Active surveillance

Overview of 20 year history

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Our world has changed

- Benefits of PSA widely accepted by urological community
- Enthusiasm for 5 ARI for chemoprevention (Thompson 2003)
- Optimism about Vit E and Selenium (SELECT)
- Benefit of RP on Pca mortality confirmed (SPCG-4, NEJM 2002)
- Menon RALP lecture SUO 2003
- 95% of low grade Pca treated radically

- USPSTF Grade D recommendation on PSA screening (Chou et al Ann Int Med 2011)
- Chemoprevention dead
  - FDA denies 5 ARI approval
  - SELECT trial negative, increased Pca Vit E arm
- No impact of RP on all cause mortality and Pca mortality in PIVOT (Wilt, NEJM 2012)
- In US: Open RP on life support, >80% RALP
- Active Surveillance

Origins of Toronto active surveillance cohort

- 1997: Lunch research meeting at Sunnybrook: L. Klotz, R. Choo, C Danjoux ‘How can we do better with localized prostate cancer’
  - Overtreatment obvious
  - ‘Watchful waiting’ too conservative
  - Most patients had PSA < 10; vs patients with advanced disease had high PSA—’window of opportunity’
- Middle ground: manage patients conservatively with selective intervention for rising PSA or grade progression
- Received first ever grant from new Prostate Cancer Canada Foundation ($35,000.) for prospective database
- Formal trial, informed consent, ‘experimental’
- Coined term ‘active surveillance’ to emphasize close monitoring/intervention

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
- Molecular biomarkers
- Modelling studies
- Longer follow up,, ~2000 publications

2017: 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

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?

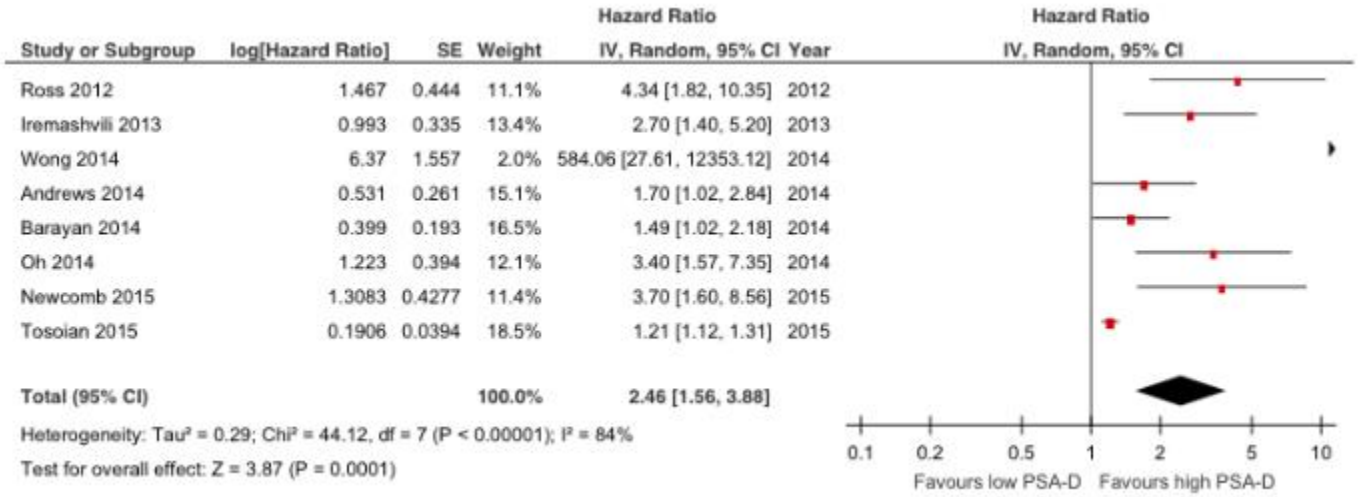
Answer: High volume is a marker for the presence of higher grade cancer

Finding the wolf in sheep's clothing:

2 different species of wolf:

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

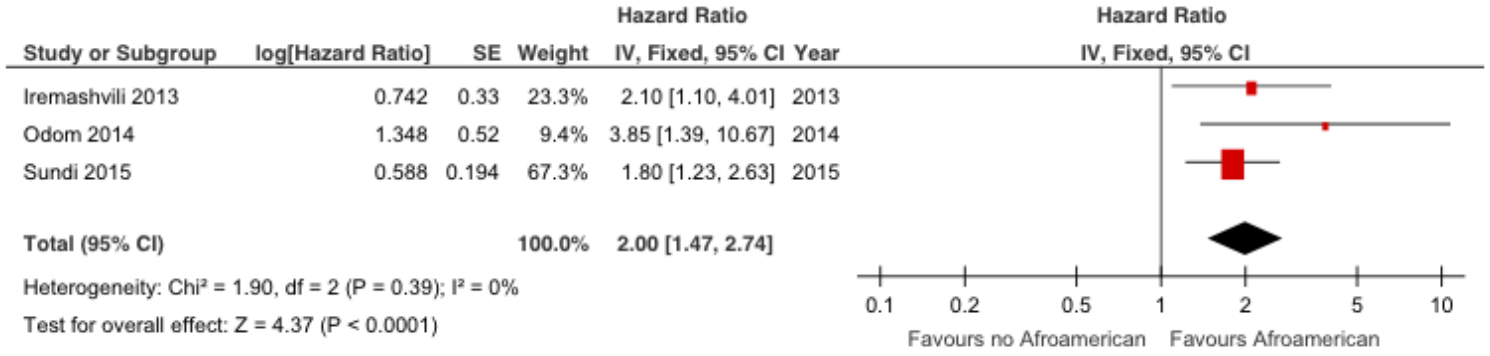
Predicting disease reclassification during AS



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%

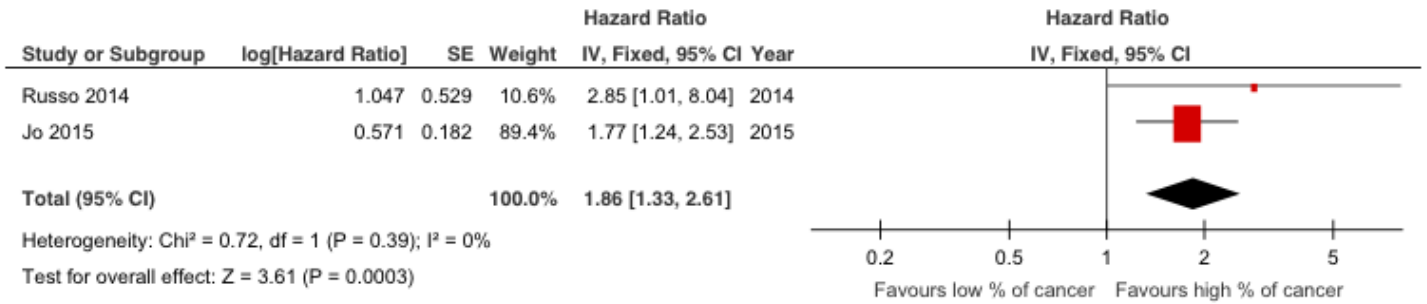
Test for overall effect: Z = 3.87 (P = 0.0001)



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)



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%

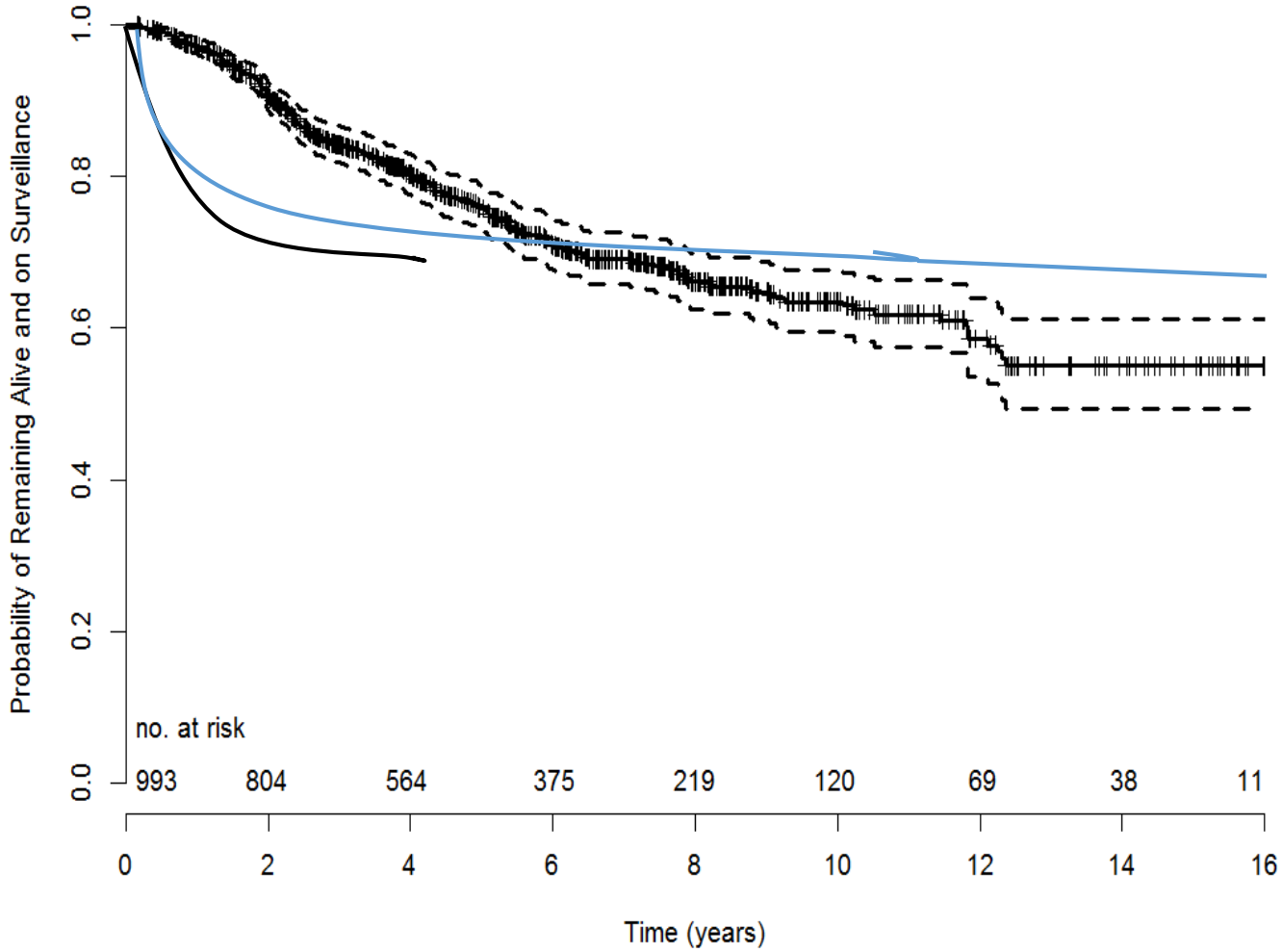
Test for overall effect: Z = 3.61 (P = 0.0003)

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	

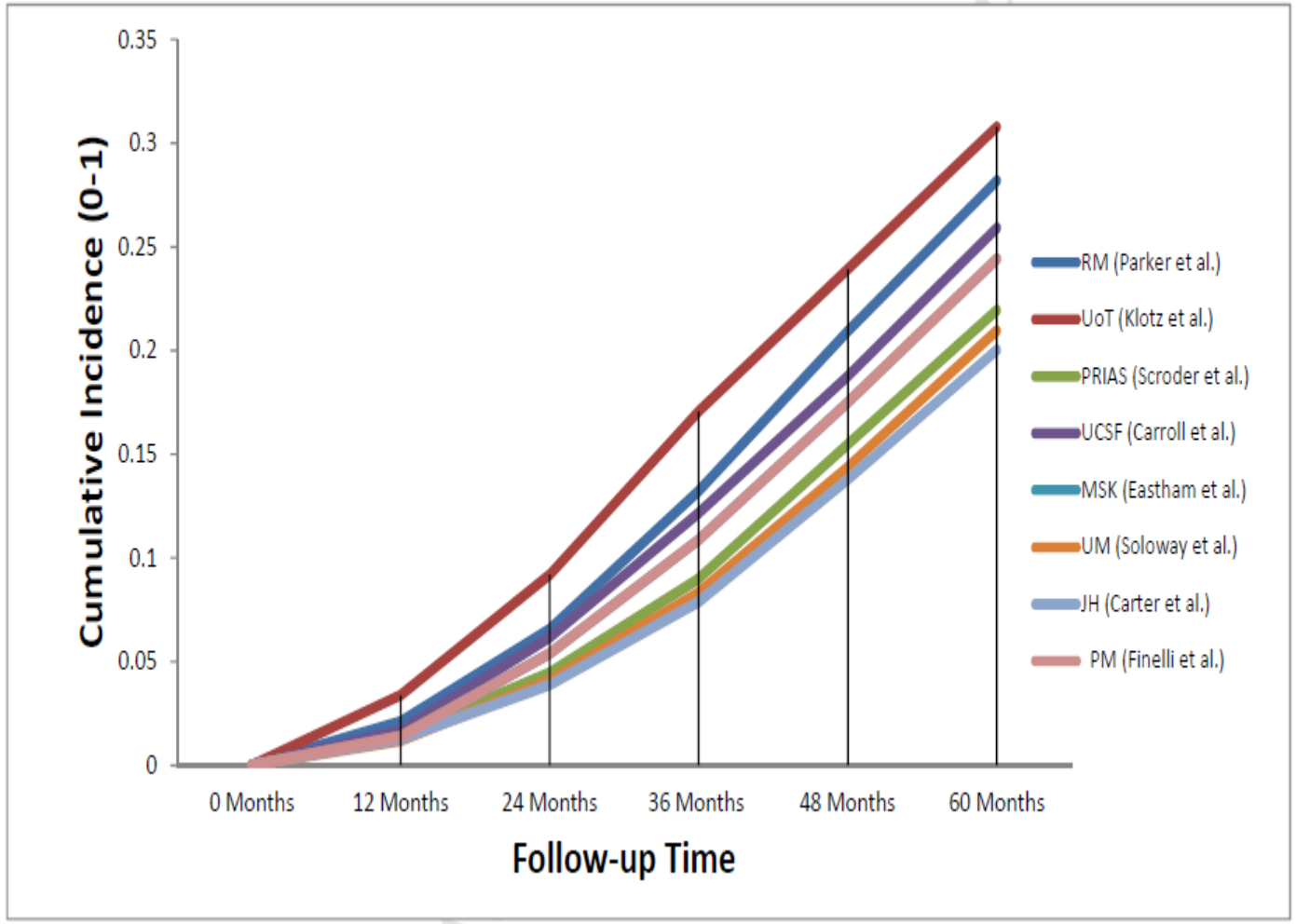
Toronto Surveillance Cohort

- 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
- 3% have developed metastases
  - 1.5% died of prostate cancer
  - 1.1% alive with mets

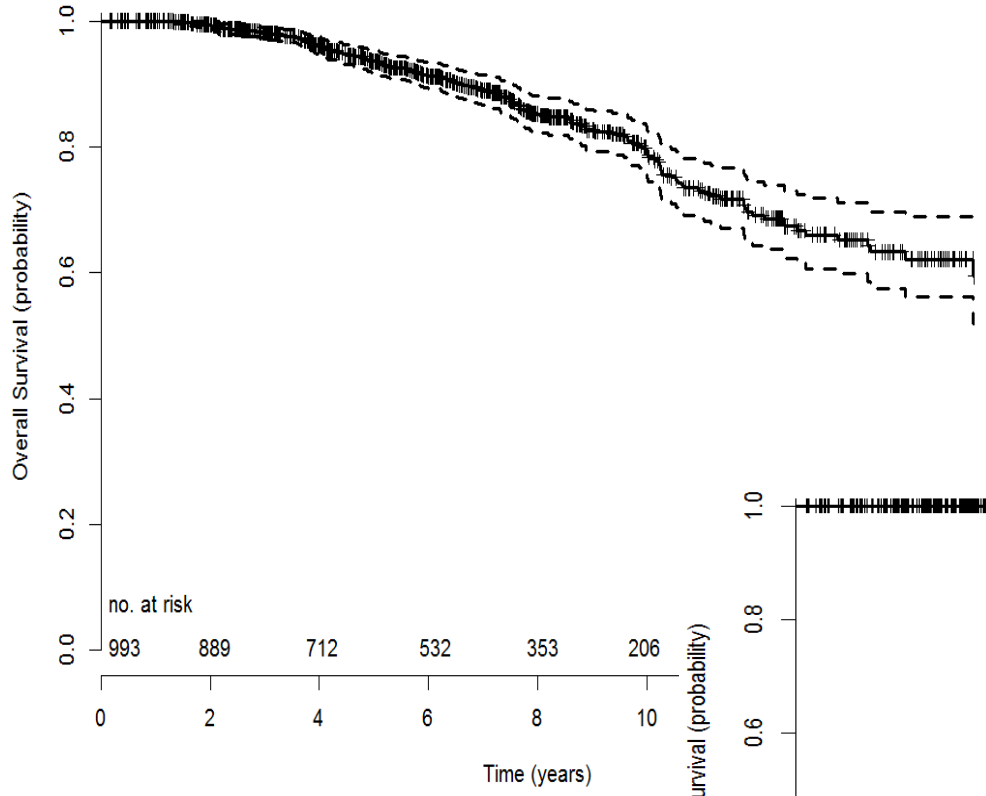
Intervention free survival in active surveillance Klotz et al JCO 33(3):272-7 2015

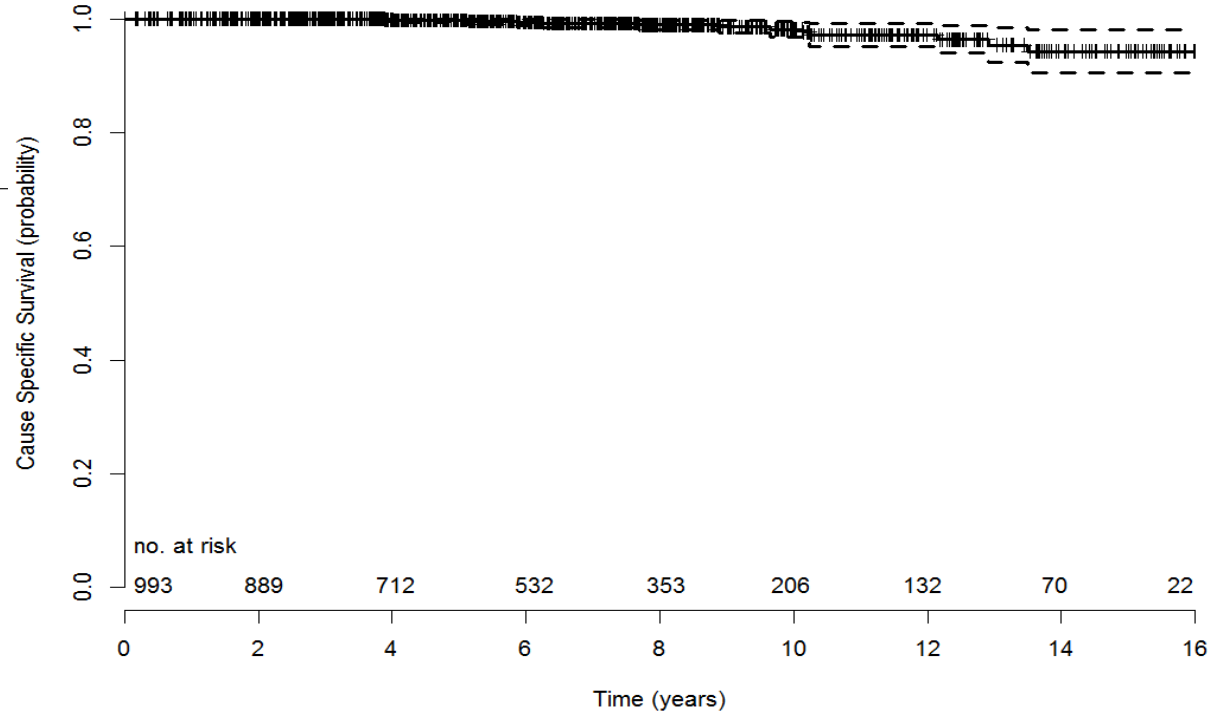


Stricter AS criteria for PCa do not result in significantly better outcomes: A comparison of protocols. Komisarenko M, Finelli A. J Urol. 196(6):1645,-50 Dec 2016



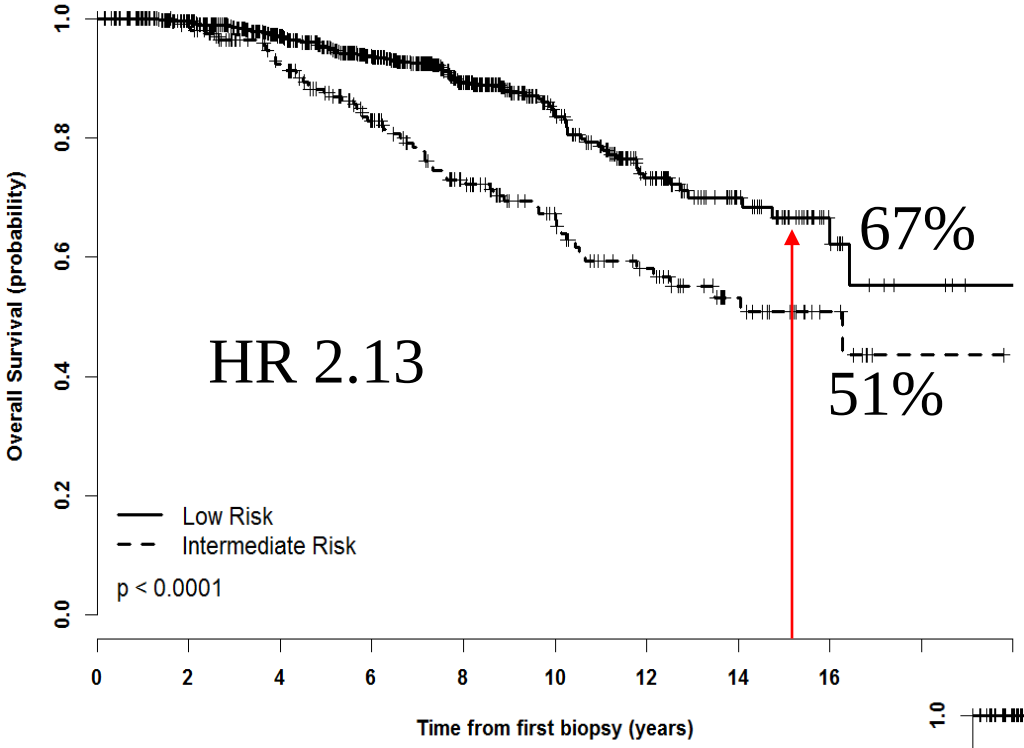
Survival with AS Klotz et al JCO 33(3):272-7 2015

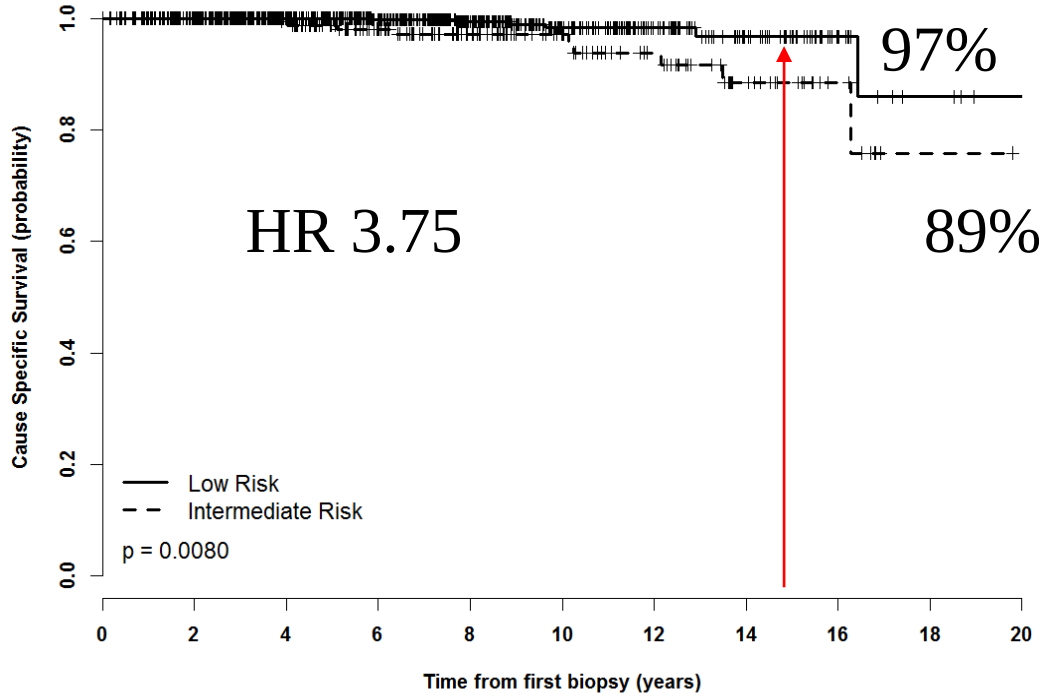




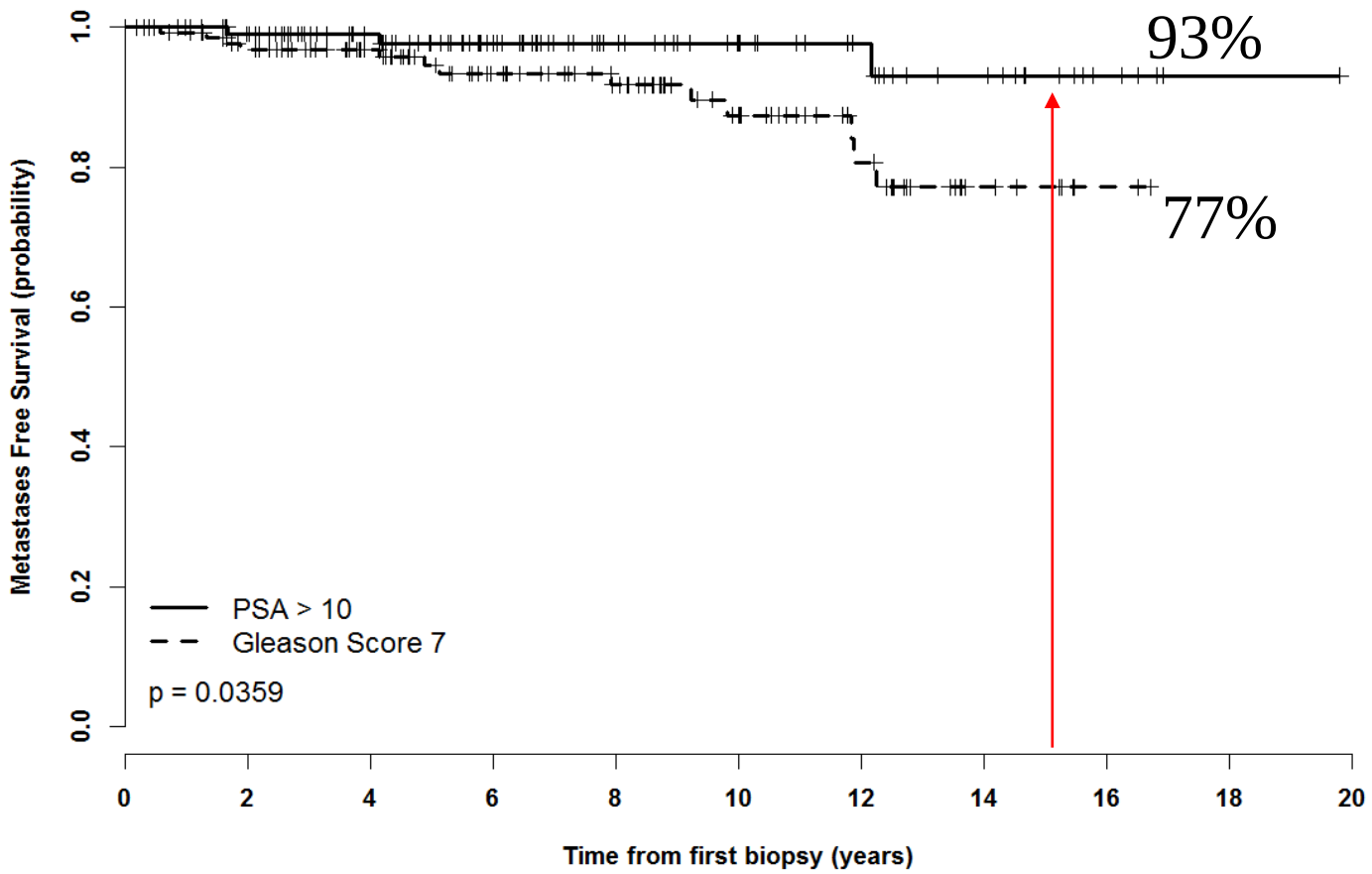
OS and CSS:

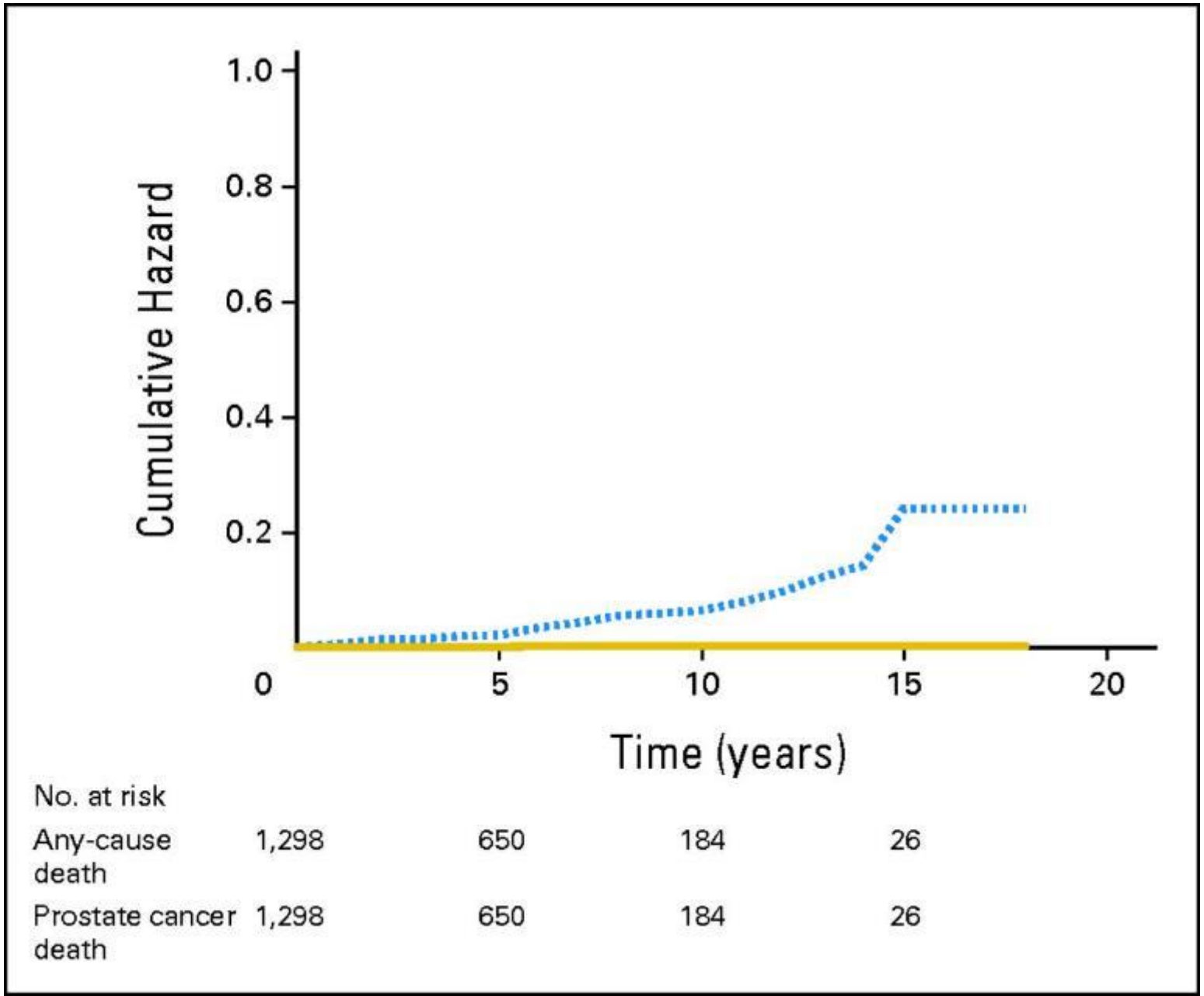
Low vs Intermediate risk (Gleason 3+4, PSA >10)





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




1.0
0.8
0.6
0.4
0.2
0
Cumulative Hazard
5
10
15
20
Time (years)
No. at risk
Any-cause death 1,298 650 184 26
Prostate cancer death 1,298 650 184 26

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%

Active surveillance

Current Paradigm

- Initial Bx and risk categorization
  - Comorbidity/life expectancy
  - Patient preference
- Re-biopsy to improve accuracy
- Periodic re-evaluation for change in risk
- Intervention:
  - Change in risk category
  - PSA anxiety
  - Patient preference

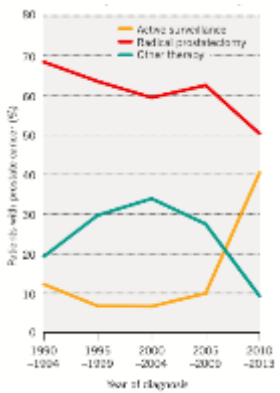
Image based/ Molecular paradigm

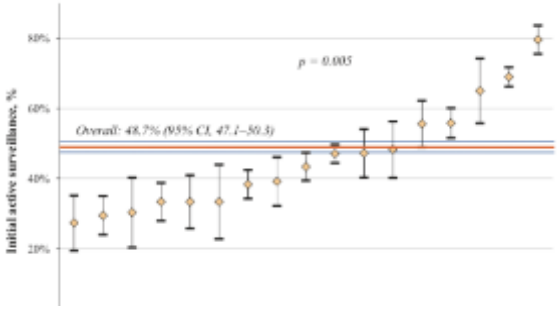
- Improved eligibility determination
  - MRI/biomarker instead of 2nd biopsy
- Improved patient selection:
  - MRI negative/favorable gene score :The new very low risk
  - MRI target/high score: greater acceptance of treatment
- Serial imaging/molecular monitoring with modulated interval
- Rational decision for intervention

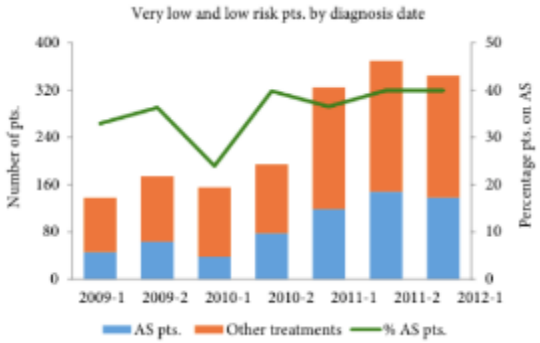
Comparison of guidelines: US, Canada, UK

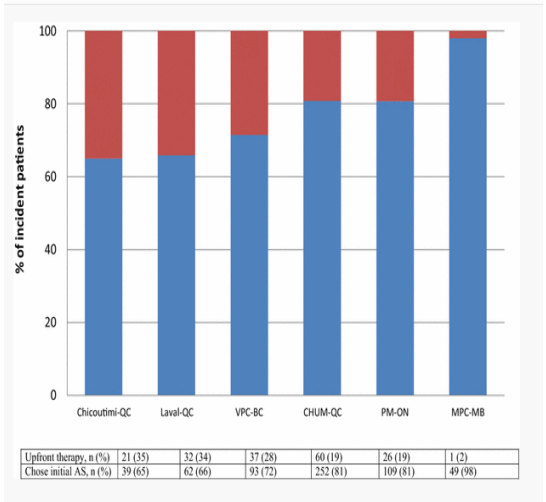
	Low risk Pca	Intermediate risk	Tests	Other tests	5 ARI
Cancer Care Ontario CUAJ 2015	AS preferred manage-ment	Active treatment; AS for selected pts	PSA q 3-6 mo DRE q 1 yr Systematic bx within 6-12 mo, then q 3-5 yrs	**MRI when clinical and path findings discordant**	**May have a role**
ASCO JCO 2016	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**	

illance: Utiliza



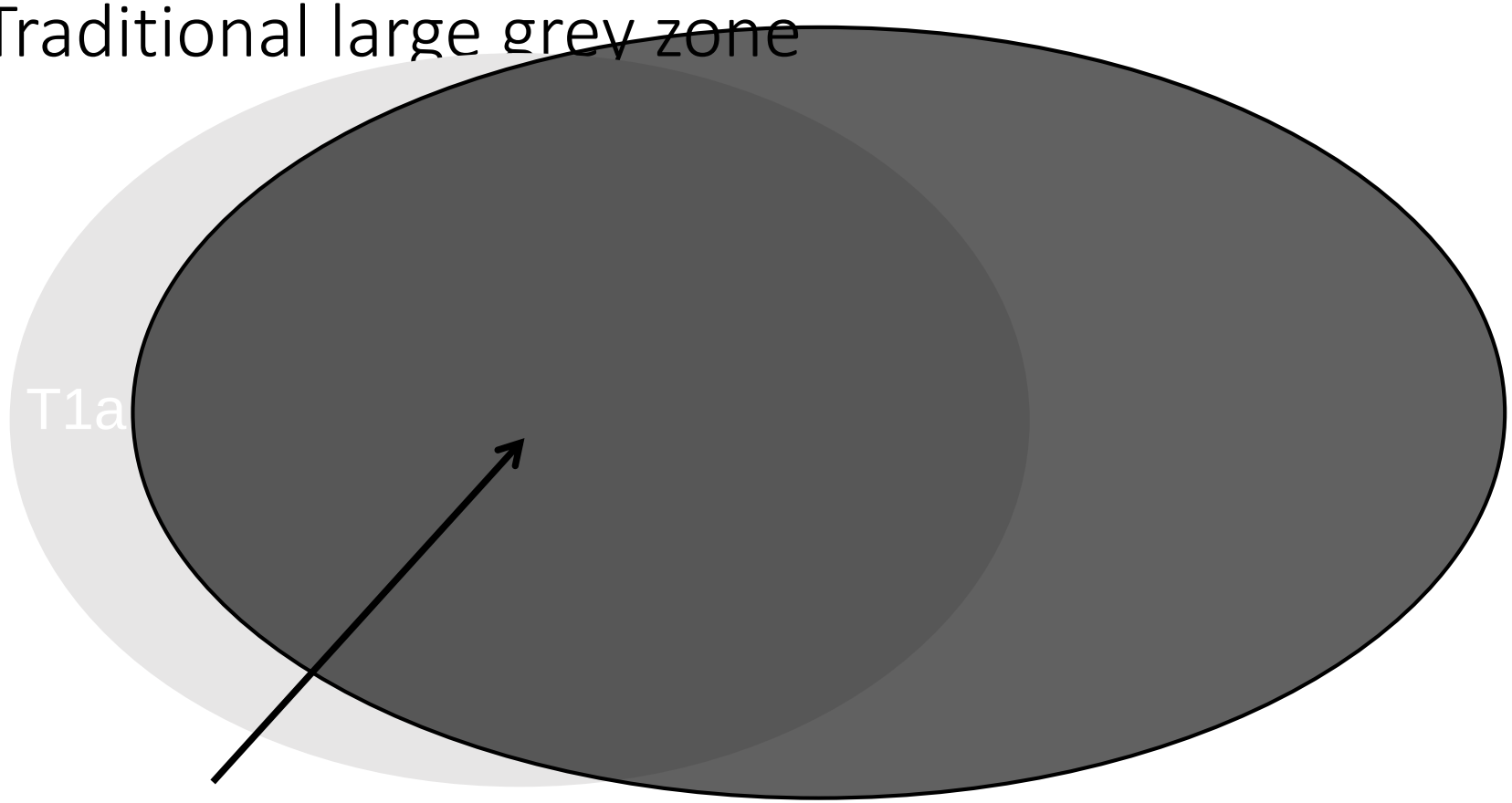




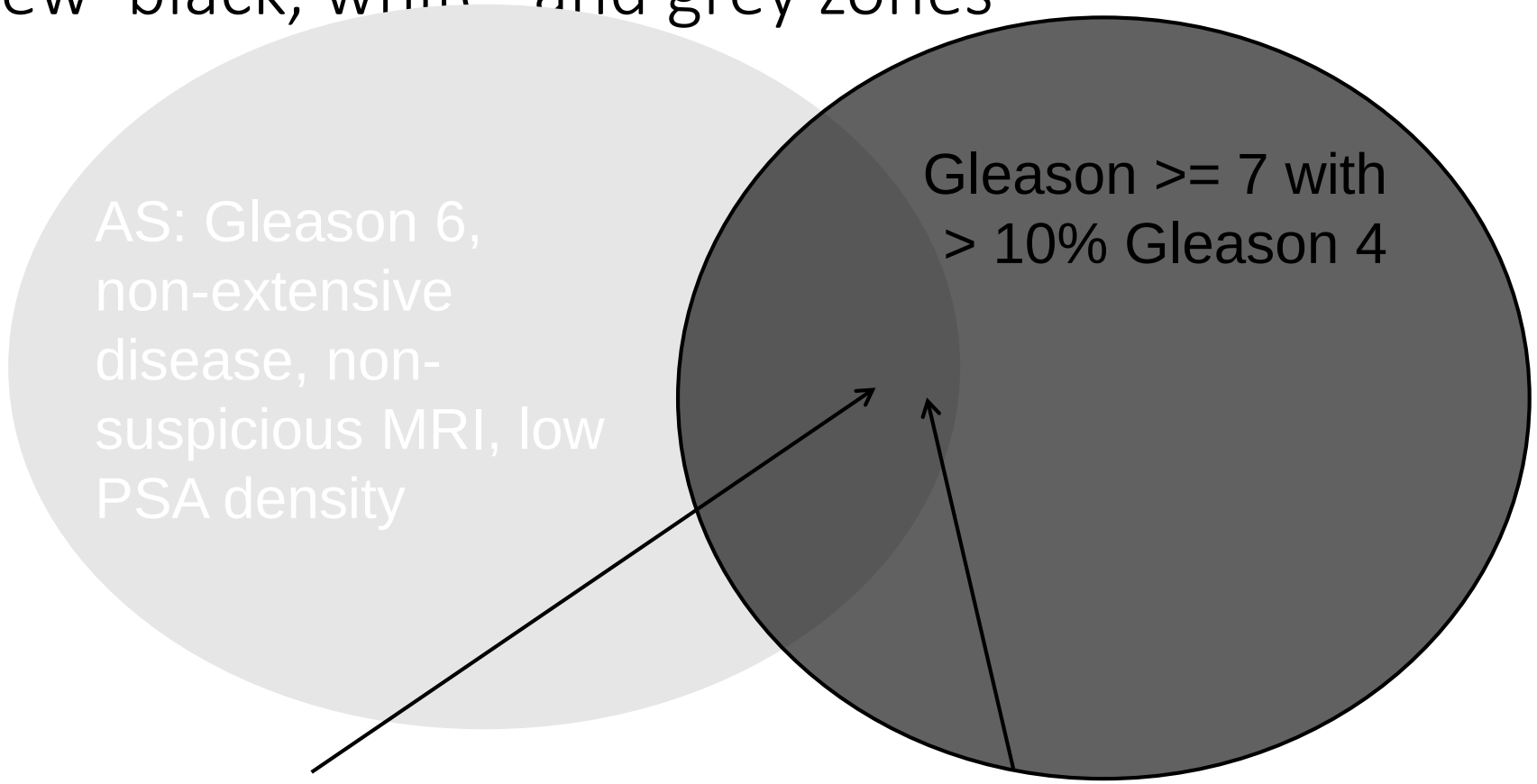


Upfront therapy, n (%)	21 (35)	32 (34)	37 (28)	60 (19)	26 (19)	1 (2)
Chose initial AS, n (%)	39 (65)	62 (66)	93 (72)	252 (81)	109 (81)	49 (98)

PCa: Traditional large grey zone



The new black, white and grey zones



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