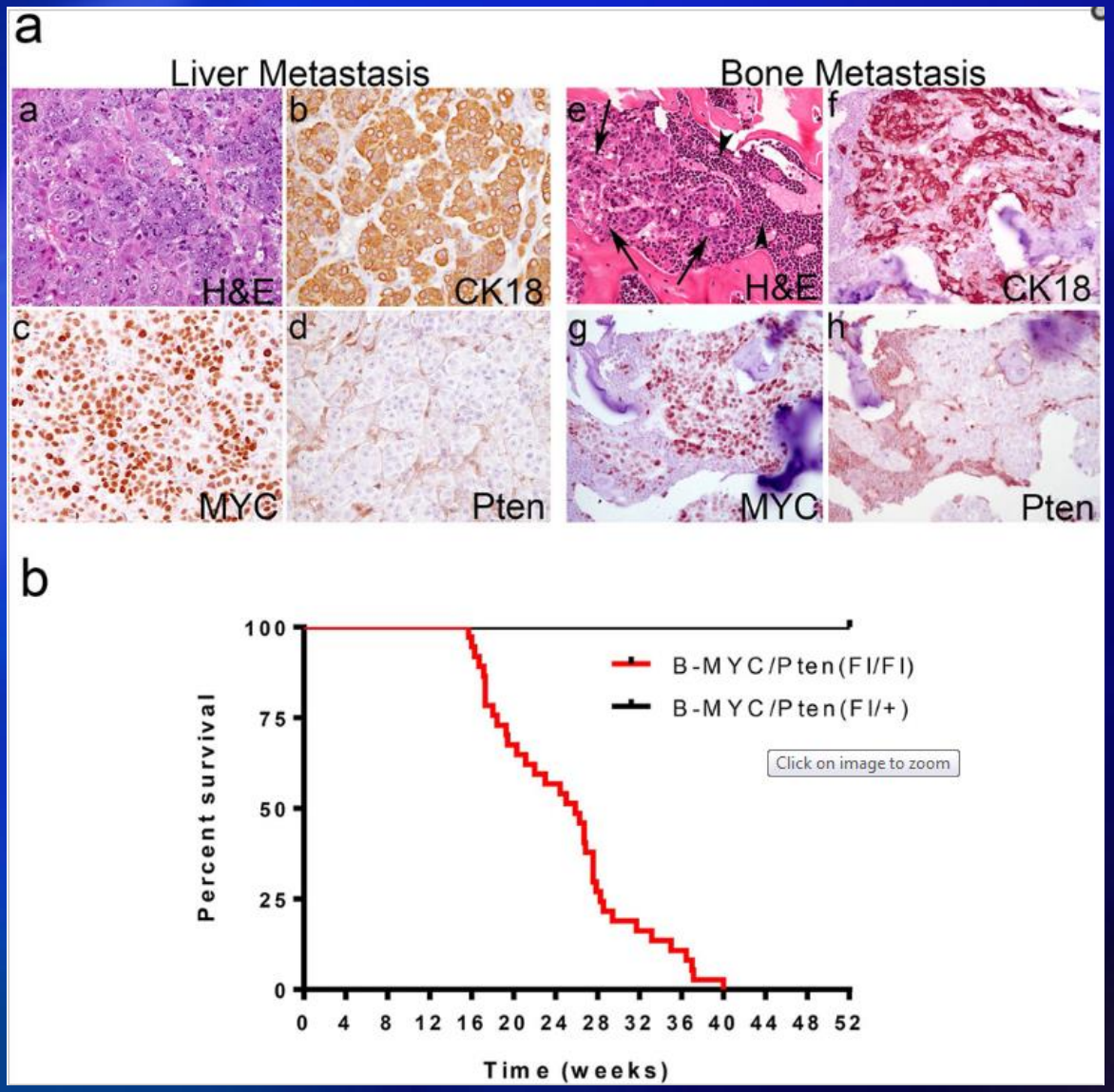
PTEN loss and chromosome 8 alterations in Gleason grade 3 cores predicts the presence of un-sampled grade 4 tumor: implications for AS. Trock B et al, Modern Path April 15 2016





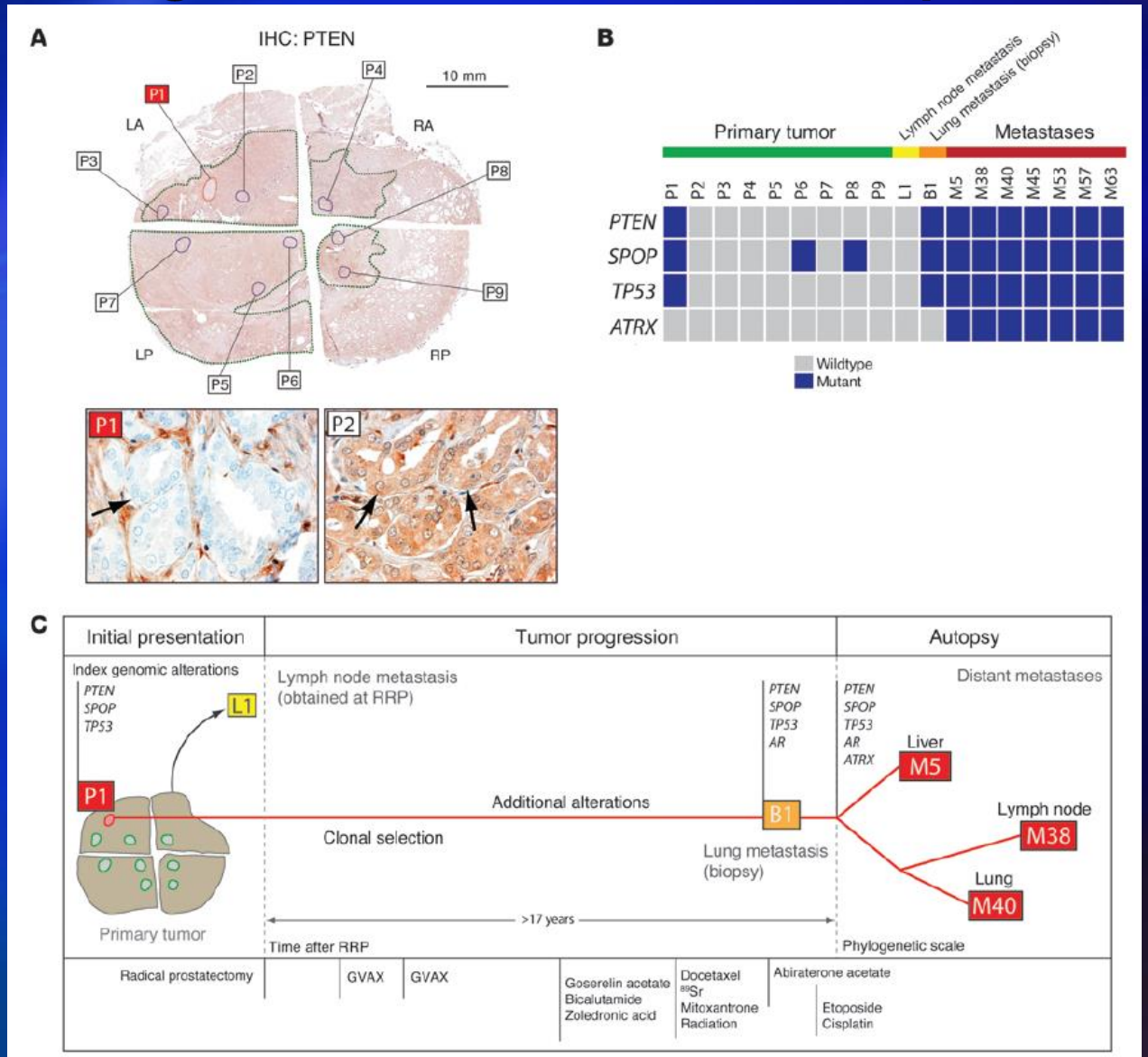
- PTEN loss, *MYC*/8q gain or *LPL*/8p loss in a Gl 3 core is a strong indicator of co-existent Gl 4. More common in Gl3 cores from Gl 4+3 than 3+4.
- Gl 3 sampled from a Gl.7 cancer is often biologically distinct from Gl 3 from a Gl 6 tumor

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



The clonal origin of lethal prostate cancer

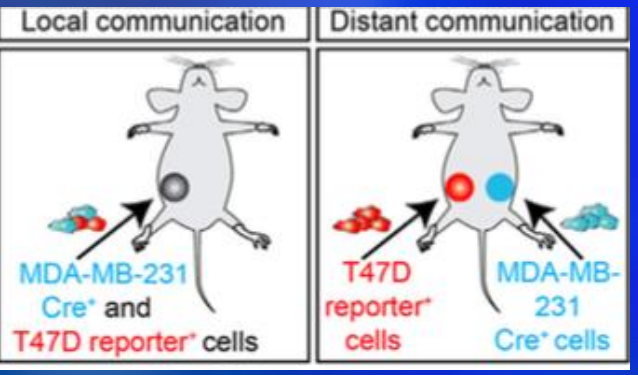
Haffner M, Yegasubramanian et al, JCI, epub Oct 29 2913

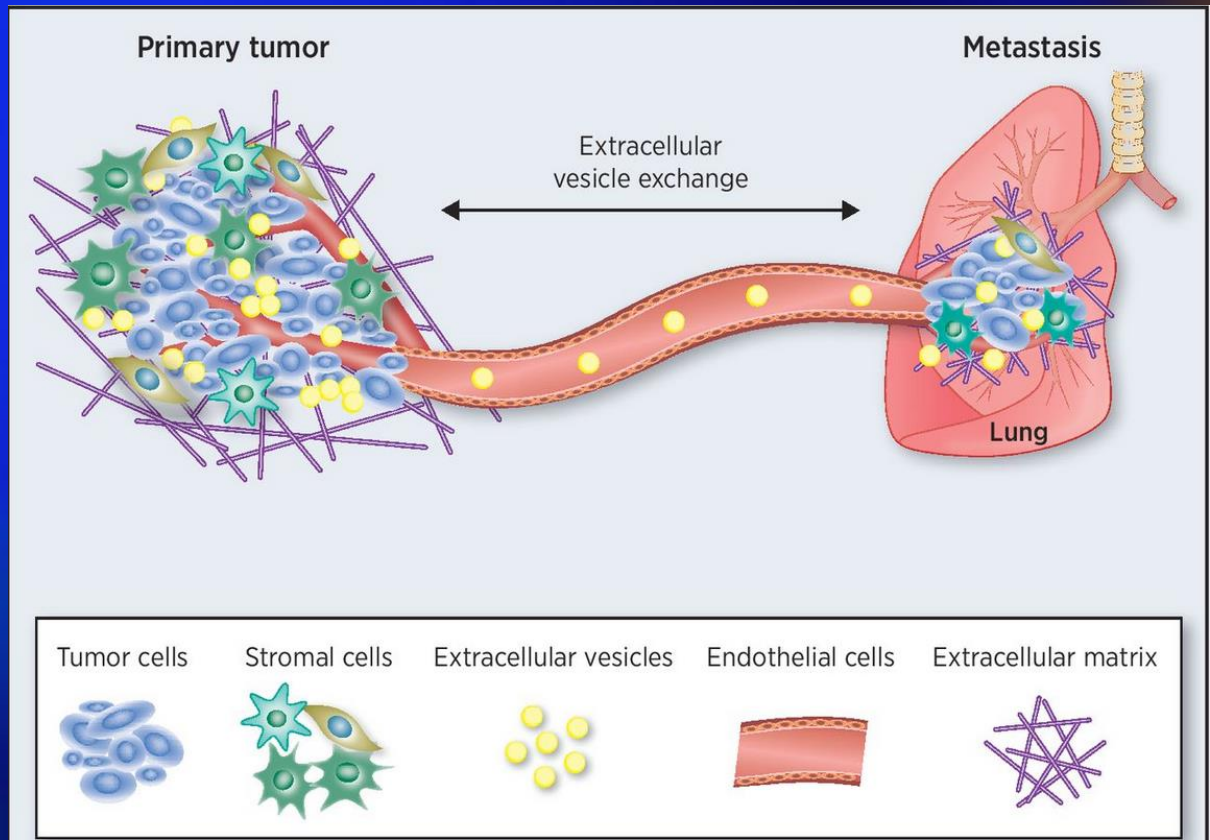


Implications of Extracellular Vesicle (EV) Transfer on Cellular Heterogeneity in Cancer:

Zomer A, Cancer Res. 2016 Apr 15;76(8):2071-5.

- **EVs released by highly malignant cells are taken up by less malignant cells within the same and distant tumors**
  - These carry mRNA involved in migration and metastasis.
  - RNA from more aggressive cells is incorporated and induces aggressive behavior in the indolent cells





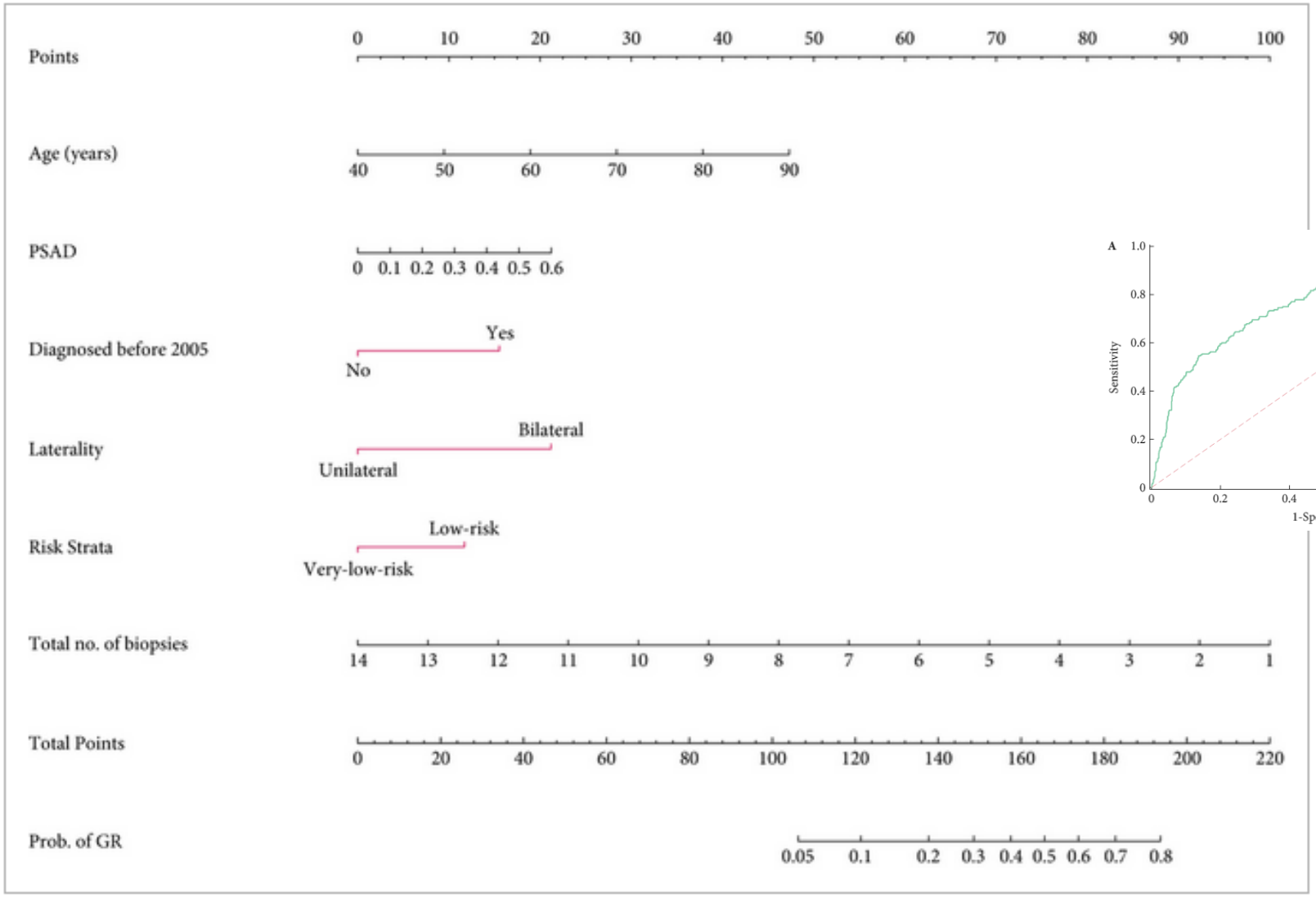
Most guidelines differentiate between very low risk and low risk based on cancer volume

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

Risk prediction tool for grade re-classification in men with favourable-risk prostate cancer on active surveillance.

Mamawala MM, Carter HB **BJU Int.** 2017 Jul;120(1):25-31



Selection Criteria for AS

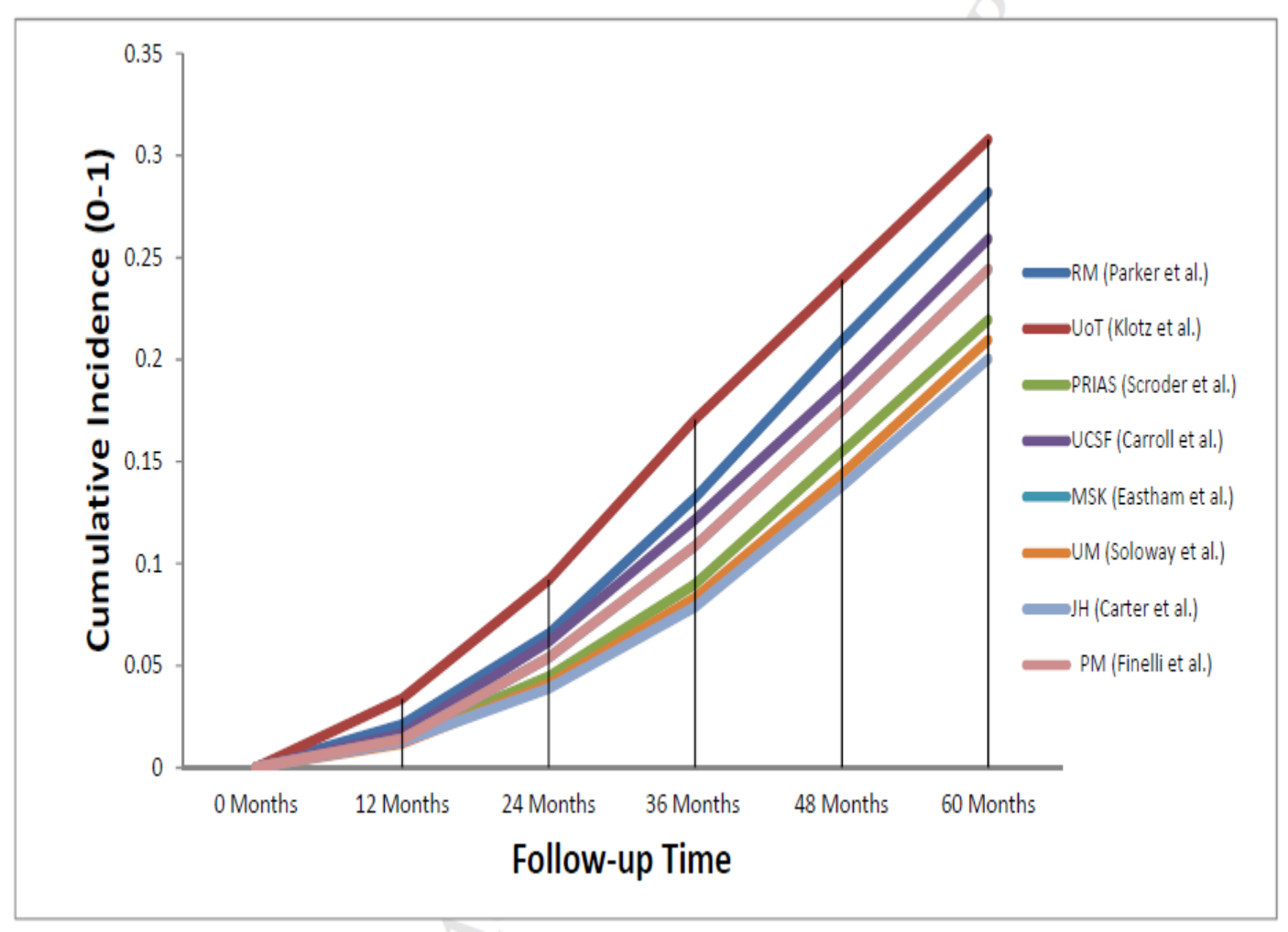
Programme	T stage	Glea-son	Pos Cores	Max % Ca	PSA	PSAD	Other
Sunnybrook Klotz		≤ 6 ≤ 3+4 (selected)			≤ 10 10-20 (selected)		
Hopkins Tosoian	T1c, T2a	≤ 6	≤ 2	≤50		< 0.15	
Goteborg Godtman	≤ T2a	≤ 6			≤ 10		
UCSF Welty	≤ T2a	≤ 6	≤33%		≤ 10		
Marsden Selvadurai	≤ T2	≤ 6 3+4	≤50%		≤ 15		Age 50-80 Age > 65
Australia Thompson	≤ T2a	≤ 6	≤30%	< 30	≤ 10		
Copenhagen Thomsen	≤ T2a	≤ 6	≤3	< 50	≤ 10		
Miami Soloway	≤ T2	≤ 6	≤2	< 20	≤ 10		Age < 80
PRIAS Bul	≤ T2	≤ 6	≤2		≤ 10	< 0.2	

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

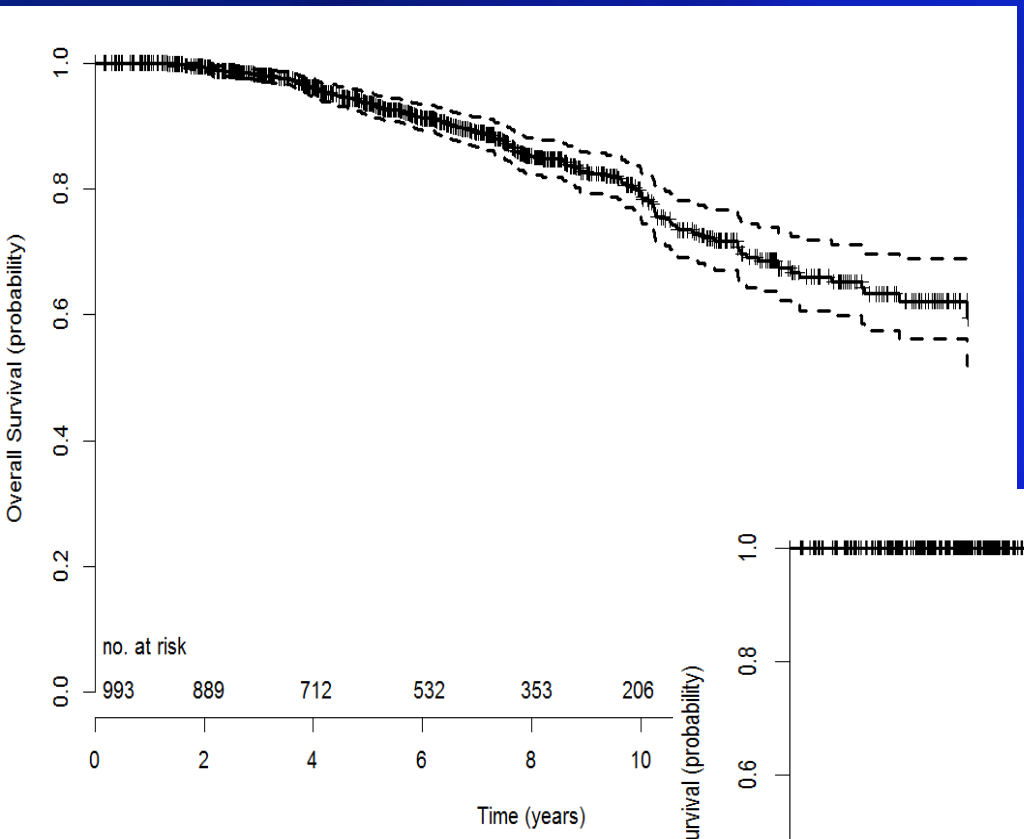
Stricter AS criteria for PCa do not result in significantly better outcomes: A comparison of protocols. Komisarenko M, Klotz L. Finelli A. J Urol. 196(6):1645,-50 Dec 2016

Intervention rates between groups

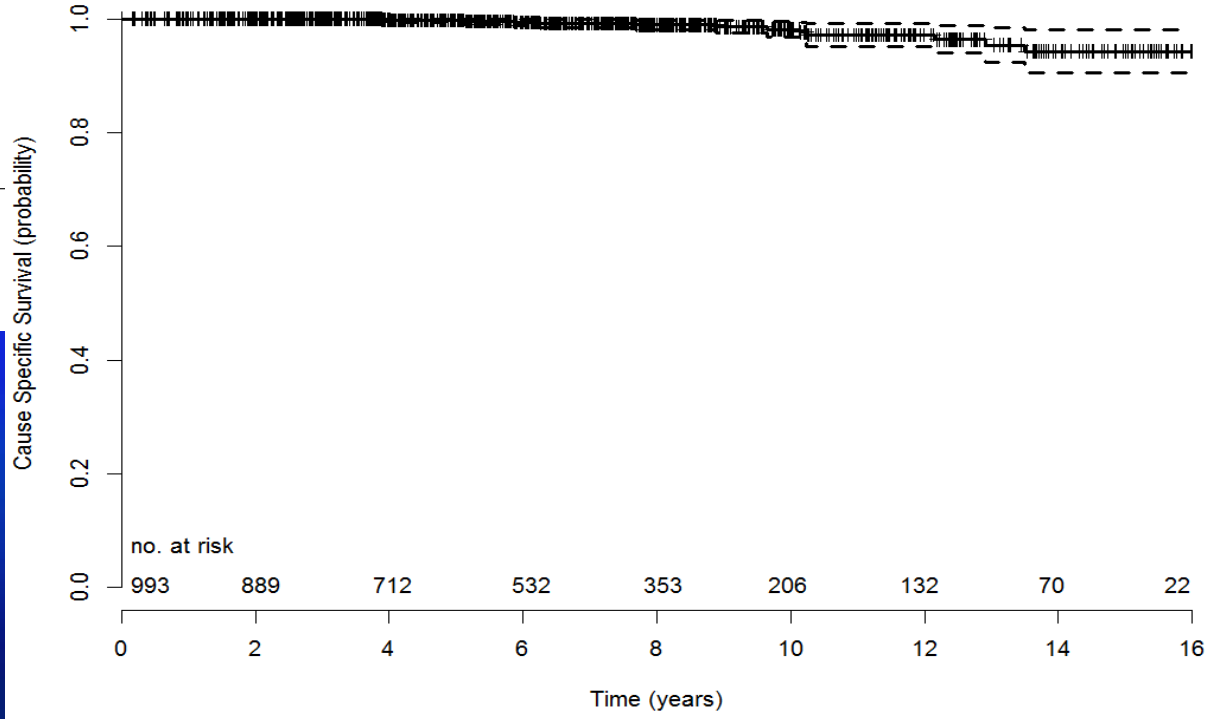


Survival with AS Klotz et al JCO 33(3):272-7 2015

OS

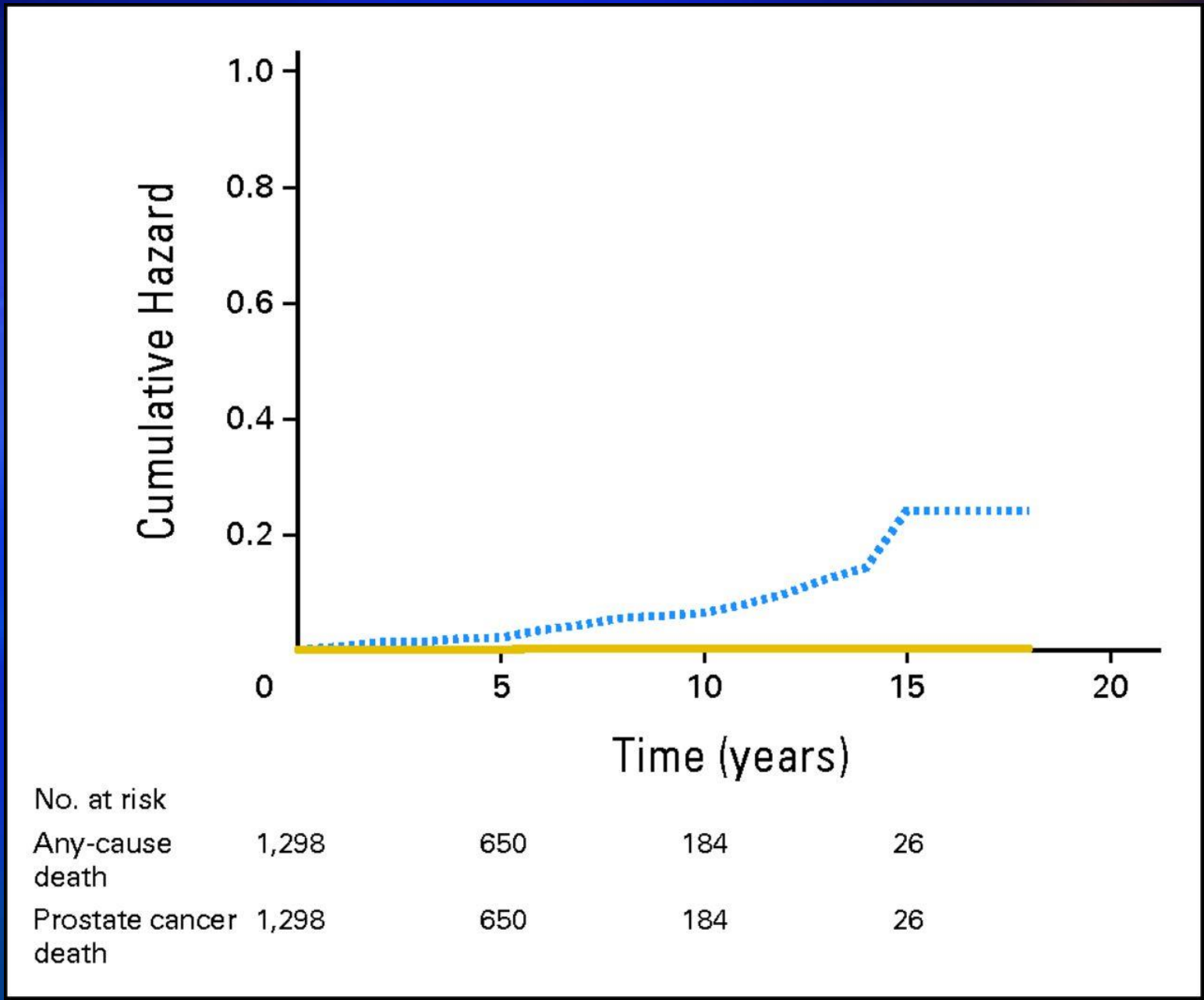


CSS



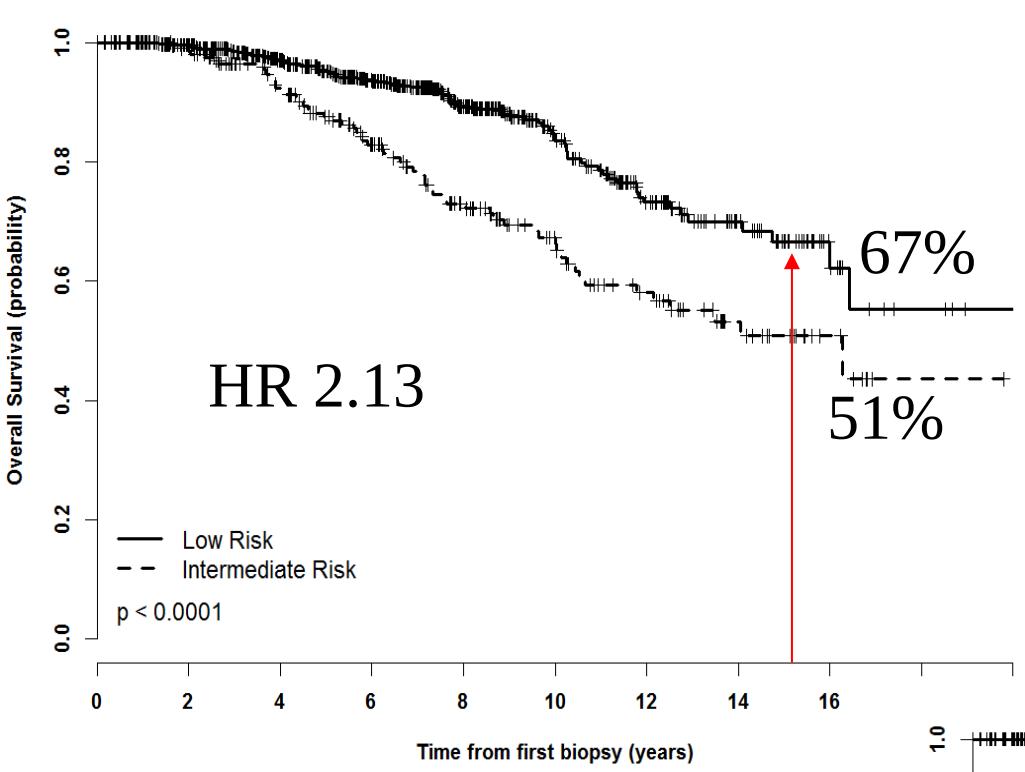
Hopkins AS long term outcome: Overall mortality and Pca mortality Tosoian J, Carter B et al. JCO.2015

Pca mortality 0.5% at 15 years

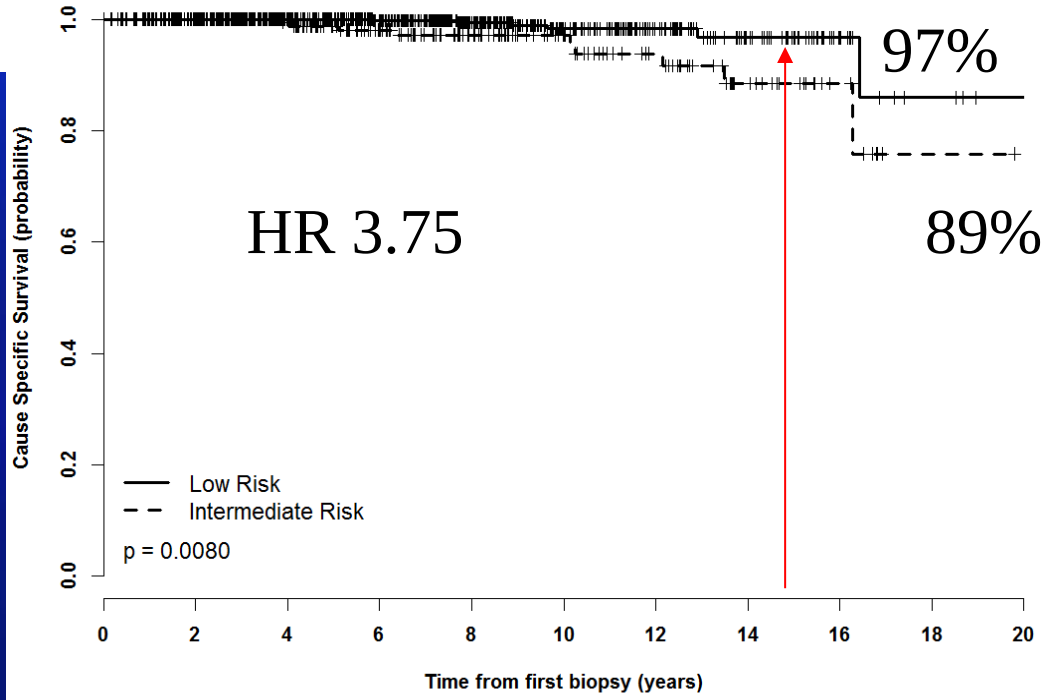


OS and CSS:
Low vs Intermediate risk (Gleason 3+4, PSA >10)

Overall Survival

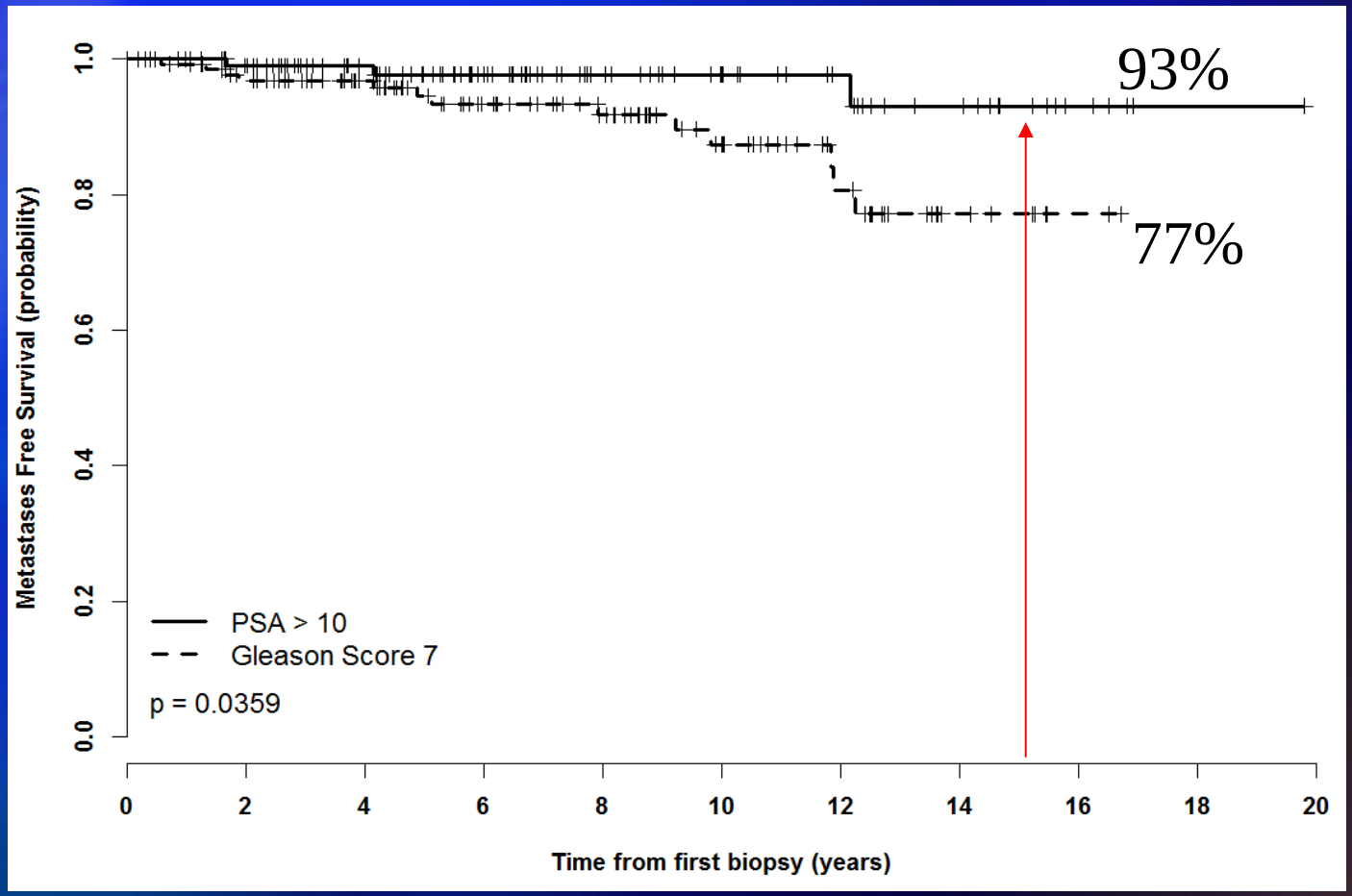


Cause Specific Survival

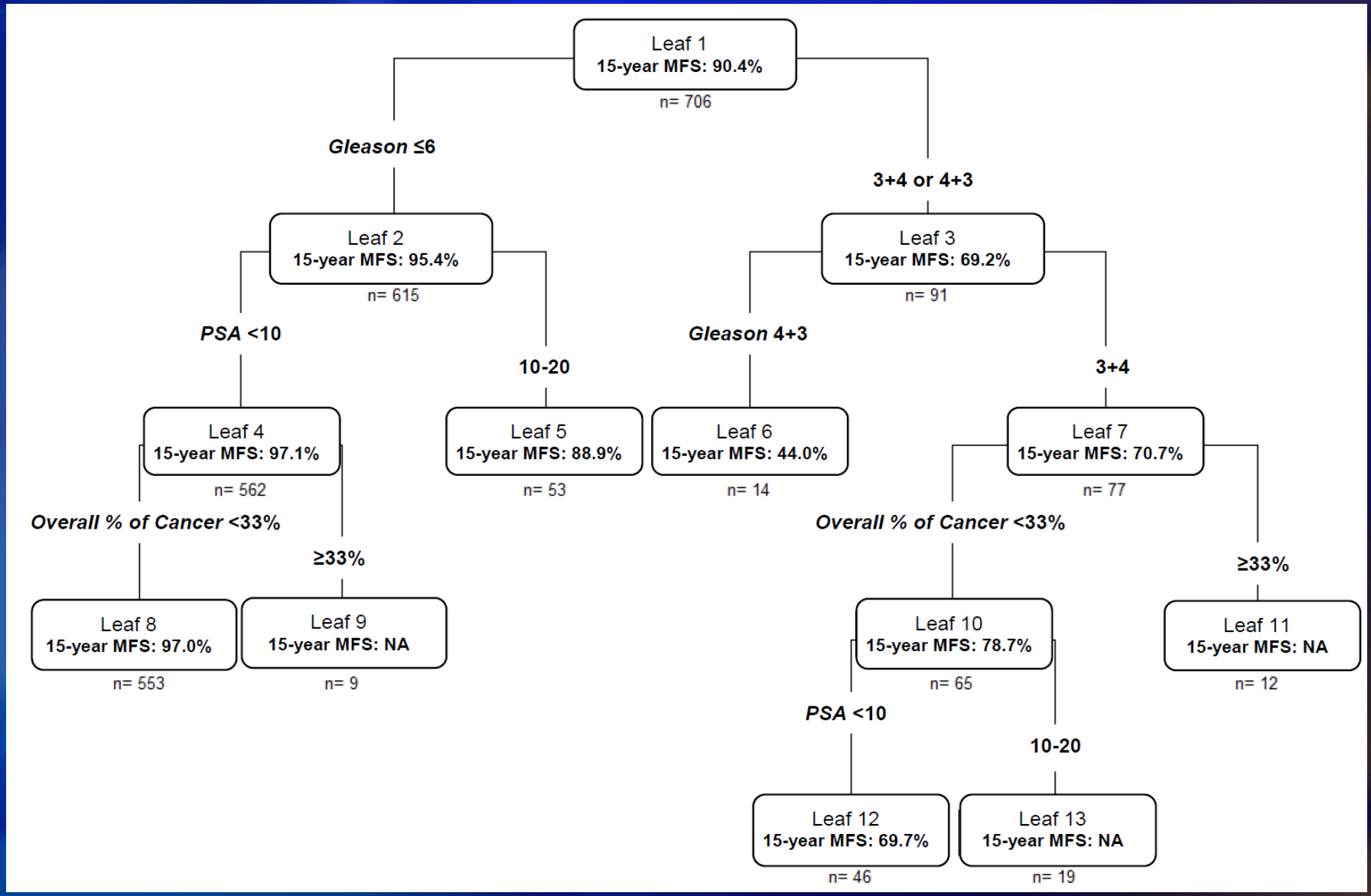


Intermediate risk group: Baseline Gleason score, not PSA, predicted for mets

Baseline PSA >10 vs GS 7, Met free survival

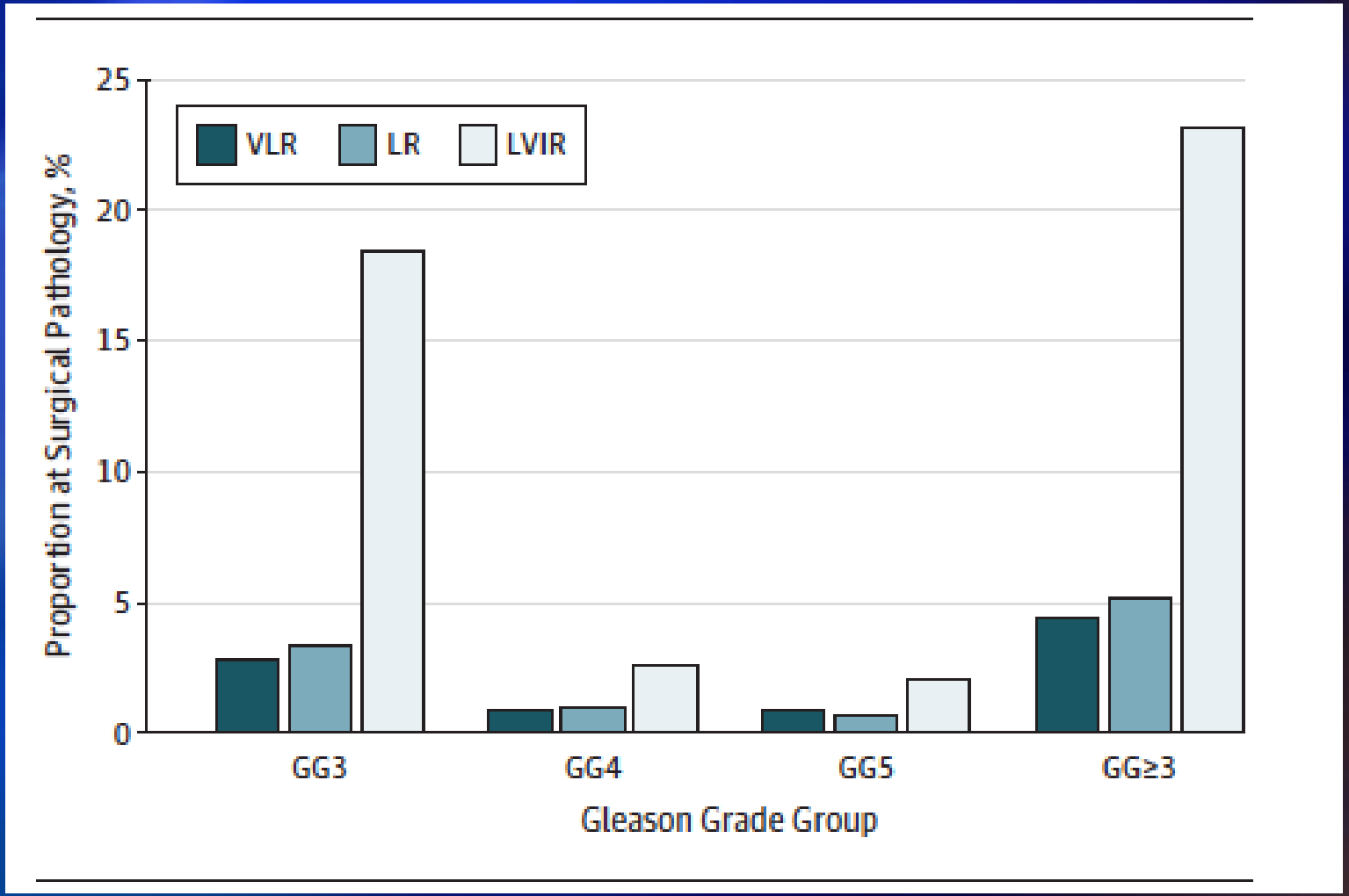


Recursive partitioning analysis: Metastasis free survival by risk group



Pathologic findings at immediate RP: Patel HD, JAMA Oncol. 2018 Jan 1;4(1):89-92.

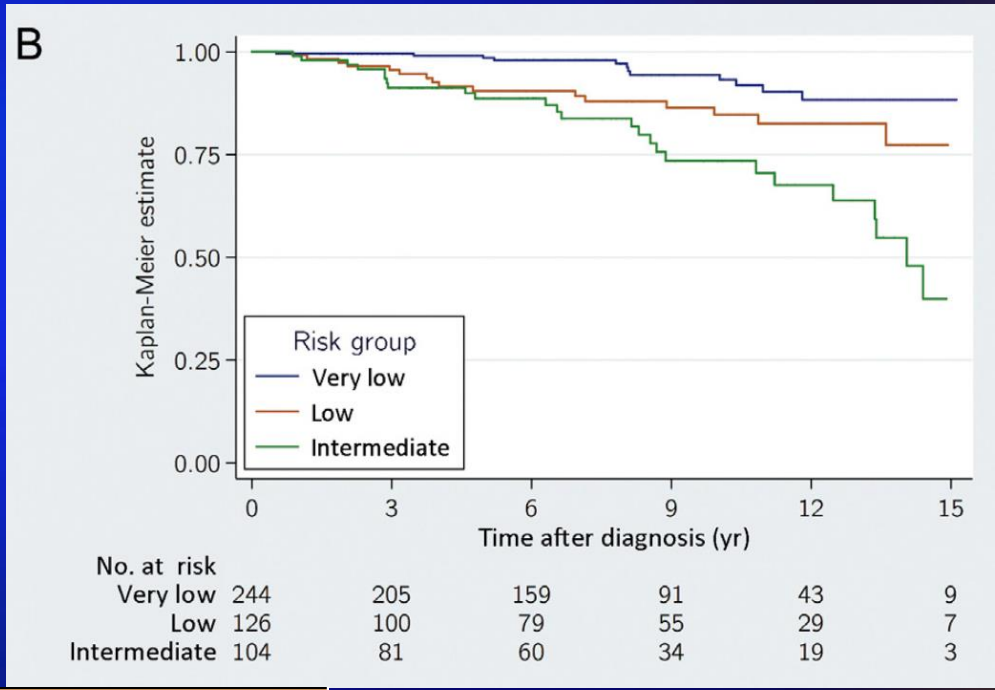
- Hopkins RP 2005-2016: VLR (1264), LR (4849), LVIR (608 patients)
- ~25% of low volume GG 2 were GG ≥ 3 at RP
- No favorable predictive criteria to identify true low risk in the LVIR



Active Surveillance in the Göteborg Prostate Cancer Screening Trial. Godtman RA, Eur Urol. 2016 Nov;70(5):760-766.

- N=474, 104 Int. Risk
- 5/6 Pca deaths in Int Risk group (4 GG2, 1 GG1 PSA 12
- HR for 'failure' for IR vs VLR: 4.8

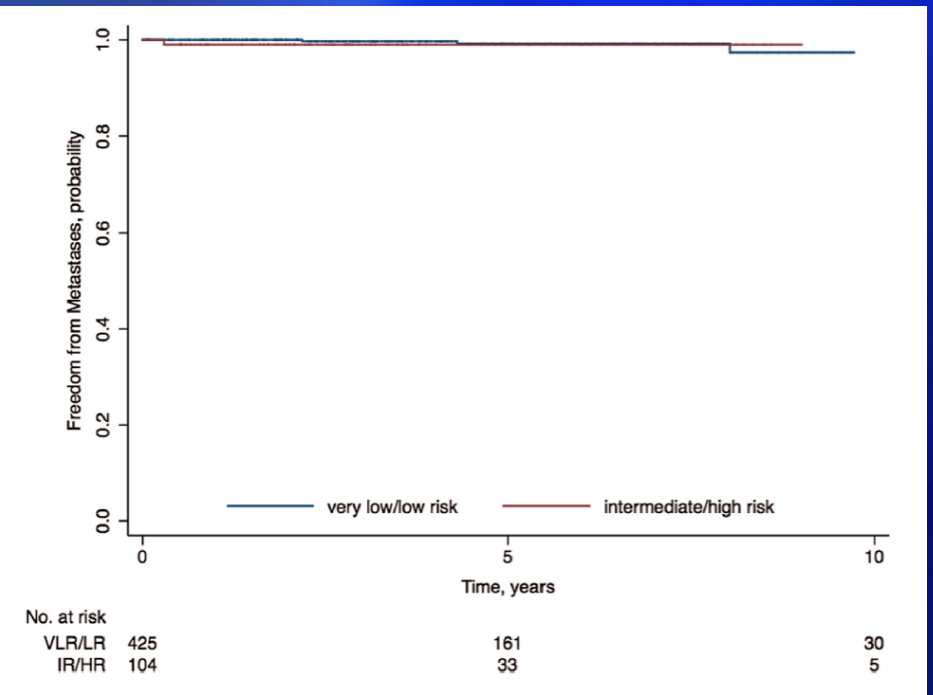
Failure free survival

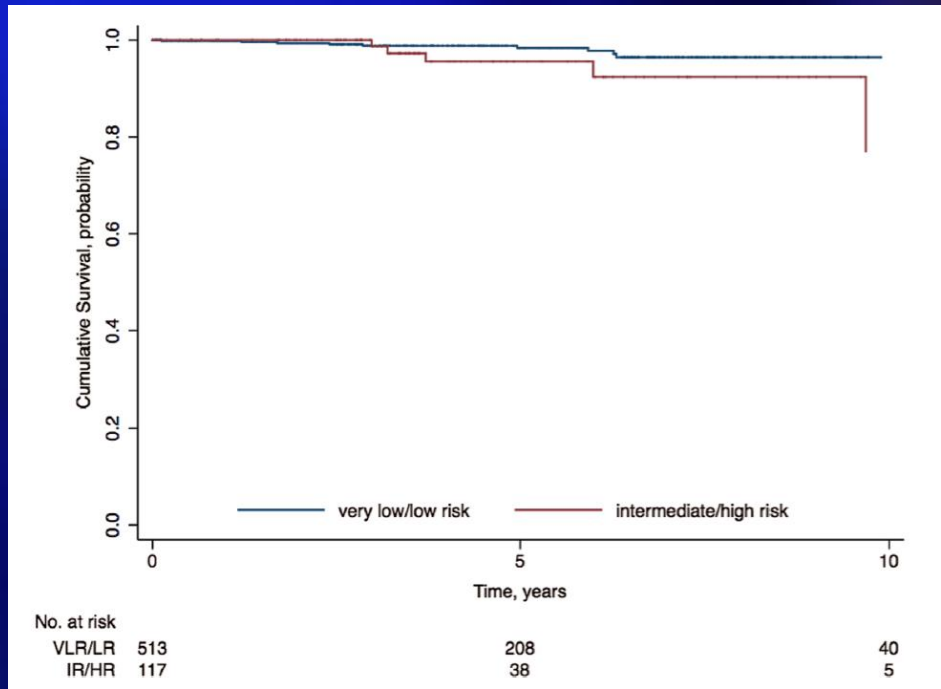


Age at diagnosis	Risk group and clinical characteristics at diagnosis	Last registered PSA before death	Time on active surveillance (yr)	Secondary treatment	Time from prostate cancer diagnosis to death (yr)	Gleason score according to the updated 2005 ISUP Gleason grading system
55	Intermediate: PSA 5.4, 19.7 mm Gleason 3+3, 4 of 6 cores, T2c	260	1.2	Combined radiation therapy	16.3	Gleason score 3+4 = 7, 4 <5%
59	Intermediate: PSA 15.6, 18.6 mm Gleason 3+3, 4 of 6 cores, T1c	1756	6.8	External radiation therapy	10.7	Gleason score 3+4 = 7, 4 <5%
61	Intermediate: PSA 3.9, 1.7 mm Gleason 3+3, 1 of 2[a] cores, T2a	470	8.6	Hormonal treatment	12.7	Gleason score 3+4 = 7, 4 5–20%
66	Intermediate: PSA 12, 0.7mm Gleason 3+3, 1 of 2 cores[b], T1c	13	1.1	Hormonal treatment	8.9	Gleason score 3+3 = 6
66[c]	Low: PSA 3.5, 3.3 mm Gleason 3+3, 2 of 6 cores, T1c	180	1.2	Permanent seeds brachytherapy	12.9	Gleason score 3+4 = 7, 4 20–50%
70	Low: PSA 4.4, 7 mm Gleason 3+3, 1 of 6 cores, T1c	810	9.9	Hormonal treatment	12.2	Gleason score 3+3 = 6

Intermediate-Term Outcomes for Men with Very Low/Low and Intermediate/High Risk Prostate Cancer Managed by Active Surveillance. Nyame Y, Stephenson A, J Urol 198: 591-599, Sept. 2017

- 117/635 men on AS were intermediate/high risk (92% int. risk)
- Median f/u 50.5 mo
- 5 and 10 yr MFS 99 and 98%
- No difference in metastases, surveillance failure or curative intervention compared to low risk.





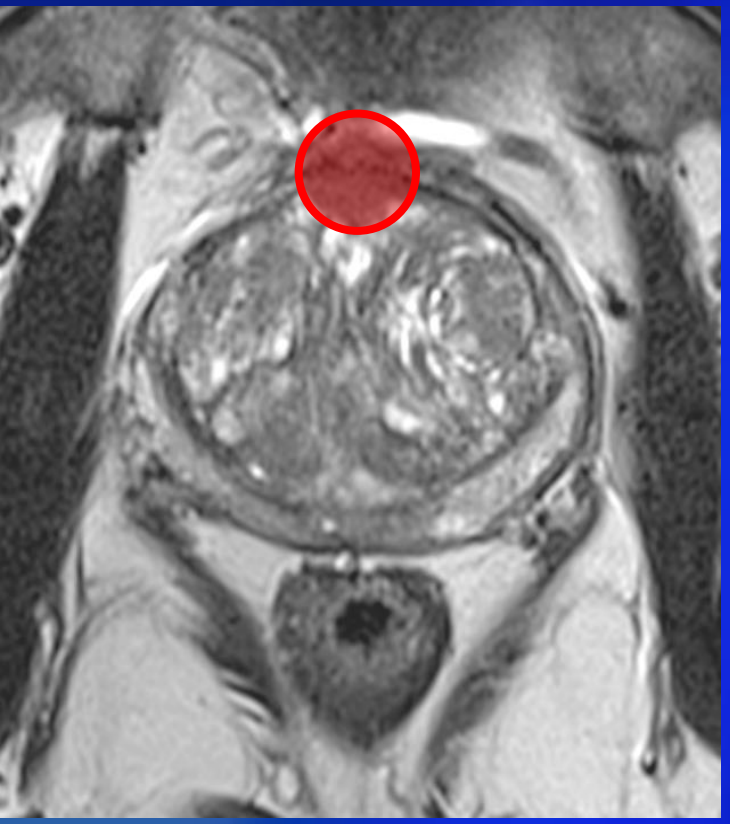
Long term outcome of surveillance reflects inclusion criteria and intervention strategy

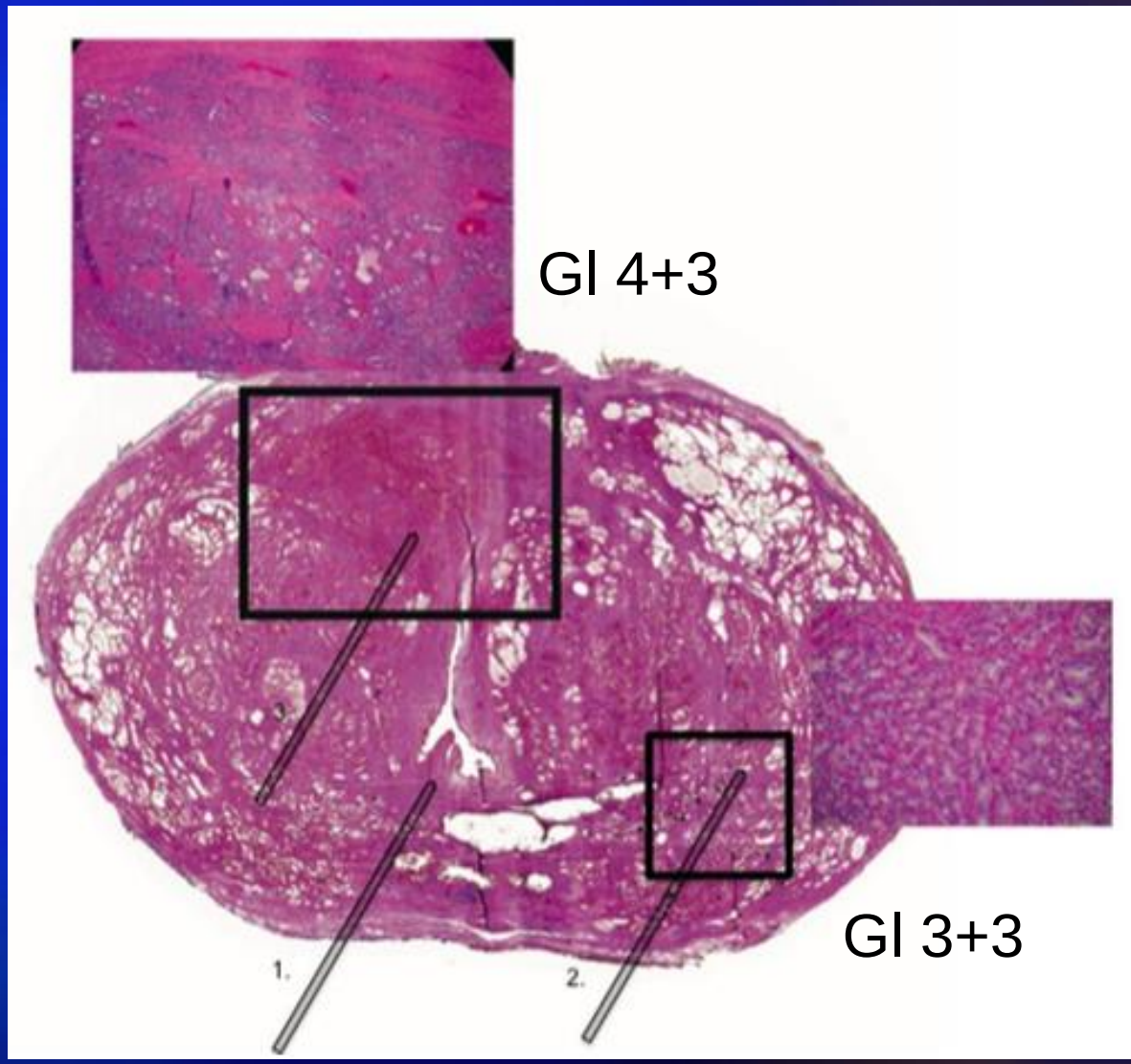
	Sunnybrook	Johns Hopkins
Eligibility	All Gleason 6, PSA <=15, and selected Gleason 3+4	NCCN low risk (<= 2 pos cores, <50% core involvement, PSAD < 0.15
Intervention	Gleason 4+3	≥ NCCN low risk (volume progression or any Gleason 4)
Proportion of Pca patients eligible	50%	20%
15 year Pca mortality	5%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

5 AS programs with > 5 yr f/u N~4000

Cohort	% GS ≥ 7	Median F/U Yrs	5 yr Treatment %	Mets %	Pca deaths %	Overall mortality %
Sunny-brook	13	6	24	2.8	1.5	15
Hopkins	0	5	37	0.4	0.15	4
Goteborg	NR	8	39	0.02	1.2	22.7
Marsden	7	6	30	NR	0.4	6
UCSF	8	5	40	0.1	0	NR

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





Can Clinically Significant Prostate Cancer Be Detected with MRI?

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
Wysock	2014	125	36	75	NR	NR	NR	NR
Salami	2014	140	65	48	NR	NR	NR	NR
Pannebianco	2015	1140	80	97	86	94	99	100

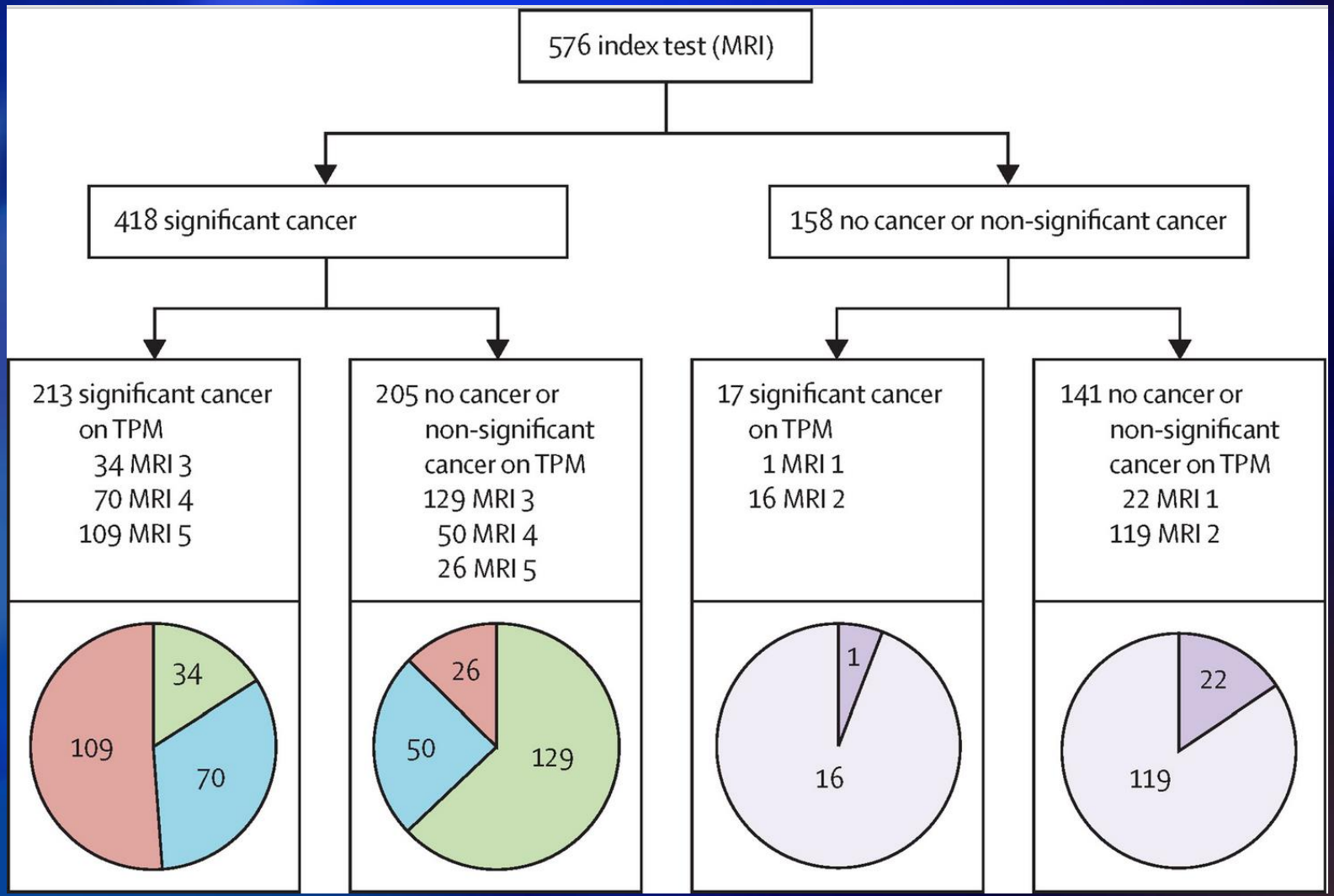
MRI and TRUS biopsy (**PROMIS**) in Pca: A Paired validation study. Ahmed HU, **Emberton** M; Lancet. 2017 Feb 25;389(10071):815-822

- 576 men with PSA < 15: MRI + TRUS Bx + Template Bx

Any Gleason score 7 (≥3+4)				
	MP-MRI, % (95% CI)	**TRUS-biopsy, % [95% CI]**	**Test ratio*[95% CI]**	**p value**
Sensitivity test	88 (84–91)	48 (43–54)	0·55 (0·49–0·62)	p<0·0001
Specificity test	45 (39–51)	99 (97–100)	2·22 (1·94–2·53)	p<0·0001
PPV	65 (60–69)	99 (95–100)	40·8 (10·2–162·8)	p<0·0001
NPV	76 (69–82)	63 (58–67)	0·53 (0·38–0·73)	p<0·0001

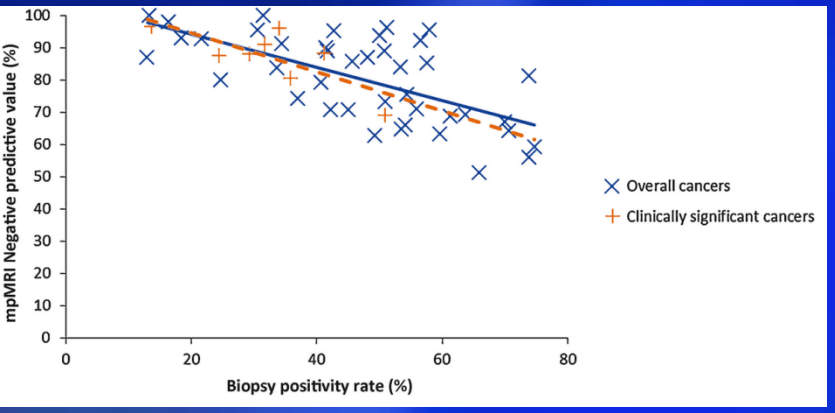
MRI and TRUS biopsy (**PROMIS**) in Pca: A Paired validation study. Ahmed HU, **Emberton** M; Lancet. 2017 Feb 25;389(10071):815-822

- MRI & Targ Bx, TRUS Bx, and Template Bx (TPM)
- MRI Sensitivity 93%, PPV 51%, Spec. 41% NPV 89%

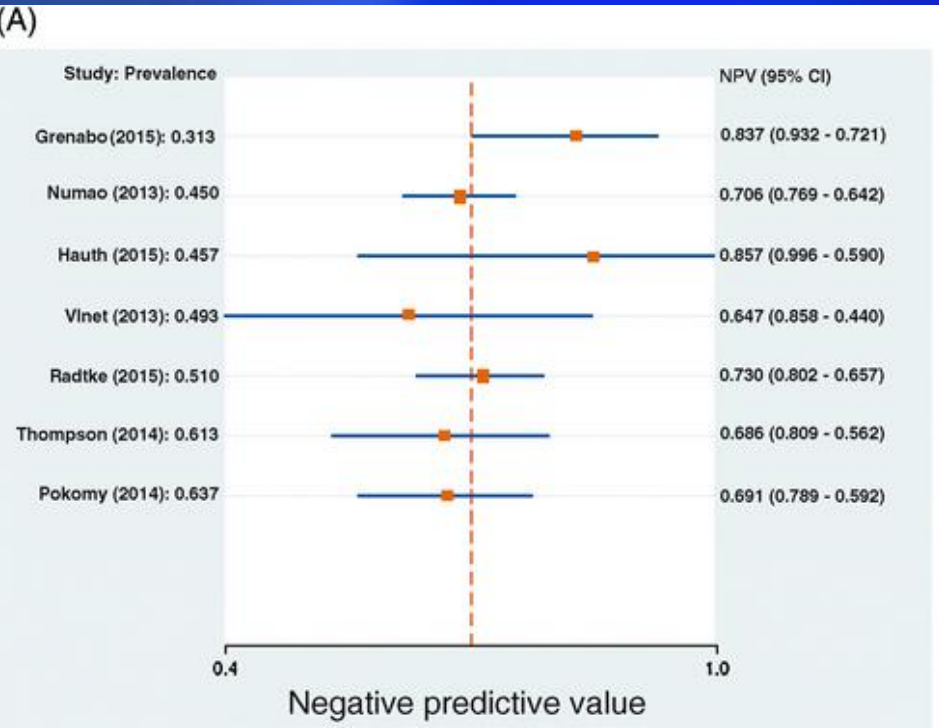


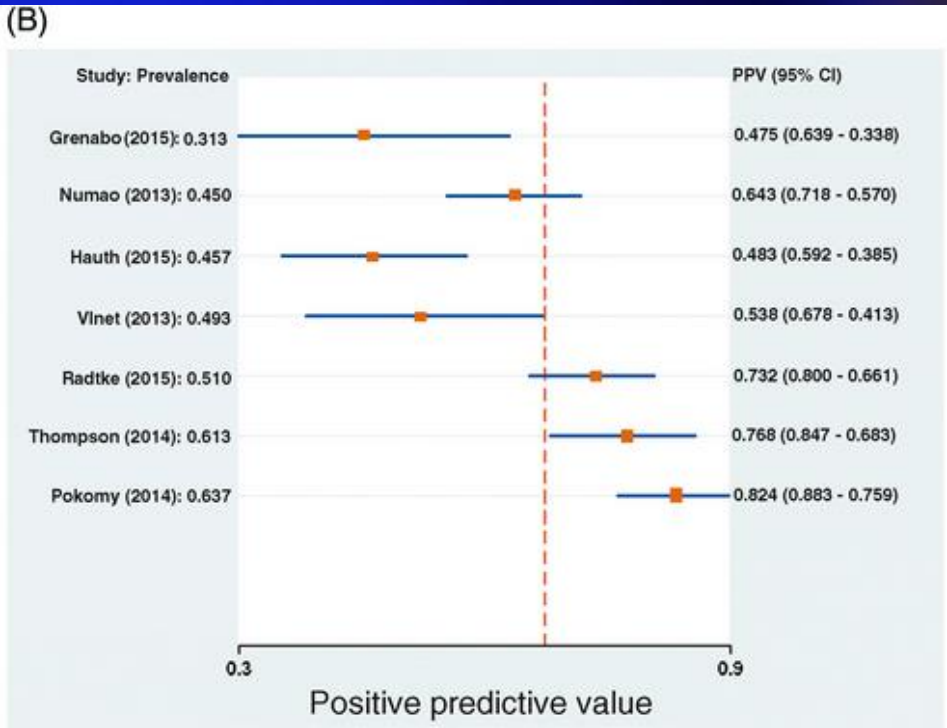
NPV of MRI: Meta-analysis from EAU Guidelines Panel. Moldovan PC Eur Urol. 2017 Aug;72(2):250-266.

Can biopsy be avoided if MRI negative?



- NPV 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%)

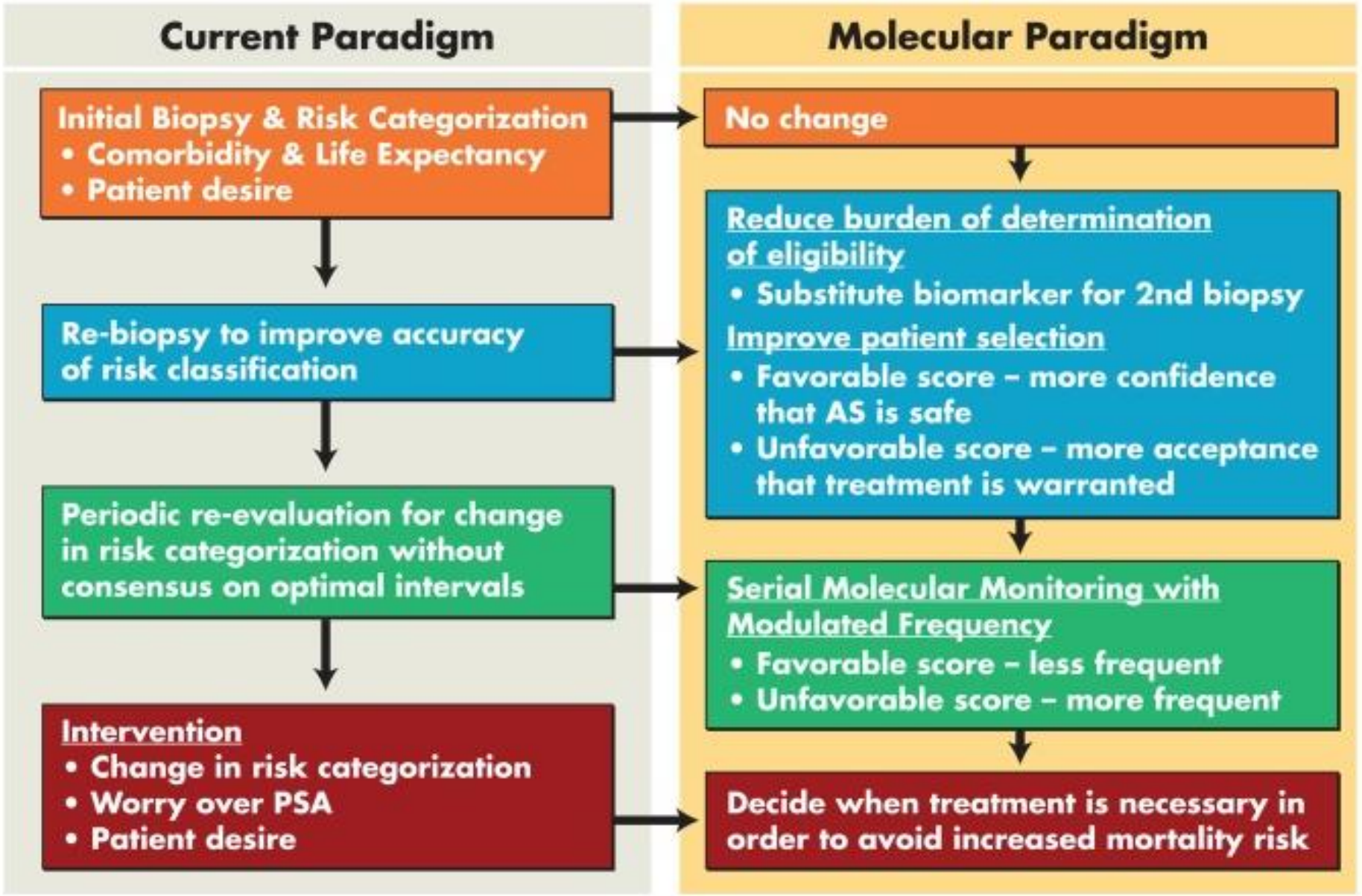




Currently available tissue-based tests for Pca

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

ACTIVE SURVEILLANCE



Comparison of guidelines: US, Canada, UK

	Low risk Pca	Intermediate risk	Tests	Other tests	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[1]	Same	Same	**Other tests remain investigational**	**No clear role**
NICE 2016	Same	Radical treatment for 'disease progression'[2]	PSA q 3-4 months, monitor kinetics, otherwise same	**MRI at enrollment**	

Active Holistic Surveillance: Berg CJ, Habibian DJ, Katz AE, Kosinski KE, Corcoran AT, Fontes AS. J Nutr Metab. 2016;2016:2917065

Advice to patients:

- **Dietary:**

- Eliminate red meats, dairy products, fried foods, refined carbohydrates

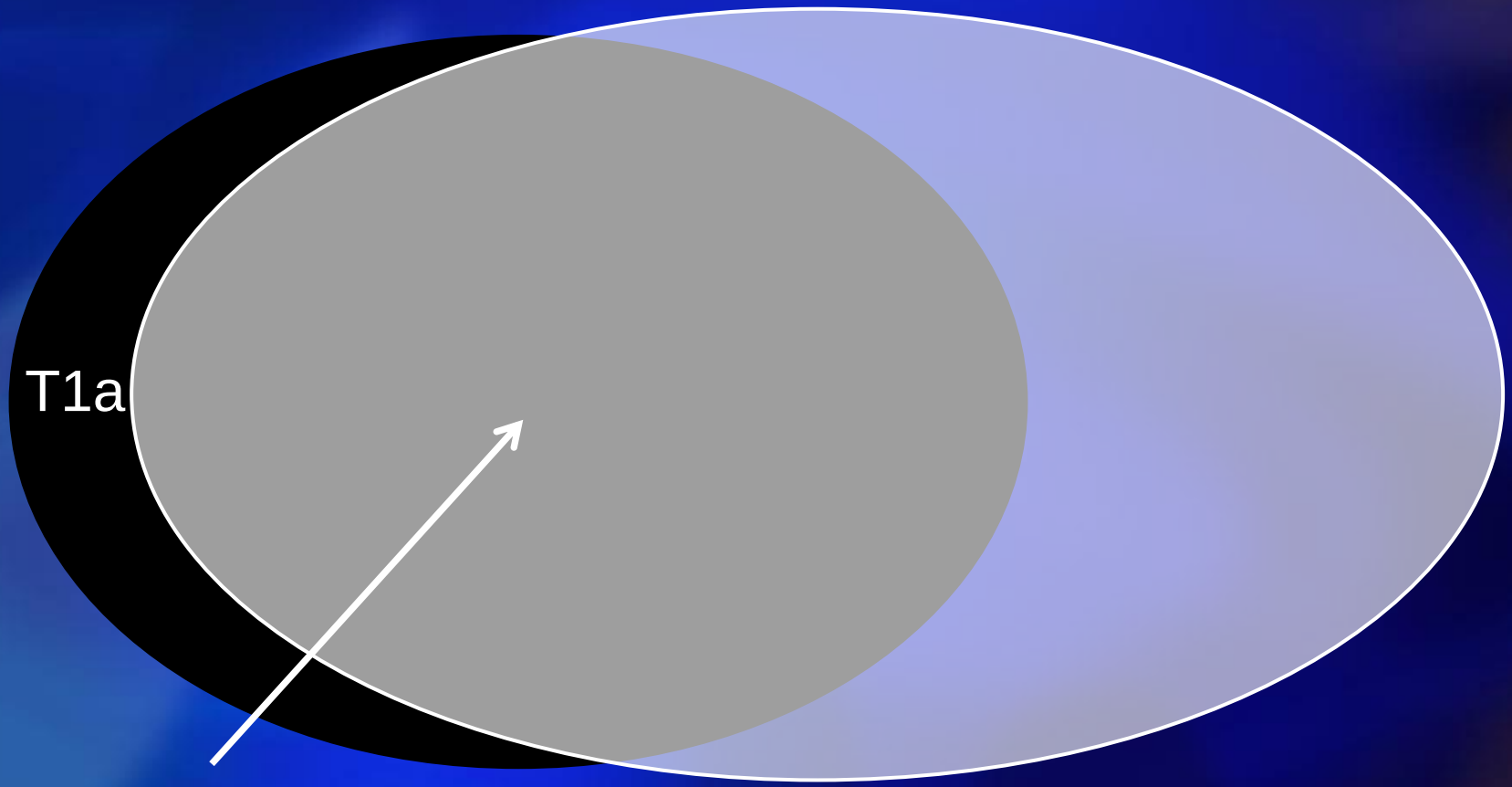
- Increase poultry, fish, green tea, soy milk, red wine, flaxseed , cruciferous vegetables.

Supplement````	Rationale
BroccoProtect	Antioxidants
Omega 3 2000 mg/day	↓ Inflammation
Zyflamend	↓ Inflammation, prolif
Vit D3	Differentiation inducer
Genikinoko 1000 mg bid	Apoptosis, ↓ angiogen
Active Hexose Correlated Compound (AHCC	Boosts immunity
Lyocell	Antioxidants
Capsaicin	↓ proliferation

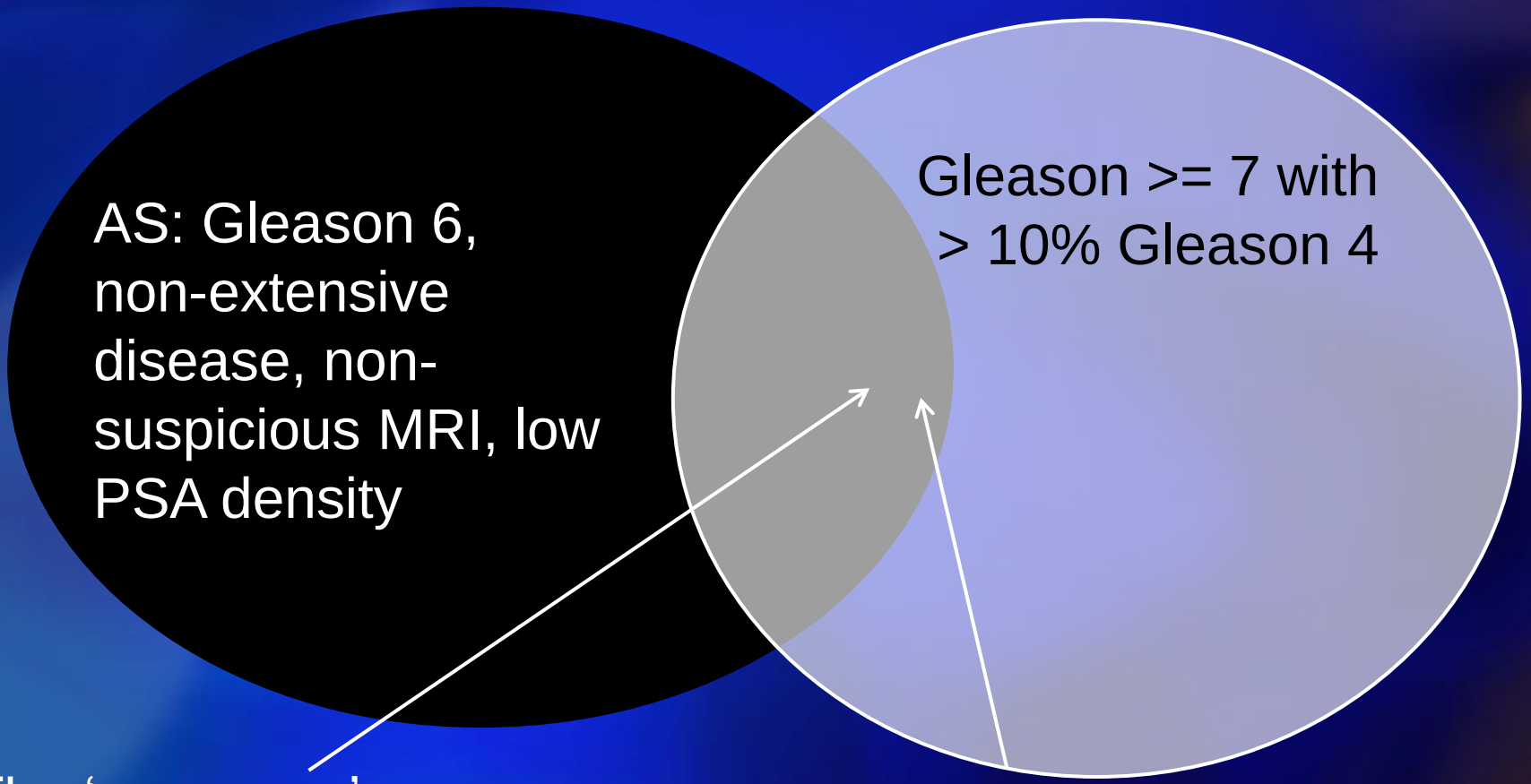
Simple heart/prostate healthy advice for patients on AS

- Stop smoking
- Regular exercise
- Dietary modification: weight management, moderate red meat intake, increase fruits/vegetables
- Low dose statin
- Vit D 1000-1500 IU/day
- ? Metformin 500 mg/day

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

Conclusions:

- Gleason pattern 3 is a non-metastasizing lesion lacking most hallmarks of cancer
- High volume Gleason 3 mainly significant as a risk factor for co-existent higher grade cancer
  - Race, high PSA density
- Presence of any Gleason 4 at baseline confers significant increased risk of metastasis at 15 years
- MRI and biomarkers will play a significant role in early identification of occult aggressive disease
  - Further risk stratification (not perfect)
  - Risk nomograms incorporating these an unmet need