Active Surveillance - a talk about nothing

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Overview

- Who is eligible?
- Is AS safe for Gleason 7?
- What’s changed in AS over the past 10-15 years?
- Imaging
- Genomics

Why do AS?

- Screening trials (PLCO and ERSPC) show the majority of Pca's are **not** harmful and over-treatment causes harm

- Recent Tx vs observation trials (PIVOT and ProTect) show 98-99% 10-15 year survival without treatment for low- and intermediate-risk Pca

- Most large AS studies (MSKCC, JHH, Toronto, PRIAS, UCSF, St Vs):
  - 98-99% 10-15yr met-free and Pca-specific survival, only 50% progress to Tx

So who is eligible? Selection criteria for AS

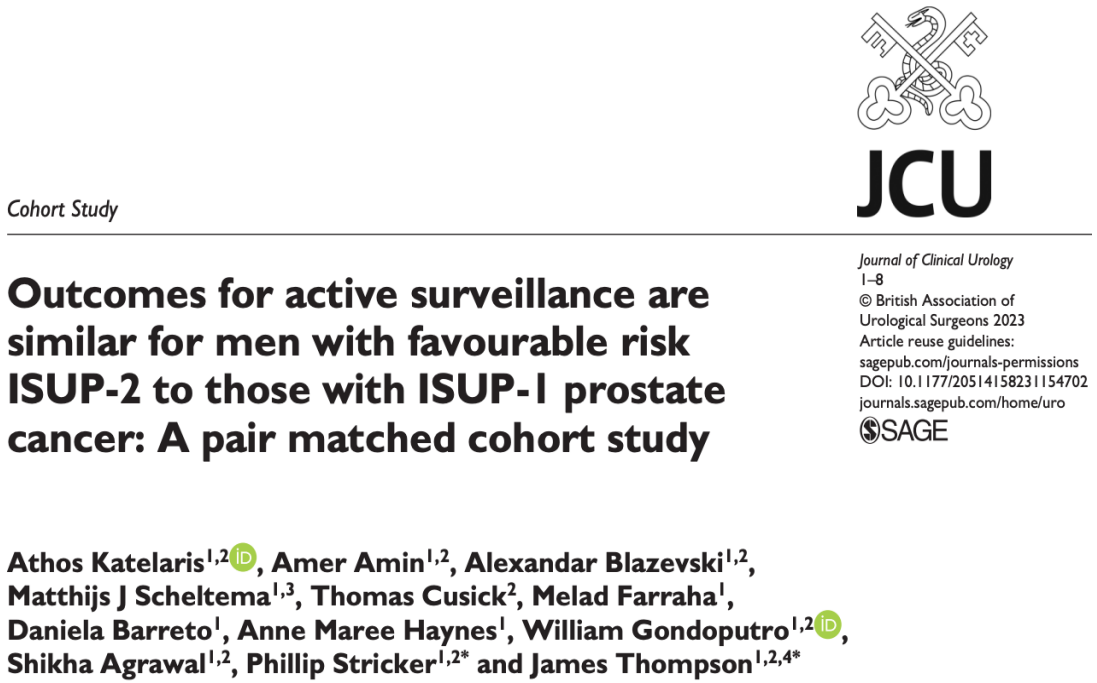
Early but now outdated (too strict):

- PRIAS: GG1, PSA <10, PSAD <0.2, cT1-2, 1-2 cores
- JHH: GG1, PSA density <0.15, cT1c, 1-2 cores, <50% core inolvement

Contemporary (broader)

- Simple: GG1 or low volume GG2
- NCCN: Very-low, Low and Favourable-intermediate-risk (One of GG2 or PSA 10-20 or cT2b-c)
- PIAS trial: Any GG1-GG2, max 2 locations GG2, max 10% or <1mm length of grade 4

Is AS for GG2 Safe? Our SVH study suggests ‘yes’



Cohort Study

Outcomes for active surveillance are similar for men with favourable risk ISUP-2 to those with ISUP-1 prostate cancer: A pair matched cohort study

Athos Katelaris[1,2], Amer Amin[1,2], Alexandar Blazevski[1,2], Matthijs J Scheltema[1,3], Thomas Cusick[2], Melad Farraha[1], Daniela Barreto[1], Anne Maree Haynes[1], William Gondoputro[1,2], Shikha Agrawal[1,2], Phillip Stricker[1,2*] and James Thompson[1,2,4*]

JCU

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Methods:

- Pair-matched cohort study
- 50 GG2 vs 100 GG1 pts enrolled on AS
- ISUP 2s </=10% g4, max 1-2 cores GG2, no cribiform
- Matched for age, PSA, year, MRI, cTs, no. cores

Results:

- Median 7 years follow-up, 57% vs 58% progressed to Tx
- 1,2,5 year prog’n rates of 10%, 30% and 80%
- No diff in adverse RP pathology or metastasis rates
- No Mets/ Pca deaths

Conclusion: AS for GG2 in carefully selected men has similar outcomes to AS for GG1

Is AS for GG2 safe? Most studies suggest 'yes'

- Carlsson et al from MSKCC (J Urol 2020)
  - Cohort of 219 men GG2
  - Median follow-up 3 yrs
  - Low 5- and 10- yr treatment rates of 40% and 50%
  - 3 BCRs, no metastases and no deaths

- Savdie et al from Vancouver (Urol Oncol 2017)
  - Prospective cohort of 150 GG2-3 vs 500 GG1
  - Low 5- and 10- yr treatment rates of 50% and 66%
  - Only 1 metastasis in GG2-3 group (0.7%)
  - Higher Grade (GG3 > 2) and higher % + cores predicted progression

AS for GG2 - Some studies suggest caution and need for better selection

- Travis-Courtney et al (Vet Affairs Study USA) (JNCCN 2023)
  - Large registry of 9,700 pts on AS, ~1,000 IR (GG2-3/PSA10-20/cT2b-c)
  - At 10-yrs
    - 45% LR vs 80% fav IR received Tx
    - 1.5% vs 9.5% metastases
    - 1.1% vs 3.7% Pca mortality
    - 23% vs 26% all cause mortality

	10-Year Cumulative Incidence (95% CI)			Gray's Test *P* Value	
Outcome	**Low Risk**	**Favorable Intermediate Risk**	**Unfavorable Intermediate Risk**	**All Risk Groups**	**Low vs Favorable Intermediate Risk**
Definitive treatment[a]	44.9% (43.7–46.1)	81.6% (78.3–84.3)	78.5% (72.2–83.6)	<.001	<.001
Metastasis	1.5% (1.2–1.9)	9.6% (7.1–12.5)	19.2% (13.4–25.9)	<.001	<.001
Prostate cancer-specific mortality	1.1% (0.8–1.4)	3.7% (2.3–5.7)	11.8% (6.8–18.4)	<.001	<.001
All-cause mortality	23.2% (22.0–24.4)	26.2% (22.0–30.6)	40.6% (31.7–49.3)	<.001	.13

- Conclusion: AS is an option but better selection tools and AS protocols needed

AS for GG2 - Some studies suggest caution and need for better selection

- Klotz et al (Sunnybrook Toronto) J Urol 2016
  - 213 pts aged >70, with GG2 or PSA >10 or cT2c (60% were GG2)
  - Median follow-up 7 yrs
  - 15-year metastasis-free survival 82% for IR vs 95% for LR

- Predictors of metastasis on AS:
  - Gleason 7 (HR 3)
  - PSADT <3 yrs (HR 3.7)
  - >2 cores positive (HR 2.7) (out of 12?)

- Conclusion:
  - These data do not support the use of AS in Gleason 7 disease

Why do some studies show worse AS outcomes?

- Broader inclusion criteria (higher PSA, high vol GG1, more GG2 & GG3)
- Less intensive biopsy (6-12 core trans-rectal biopsy)
- Lack of any imaging (MRI/PSMA)
- Less intensive observation (PSA only, no biopsy)
- No radical treatment or high threshold for salvage treatment

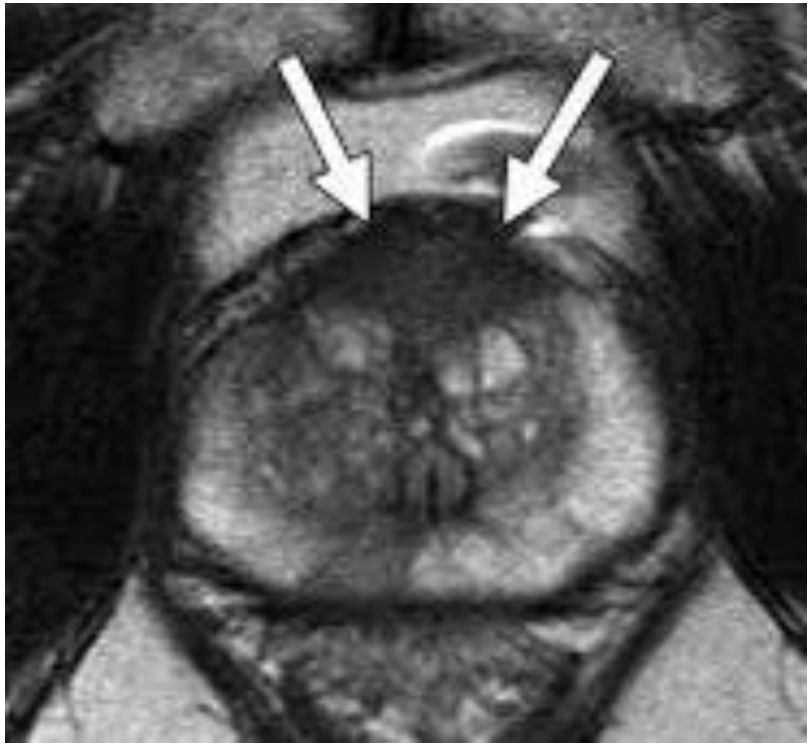
What's changed in AS in the last 10-15 years?

- Grade shift with ISUP Gleason grade changes (2008)
- Shift from 10-12 core Trans-Rectal to 20-40 core Trans-Perineal biopsy
  - More accurate grade and volume assessment
- Revolution of mpMRI and PSMA
  - More accurate grade and volume assessment
- Trials showing >95% 15yr survival with observation of GG1-2
  - PIVOT and ProTect
  - Recognition that most (not all) GG1-2s have an indolent course

Potential benefits of reliable imaging in AS

- Improved early detection of csPCa via targeted biopsy
- Reduced biopsy frequency **OR** avoidance of routine biopsy
- Reduced number of template cores **OR** avoidance of template biopsy
- Reduced patient and physician anxiety
  - Better uptake, better compliance, less-over-treatment

1st phase of our imaging Research:
MRI to better detect csPCa at baseline



St Vincents Trial (Thompson, Stricker et al J Urol 2014 & 2016)

Prospective trial, 400 men with abnormal PSA/ DRE

- mpMRI then TP saturation + MR targeted biopsy

Results:

- 95% NPV, 50% PPV for clinically significant Pca
- If we did NOT biopsy PIRADS 1-2:
  - Avoid **one-third** of unnecessary biopsies (men without Pca)
  - Avoid **one-third** of over-detection (insign Pca)

Other Landmark studies - MRI to detect csPCa

PROMIS Study (Ahmed et al, Lancet 2015)

- 576 men, mpMRI then 5mm TP mapping bx AND 12-core TR biopsy
  - 90% NPV and 50% PPV of MRI for csPCa
  - Poor sensitivity of 12-core TR vs MRI and vs 48-core TP saturation bx

PRECISION Study (Veeru Kasi… et al, NEJM 2018)

- Multicentre RCT of 500 men with abnormal PSA/DRE
- Randomised to:
  - 12-core TRUS (no MRI) OR
  - MRI + Targeted biopsy (if PIRADS 3-5) or no biopsy (PIRADS 1-2)
- Results:
  - Better detection of csPCa in the MRI arm (38%) vs control arm (26%) (p=0.005)
  - Less over-detection insign-PCa in the MRI arm (9%) vs control arm (22%) (p=0.001)
  - Less biopsies needed, 28% avoided biopsy in the MRI arm

2nd phase of MRI Research: The MRI-AS trial

(Amin, Thompson, Stricker et al J Urol 2020 ; Doan, Thompson, Stricker et al, J Urol 2022)

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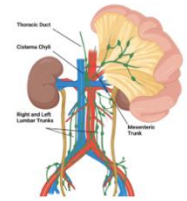

Methods:

- Design: Prospective single-arm trial
  - novel AS strategy: Annual MRI + q3-6mo PSA + 3-year saturation TP biopsy
- Popn: 170 men, newly diagnosed low-intermed risk Pca (3+3 / tiny 3+4)
- Intervention: MRI at years 0, 1 & 2: 'early biopsy' < 3 yrs **only** if new PIRADS 3-5 or persistent PIRADS 4-5
- Ref test: Protocol TP saturation template +/- MR-targeted bx at year 3

St Vincents MRI-AS trial

(Amin, Thompson et al J Urol 2020 ; Doan, Thompson et al, J Urol 2022)

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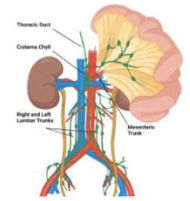


Results:

- 10 year trial
- 23% progressed at 3 years
- Accuracy
  - MRI Sensitivity = 57% and Specificity = 82%
  - PPV = 50% for predicting csPCa
  - NPV = 86% for 'ruling out' csPCa
- 10% had csPCa missed by MRI
  - 2% had aggressive Pca missed by MRI (e.g. GG3-5 >0.5cc / or T3)
  - 8% were pT2 and GG2 or <0.5cc GG3

Safety:

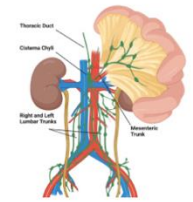
- 100% metastasis-free survival (median 70 months)
- 99.3% free from treatment or from BCR post-treatment (n=1 BCR post-RP; now BCR free post-SRT)

MRIAS Trial: csPCas missed by MRI

Table 2. Features of csPCa missed on mpMRI

Pt No.	PI-RADS score	No. Grade Group (% high grade on Biopsy	No. Cores Pos/Cores Taken	PSAD (ng/ml)	Definitive Treatment at latest follow-up	RP Gleason Score	Tumour Volume (cm^3)
1	2	2 (20)	4/33	0.10	Robotic-assisted RP	3+4	3.3
2	2	2 (35)	10/38	0.14	Robotic-assisted RP	3+4	0.8
3	2	4 (60)	3/30	0.07	Robotic-assisted RP	3+5	0.2
4	2	2 (40)	6/23	0.12	Robotic-assisted RP	3+4	1.6
5	3	4 (100)	4/27	0.10	Brachytherapy	Not applicable	Not applicable
6	2	2 (5)	7/15	0.14	Brachytherapy	Not applicable	Not applicable
7	2	4 (25)	4/34	0.08	Robotic-assisted RP	5+3	1.8
8	2	3 (50)	10/38	0.14	Robotic-assisted RP	4+3	0.8
9	2	4 (30)	5/37	0.17	Robotic-assisted RP	3+5	3.9
10	2	2 (10)	6/33	0.09	Robotic-assisted RP	3+4	0.43
11	3	2 (10)	12/43	0.19	Robotic-assisted RP	3+4	2.5
12	3	2 (10)	2/35	0.17	Robotic-assisted RP	3+4	0.52
13	2	2 (30)	5/37	0.17	Brachytherapy	Not applicable	Not applicable
14	3	5 (100)	3/37	0.13	Robotic-assisted RP	4+5	0.2
15	2	2 (5)	6/38	0.10	Nanoknife	Not applicable	Not applicable

St Vincents MRI-AS trial (Amin, Thompson et al J Urol 2020 ; Doan, Thompson et al, J Urol 2022)



Risk of csPCa by PIRADS score:

- 70% for persistent PIRADS 4/5
- 50% for new PIRADS 4/5
- 30% for new PIRADS 3
- 10% for stable PIRADS 2/3

Conclusions:

MRI in AS improves detection of progression & deferral of confirmatory Bx in some men

but periodic protocol Bx‘s are still mandatory

Other Trials of MRI in AS - ASIST Klotz et al Eur Urol 2019

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available at www.sciencedirect.com
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European Association of Urology

Prostate Cancer

Active Surveillance Magnetic Resonance Imaging Study (ASIST): Results of a Randomized Multicenter Prospective Trial

Laurence Klotz[a,], Andrew Loblaw[a], Linda Sugar[b], Madeline Moussa[c], David M. Berman[d], Theo Van der Kwast[e], Danny Vesprini[a], Laurent Milot[b], Marlene Kebabdjian[b], Neil Fleshner[f], Sangeet Ghai[f], Joe Chin[c], Gregory R. Pond[g], Masoom Haider[b]*

[a] Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [b] Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; [c] University of Western Ontario, London, ON, Canada; [d] Queen's University, Kingston, ON, Canada; [e] University Health Network, Toronto, Canada; [f] Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; [g] McMaster University, Hamilton, ON, Canada

Study Design

- Multicentre RCT (3 sites)

Study Pop'n

- 273 men with GG1 enrolled on AS after Diagnostic 12-core TRUS Bx
- Randomised to 12-core TRUSBx vs MRI +/- MR-TBx & TRUSBx at 1-yr

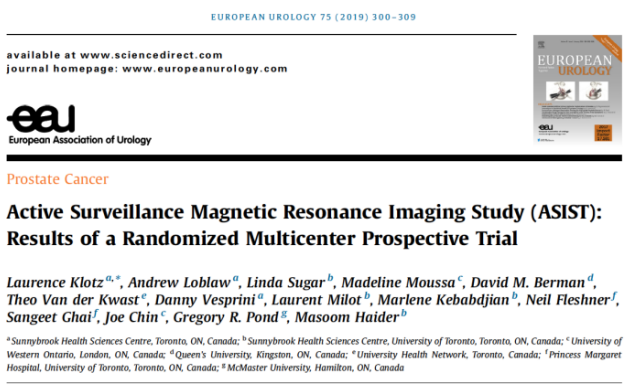
Results

- 27% in TRUS Bx arm vs 33% in MRI arm were upgraded at 1-yr confirmatory biopsy (non-sign p=0.3)
- MRI had NPV of 85% for 'ruling out' GG2-5
- 64% in the MRI arm had an ROI
- Only 2 targeted cores were taken per ROI (under-sampled…?)
- 2 of 3 centres were inexperienced in the MR-Bx: detection rates of 8-10% vs 33% for MR-TBx

Conclusion

- MRI **didn't** improve detection of csPCa at confirmatory biopsy
- Confounded by differences between more and less experienced centres in MR-TBx
- Systematic biopsies should be performed regardless of MRI findings

3-year Bx followup - ASIST Trial Klotz et al Eur Urol 2020



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Study Pop'n:

- 199 men with GG1 continued on AS after Confirmatory Bx
- 2 years later, men again underwent 12-core template TRUSBx OR MRI then 12-core TRUSBx +- MR-TBx

Results

- At 3-years, lower progression in the MRI arm (19% vs 35%, $p<0.02$)
- At 3-years, less csPCa at biopsy in the MRI arm (10% vs 23%, $p<0.05$)
- Upgrading rates in the MRI arm differed dramatically between sites
  - 4% for MRI-experienced vs 27% for inexperienced)

Conclusions

- MRI pre-Bx reduces risk of subsequent progression on AS
- Differences exist between more and less experienced centres in MRI / TBx

Cambridge Trial of MRI in AS Thurtle et al BJUI 2018

Study Design

- Prospective single-arm study

Study Popn:

- 104 men enrolled on AS (85% GG1)
- Annual MRI, q3m PSA and TP Template +/- MR-targeted Protocol Bx at 1 & 3 years

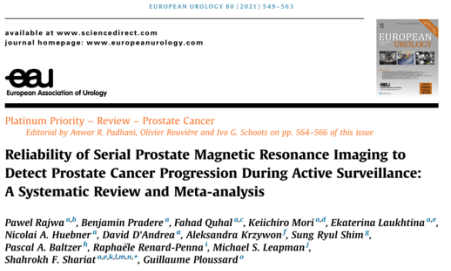
Results

- 19% progressed by 3 years
- MRI had Sensitivity of 50%, specificity of 87%, PPV of 50% and NPV of 87% for 'ruling out' csPCa
- 10% of the AS cohort had csPCa missed by MRI
- PSA + MRI still had only 70% sensitivity for csPCa

Conclusions

- MRI improves selection for AS and improves detection of progression **but** can't replace protocol Bx

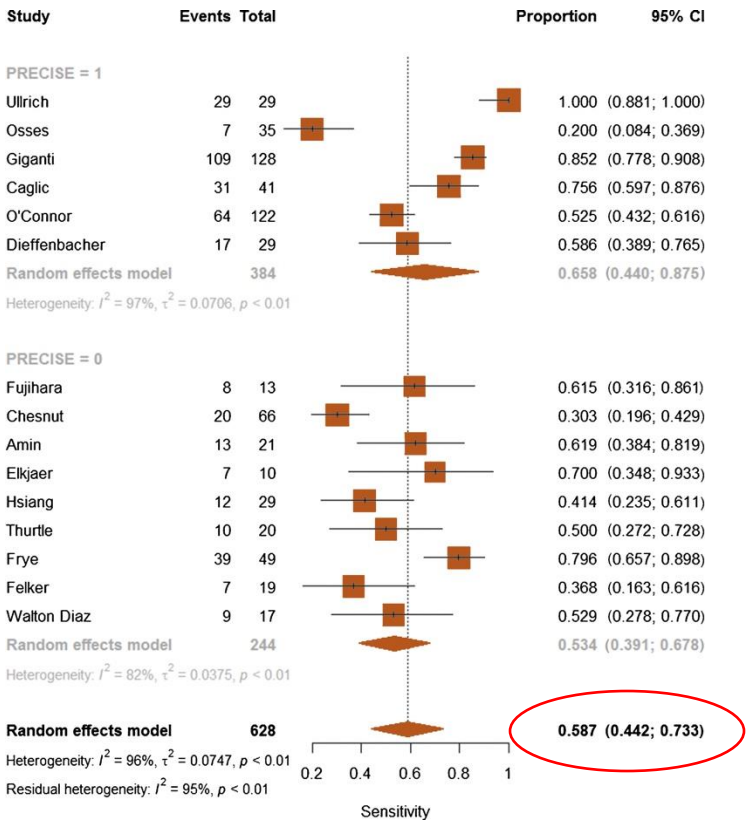
Meta-analysis of MRI in AS

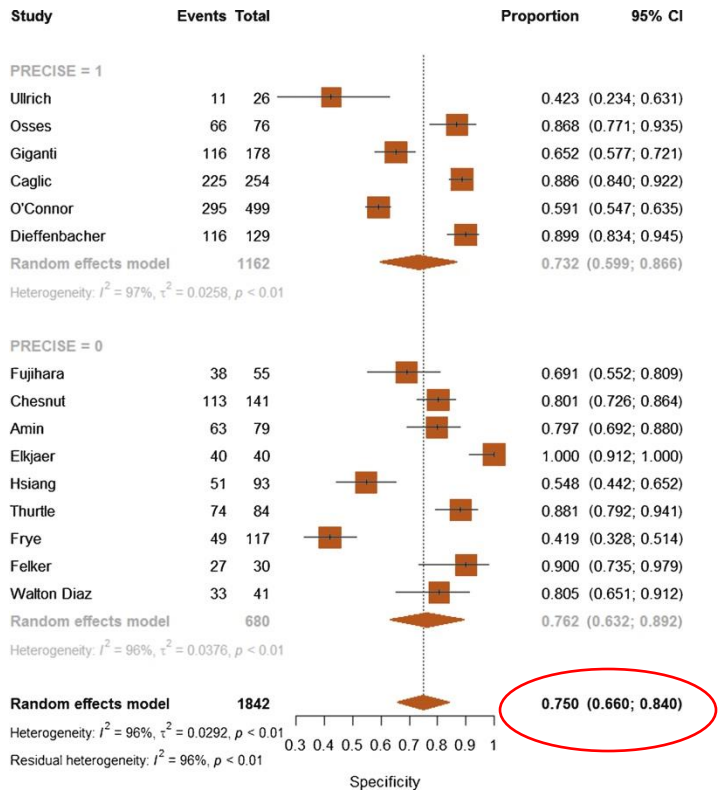


Rajwa et al Eur Urol 2021

- Combined 15 studies with 2,240 patients

Pooled sensitivity 60%





Pooled specificity 75%

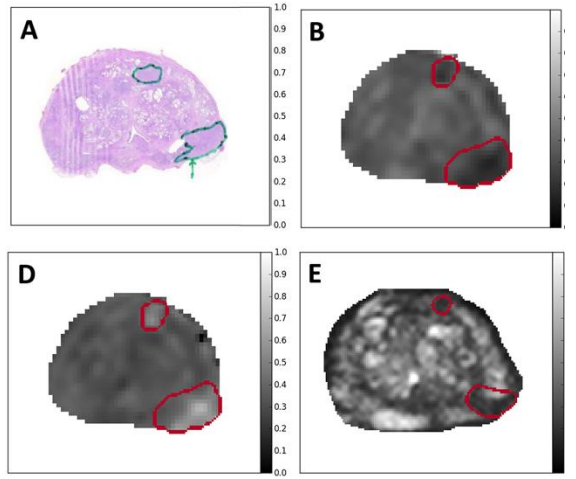
<u>Conclusions:</u> MRI would allow avoidance of biopsy in 65% of men but miss progression in 12%.
Serial MRI cannot be used alone for excluding PCa progression and triggering biopsy in AS.

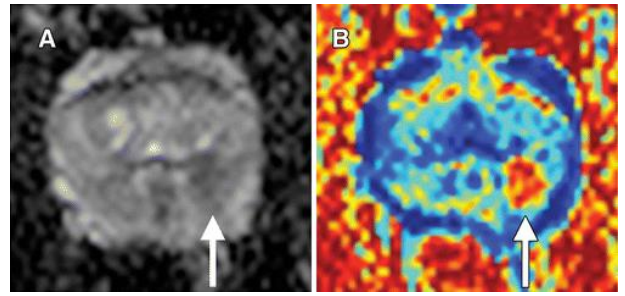
Novel advances in MRI

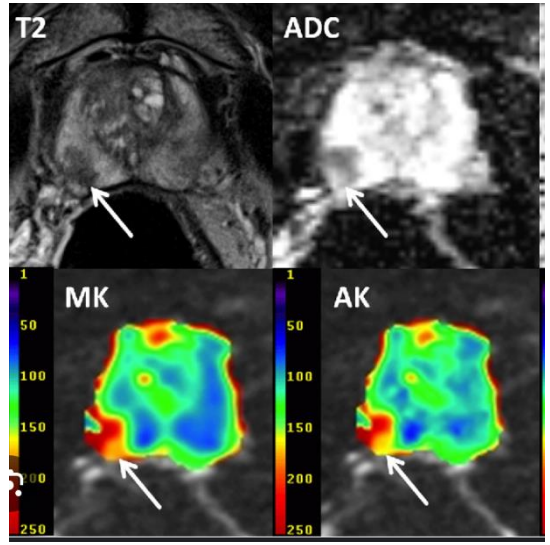
- Artificial Intelligence/ Machine Learning
  - Radiomics collaboration with Case Western USA
  - Per Voxel based analysis
    - detect smaller high-grade Ca
    - Detect subtle changes in T2, ADC, enhancement on serial MRIs
    - Reduce ‘reporter misses/ errors’

- Fractional DWI
  - LWI (Luminal Water Imaging)
  - VERDICT (intra-cellular vs interstitial vs intra-vascular H20)
  - RSI (Restriction Spectrum Imaging)

- Diffusion Kurtosis Imaging (DKI)
  - Early research collaboration with UNSW/ Siemens/ Imed
  - Advanced diffusion analysis
  - May better detect small high grade tumours than conventional DWI







PSMA in AS – Our PIAS Trial

- World-first prospective PSMA-PET in AS trial
  - Currently open at sites across NSW, Qld and Vic
  - Potential to open new recruitment sites (to existing PSMA scanners)

- Design
  - N=225 planned
  - ‘High-risk’ men: high vol GG1, low vol GG2, PIRADS 4-5, suspicious baseline PSMA
  - MRI + PSMA PET + TP Satn Template +/- Targeted Confirmatory Bx
  - Ga-68 PSMA: 3x Expert Centres, Double-reported, Primary Pattern Score 1-4 TZ/ PZ

- Primary Endpoint
  - Accuracy of PSMA vs MRI vs combination
  - Pathologic Upgrading to GG2 with >/=10% g4 or >/=1mm g4

PIAS Trial Preliminary Results - Oct 2024

- 82 pts enrolled, 55 completed first phase of trial with MRI, PSMA & 1-year biopsy, 46 with full data for analysis

	Positive PSMA-PET	Negative PSMA-PET
Pathological progression	17	4
No pathological progression	12	15

PSMA alone:

Sensitivity	**85**
Specificity	**63**
PPV	**66**
NPV	**84**

PIAS Trial Preliminary Results

- 20/46 had pathological progression
  - 17/20 had positive PSMA-PET
  - Of the 3 with negative PSMA-PET
    - All 3 had PIRADS 4 on MRI
    - Combined sensitivity (MRI (P4-5) and/ or PSMA+) = 100% (95% if classifying a pt with tiny focus <1mm grade 4 as false negative)
- 26/46 had no pathological progression
  - 15 had negative PSMA-PET
    - Of these 7 had PIRADS 2 MRI, 4 had PIRADS 3, 4 had PIRADS 4

- If all patients with negative PSMA-PET and PIRADS 2-3 MRI avoided 12-month biopsy
  - 24% (11/46) would have avoided biopsy and 0-5% (0-1/46) would have missed pathological progression

PIAS Case Study 1 – borderline false negative

- 75yo man, PSA 4.2, MRI PIRADS 2 65cc
  - Bx: 1/34 cores + for GG2 (left apex mid)
  - 13mm core, 10% cancer ~1mm, 20% grade 4 i.e. 0.2mm of grade 4
  - Borderline for enrolment given 20% grade 4, but allowed since <1mm grade 4

- 12 months later, PSA down to 3.6, MRI still PIRADS 2, PSMA negative
  - Surveillance biopsy: 3/47 cores +
  - 10 cores from left apex ant/mid - 1 showed a <1mm focus of high grade GG3

- Classified as grade progression and treated with EBRT
  - But still <1mm of high grade tumour, so significance debatable in a 76yo
  - PIAS ‘a priori’ defn of path progression is >1mm total length of pattern 4

PIAS Case 2 – csPCa seen on PSMA, missed by MRI

66yo male with PSA 6, normal DRE

- Mid 2020:
  - MRI PIRADS 2
  - Biopsy low vol 3+4, 2% g4

Low-grade change without discrete high-grade nodule (PI-RADS 2).

Composite Gleason Score (ISUP 2014):	3+4 = 7
% High Grade 4/5:	Less than 2%
Intraduct carcinoma:	Absent
Number of cores involved:	3
Total number of cores:	17

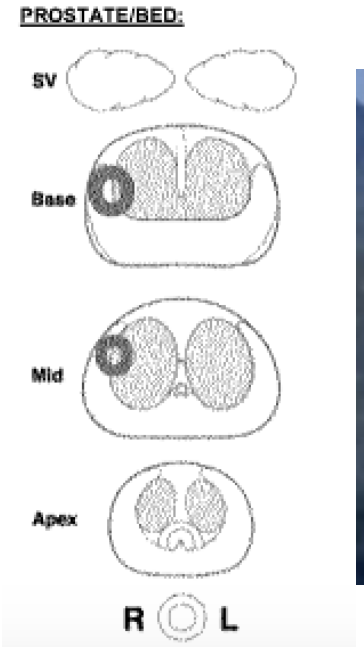
- Early 2022:
  - PSA rising 6 to 8
  - MRI still PIRADS 2

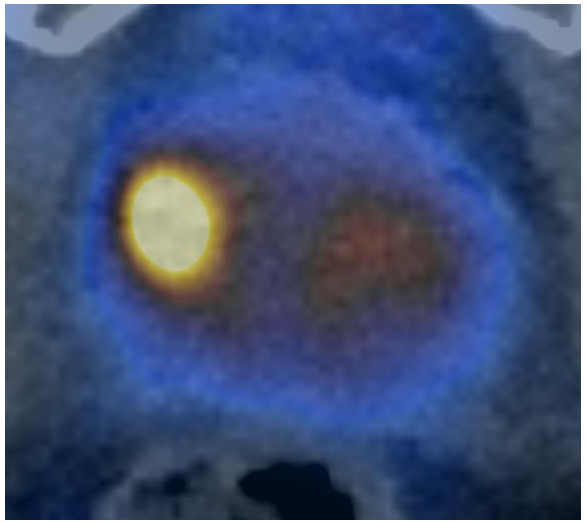
RADS 2). Stable transition zone with no suspicious nodule identified (PI-RADS 2).
- No clinically significant disease is detected.

- Enrolled into PIAS

PIAS Case 2 – csPCa seen on PSMA, missed by MRI

PSMA

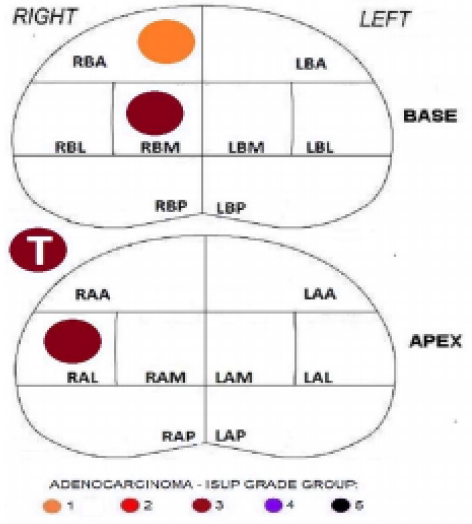




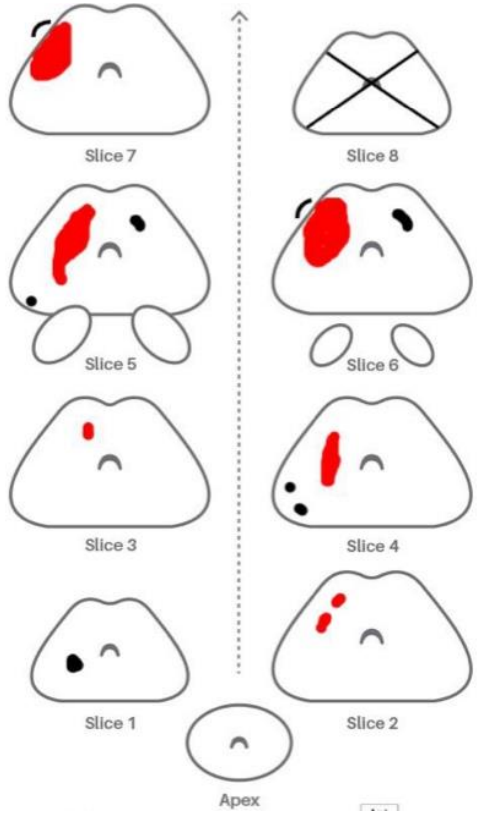
Pattern	*Focal peripheral and transition zone activity*
***SUVmax** For All Findings*	*13.3*
Was there evidence of significant malignancy	☒ Yes ☐ No
Certainty of conclusion regarding presence of significant malignancy	Definitely positive

Biopsy

Composite Gleason Score (ISUP 2014):	4+3 =7
% High Grade 4/5:	55%
Intraduct carcinoma:	Absent
Number of cores involved:	6
Total number of cores:	23
Perineural invasion:	Absent
Vascular infiltration:	Absent
Extra prostatic extension:	Absent

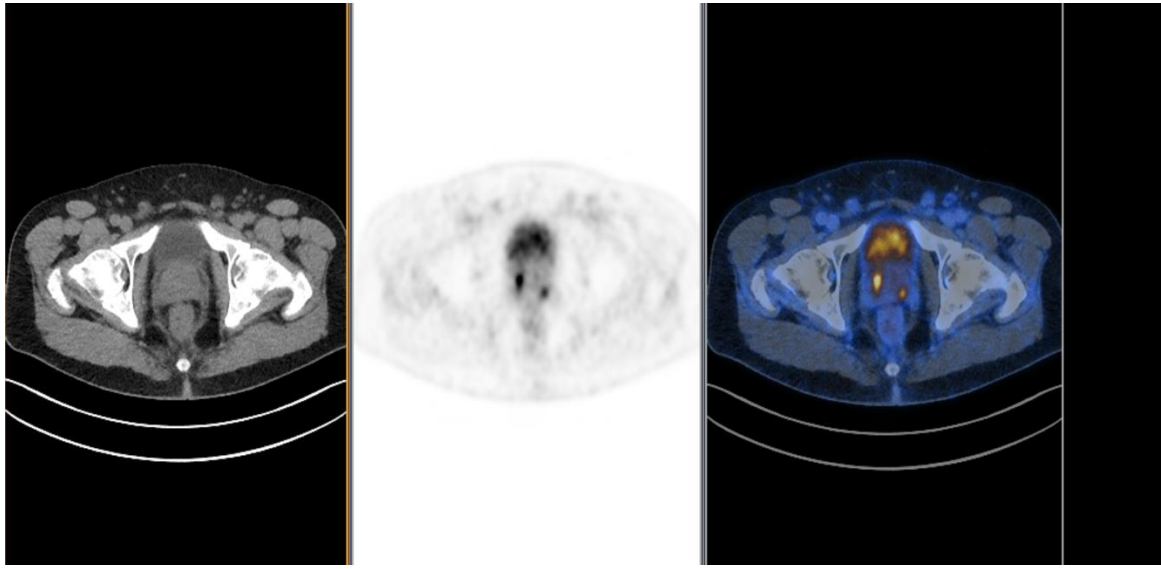


RP



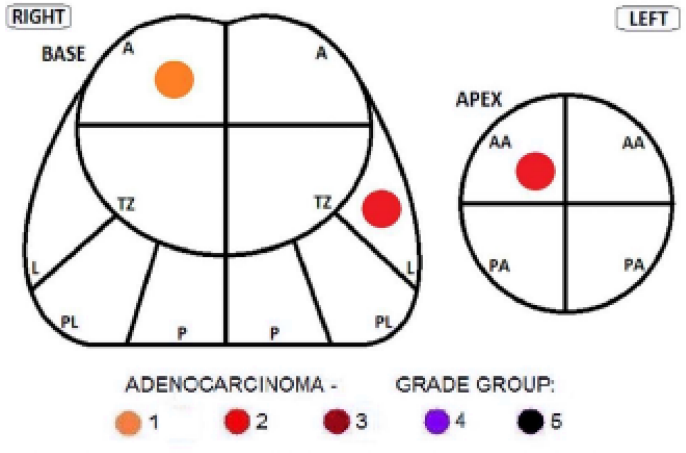
GG3 pT3a 1.5cc TV

PIAS Case 3 – csPCa on PSMA, equivocal MRI&Bx



- 59yo, PSA 3.0 to 3.8, MRI PIRADS 3
- Enrolled onto PRIMARY 1 trial (PSMA then Bx)
  - Baseline PSMA abnormal right TZ and left PL
- Biopsy GG2
  - <5% g4, low vol core involvement 5% and 15%
  - Enrolled onto PIAS

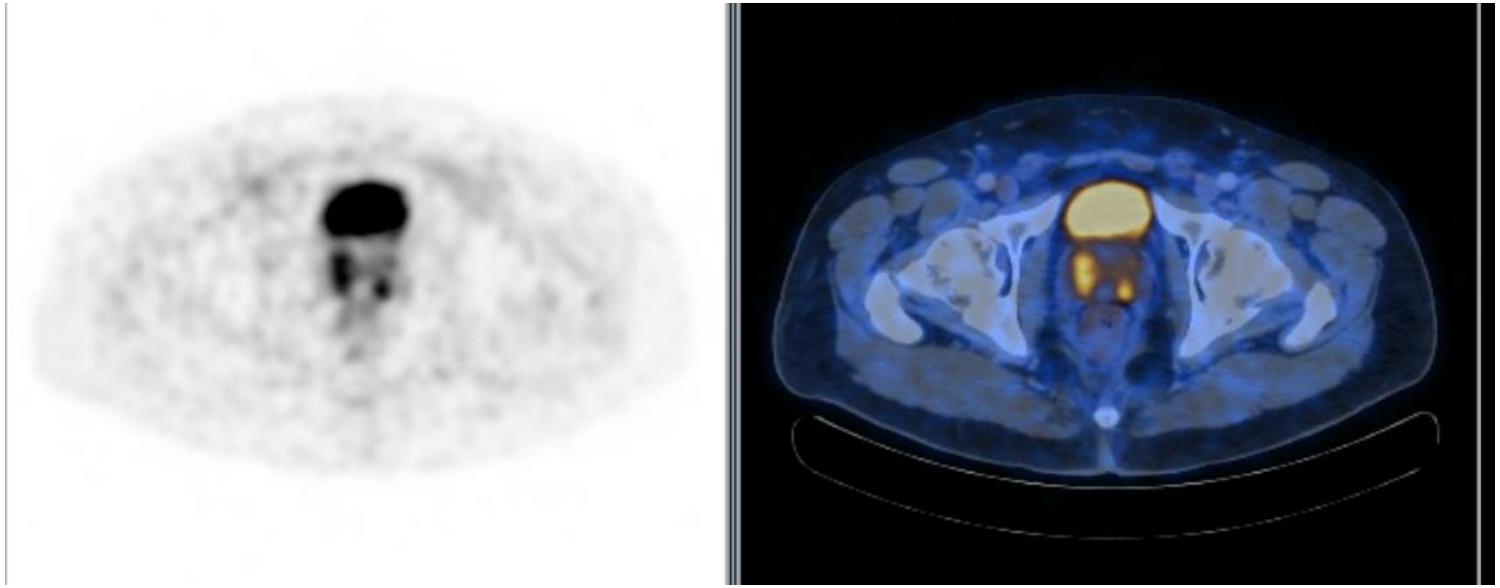
Location Other Involved Sites:	Right anterior
Composite Gleason Score (ISUP 2014):	3+4 = 7
% High Grade 4/5:	Less than 5%
Intraduct carcinoma:	Absent
Number of cores involved:	4
Total number of cores:	28
Perineural invasion:	Present
Vascular infiltration:	Absent
Extra prostatic extension:	Absent



PIAS Case 3: 12 mo later

PSA rose from 3.8 to 6.8 , **MRI** stable – downgraded to PIRADS 2

Rpt PSMA
SUV up from 6 to 11



Rpt BIOPSY
Increase cancer volume and % grade 4

2. 'Right transitional zone prostate biopsy MRI targeted'. Sections show adenocarcinoma, **Grade Group 2** (Gleason Score 3+4=7), with the percentage of high grade (pattern 4) being 20% involving 3 of the 7 cores, spanning 60%, 50% and 25% respectively.

RP:
Final histo - pT3a G3+4=7 30% g4, 1.5cc TV

PIAS Case 4 – csPCa seen on MRI & PSMA, missed on Bx

- 61yo PSA 1.2 to 2.8, strong FHx of Pca
  - MRI PIRADS 4 Left anterior
  - Biopsy 6/33 cores G3+3 (GG1)
  - Enrolled onto PIAS

- 12mo later
  - PSA up to 3.5 then 4.5
  - MRI – PIRADS 4 Left anterior 5mm and right posterior 5mm
  - PSMA – positive Left anterior SUV 5.5
  - AS Biopsy – 12/22 cores G3+3=6 up to 80% MCCV in targets (LA and RP)

- Pt elected RP despite still only GG1 (based on vol prog, MRI and PSMA)

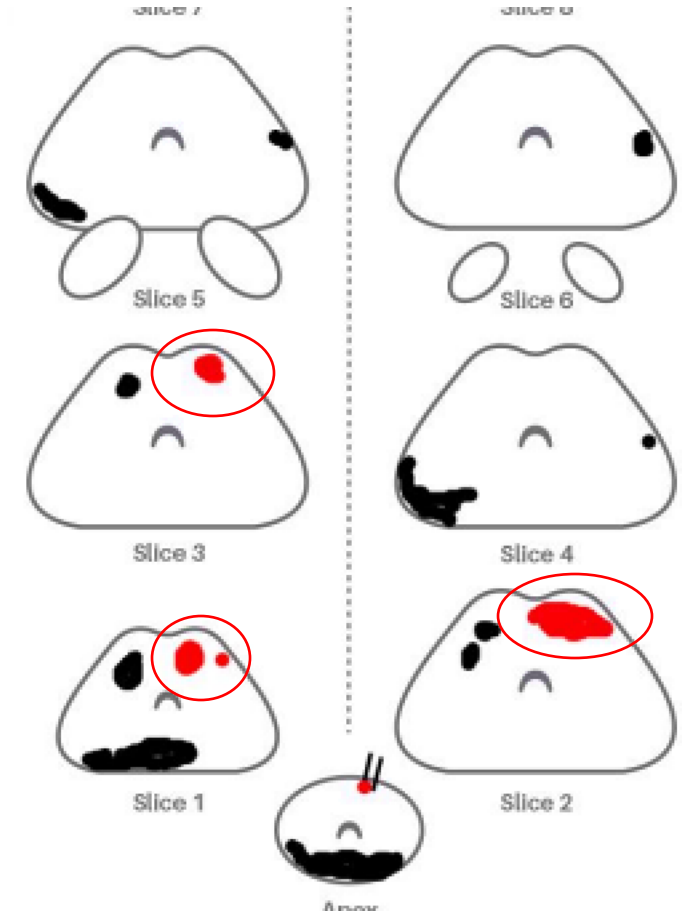
Final RP Histo

Left Ant GG2 c/w PSMA , additional Right Post GG1 c/w MRI

Index carcinoma	
Grade Group	2
Index Gleason Score (ISUP 2014)	3+4=7
Primary pattern	3
Secondary pattern	4
Tertiary pattern	-
Percentage high grade (4 and/or 5)	25 %

Composite carcinoma	
Composite Global Gleason Score	3+4=7
Percentage high grade (4 and/or 5)	15 %
Cribriform architecture	Present
Intraductal carcinoma	Absent
Lymphovascular invasion	Absent

TUMOUR EXTENT	
Volume (total)	0.65 cm³ (3D volume estimate method)
Extraprostatic extension	Absent
EPE distance	-



PIAS example 5 – no csPCa, equiv MRI, neg PSMA

- 72yo man, PSA 8, heavy smoker and drinker
  - MRI: PIRADS 3 Right TZ
  - Biopsy: 4/41 cores, G3+4=7, 5% grade 4, 5mm/70% positive, 10% grade 4
  - Enrolled onto PIAS trial
- 12 months later
  - PSA down from 8 to 4 on Duodart
  - Rpt MRI stable PIRADS 3
  - PSMA negative
  - Biopsy Stable 4/31 cores, low volume GG2, MCCL 1mm / 5%, 10% grade 4
- 2 years later
  - Continues on AS, PSA stable at 4.

PIAS example 6 – equiv MRI, neg PSMA

- 52yo, PSA 3.5, MRI PIRADS 3 diffuse
- Biopsy GG2 L Lat, 3mm, 1-2% grade 4

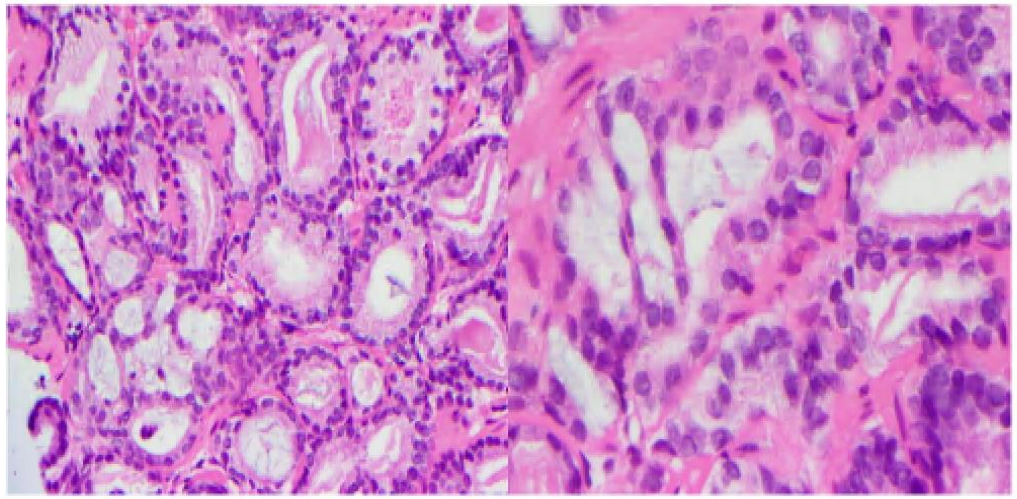
Composite Gleason Score (ISUP 2014):	3+4 = 7
% High Grade 4/5:	1%
Intraduct carcinoma:	Absent
Number of cores involved:	3
Total number of cores:	23
Perineural invasion:	Absent
Vascular infiltration:	Absent
Extra prostatic extension:	Absent

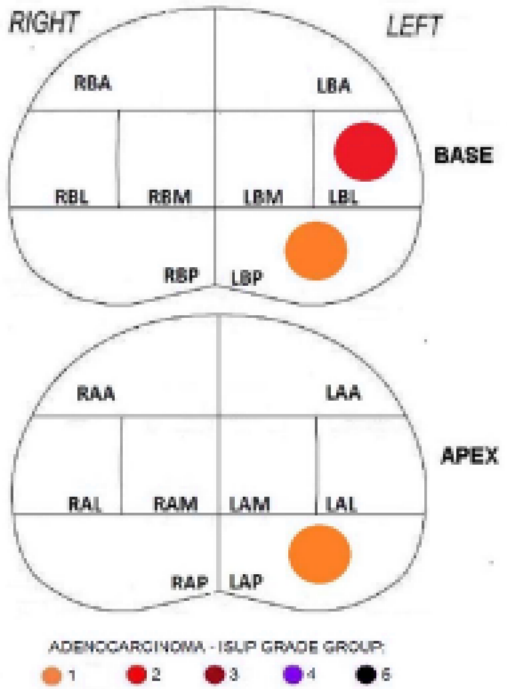
DIAGNOSIS:

PROSTATE BIOPSIES - **ADENOCARCINOMA**
- **GRADE GROUP 2**

Reported by A/Prof Jenny Turner (0298555481)

'Left base lateral'. Sections show adenocarcinoma, **Grade Group 2** (Gleason Score 3+4=7), with the percentage of high grade (pattern 4) being 2%. The carcinoma involves 20% (3 mm) of 1 core. Pattern 4 is represented by a single gland showing a complex, but not definitely cribriform, architecture across 2 of 3 levels. Professor Warick Delprado has seen the specimen, and agrees with Gleason score 3+4 = 7 with a tiny amount of pattern 4.





PIAS example 6 – equiv MRI, true neg PSMA

- 12 months later
  - PSA stable 3.5
  - MRI – improved to PIRADS 2
  - PSMA - normal
  - AS Bx – stable G3+4=7, 1/30 cores, 5mm length (30% of core), 5% g4

2 years later

- Continues on AS, with stable PSA

What about Genomics? DECIPHER

- Uses biopsy tissue to test 22 cell-cycle genes, generating a 'Decipher score'
  - Stratifies pts into risk groups to guide treatment decisions

    < 0.3 = low risk vs 0.3 - 0.6 = int risk vs > 0.6 = high risk

- Press et al UCSF (Eur Urol 2022)
  - 133 pts enrolled on AS, 76% GG1, 24% GG2, Decipher then surveillance biopsy
  - Higher Decipher "associated with" upgrading from GG1 to 2, but not GG2 to GG3-5;
  - AUC of predictive model improved from 0.63 to 0.69 (i.e. still poor)

- Herlemann et al (PCPD 2020)
  - 220 pts with favourable IR disease (GG2 or PSA 10-20 or cT2b-c) Tx'd with upfront RP
  - Decipher high-risk was "associated with" increased risk of AP (GG3-5, pT3b, LNI)
  - Median Decipher score was 0.38 in AP group vs 0.30 in non-AP group
  - AUC-ROC was again poor at 0.65

DECIPHER to predict adverse pathology

- Kim et al (PCPD 2018)
  - 266 pts (65% low-risk, 35% fav int-risk) underwent Decipher and upfront RP
  - 12% had adverse pathology (GG3-5 / pT3b / N1)
  - Decipher increased AUC-ROC *slightly* from 0.57 to 0.65
  - To predict AP (Spec 84%), high threshold required of 0.45
    - But 82% of pts were below 0.45
  - To exclude AP (Sens 88%), low threshold required of 0.2
    - But 67% of pts were above 0.2
- Conclusion:
  - Decipher has poor sens or spec depending on threshold
  - The definition of AP also neglects pT3a, PSMs or GG2

Sensitivity and specificity of Decipher risk thresholds for predicting AP in biopsy cohort

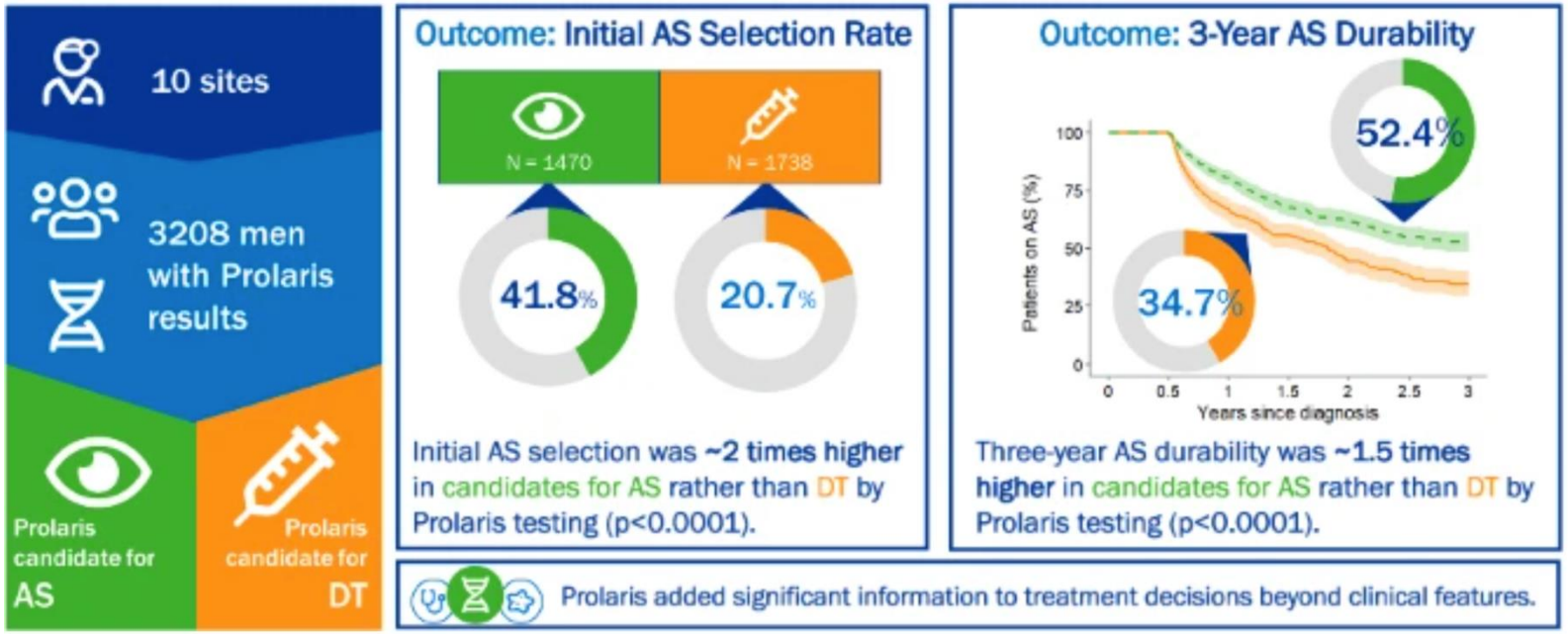
Cut point	Proportion (%)[a]	Sensitivity (95% CI)	Specificity (95% CI)
0.45	17.7	28% (16–45%)	84% (78–88%)
0.40	22.9	34% (20–52%)	79% (73–83%)
0.35	32.3	50% (34–66%)	70% (64–76%)
0.30	45.5	56% (39–72%)	56% (50–62%)
0.25	57.5	78% (61–89%)	45% (39–52%)
0.20	66.9	88% (72–95%)	36% (30–42%)

Open in a new tab

[a]Proportion of patients with Decipher score greater than the cut point

What about Genomics? PROLARIS (Lenz et al, PCPD 2024)

- A Panel of 31 cell cycle genes measured on biopsy tissue
  - Combined with CAPRA score to give a recommendation for AS vs Treatment
  - In 3200 pts across 10 centres:
    - 'Low-risk' PROLARIS score pts twice as likely to choose AS (40% chose AS) vs high-risk scores (20%)
    - Low-risk POLARIS score pts had better survival on AS at 3 years (52%) vs high-risk scores (35%)



Green = low-risk score
Orange = high-risk score

Conclusion: PROLARIS may improve selection for and survival on AS for IR pts

Take home points - Genomic tests in AS

- None currently available in Aus
- Expensive ($2,000)
- Most results (>50%) are equivocal ie ‘intermediate’
- Low utility (poor AUC) to guide binary treatment choices
- A ‘low-risk’ result is uncommon (20%) but ‘supports’ AS
- A ‘high-risk’ result is uncommon (10%) but ‘supports’ Active Tx
- Inferior to imaging (MRI/PSMA)
  - Doesn’t allow targeted biopsy to ‘find’ the Pca
  - Lower AUC/NPV/PPV
  - Never tested head to head against imaging
  - Probably even lower incremental utility when added to imaging

Take home points – How to do AS in 2024

- AS is standard of care for almost 100% of men with low-risk GG1

- Identify Low-risk men: PSA <10, Density <0.15, cT1c, GG1, <50% MCCV, <30% cores, no strong FHx
  - Low intensity AS with 6-monthly PSA, MRI at 1yr then 3 yearly, DRE yearly, Biopsy at 3 years then 3-5 yearly

- Identify Higher-risk men (not meeting low-risk criteria above)
  - Higher intensity AS with 3-monthly PSA, MRI 1 at year then ~2 yearly, DRE yearly, Biopsy at 1 year then 2 yearly
  - Add PSMA-PET within PIAS trial

- Threshold for treatment should be nuanced
  - Varies with age, co-morbidity, genetics, PSA kinetics, tumour large enough to be visible on MRI or PSMA, grade progression, volume of pattern 4 (total length not just %), volume of cancer (no. cores + and MCCL)

- Better AS tools improves AS safety and may reduce biopsy thus improves appeal

- **BUT** better focal therapy, robotic surgery & radiation has reduced QOL impacts of treatment
  - The average patient suitable for AS will also have excellent QOL with Nanoknife, bilateral NS RARP & MR-Linac RT
  - Tumour large enough to be visible on MRI or PSMA usually warrants Tx

Thank you!

Questions?