Management of intermediate-risk prostate cancer – the role of imaging

Focus on MRI

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Conflicts of interest 2022

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Siemens Healthineers
Receipt of honoraria or consultation fees	Siemens Healthineers
Participation in a company sponsored speaker's bureau	Siemens Healthineers
Stock shareholder	Lucida Medical

	Known cancer
	Intermediate risk
	PSA 10-20 or GS 7 (GG2 or GG3) or cT2b
Clinical state	Favorable subgroup suited for AS (EAU): GG2 patients with < 10% pattern 4, PSA <10 ng/mL, <cT2a, low disease extent on MRI and low biopsy extent Unfavorable subgroup: Gleason GG3 and/or >50% positive biopsies and/or >1 intermediate risk factors
Role of imaging in promoting therapy	**Define adverse/non-adverse features that enable allow appropriate Rx triage** **If initial AS is considered, then it is important not to underestimate tumor grade/volume/stage** **For EBRT, the presence of unfavorable disease affects duration of adjuvant hormonal Rx** **For focal therapy, index lesion localization/volume is needed** **For surgery, accurate staging enables curative treatment with negative margins & nerve sparing if possible**

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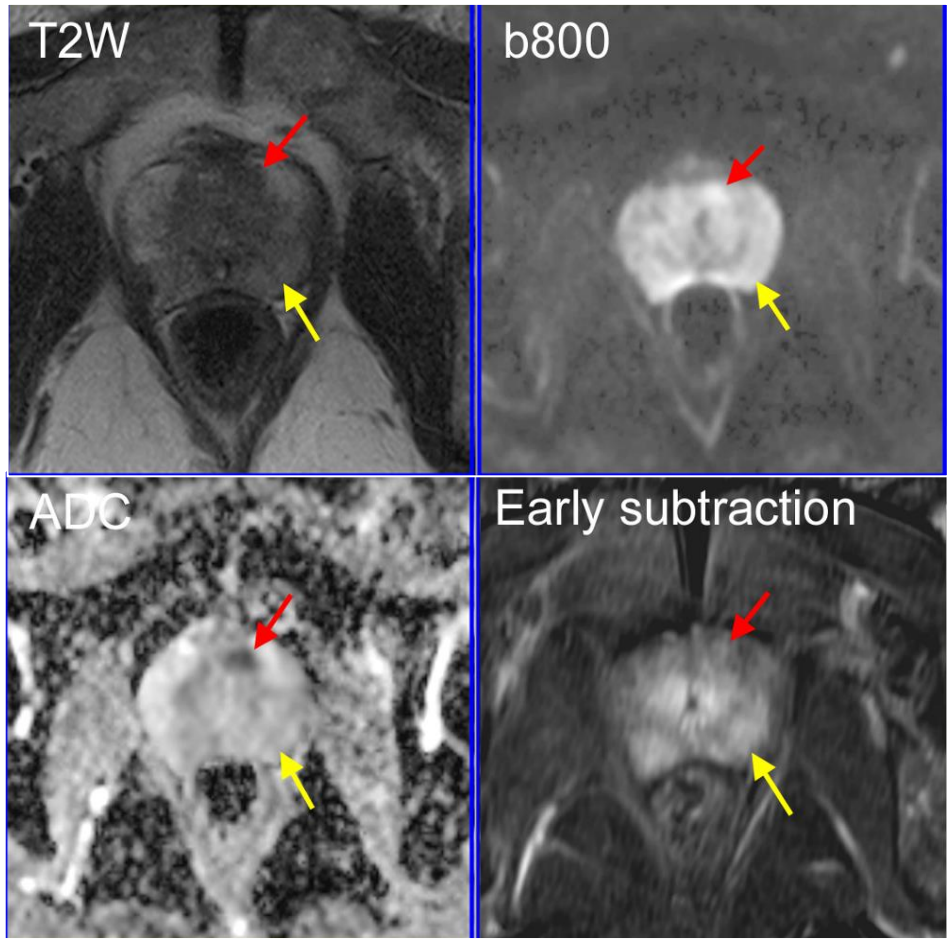
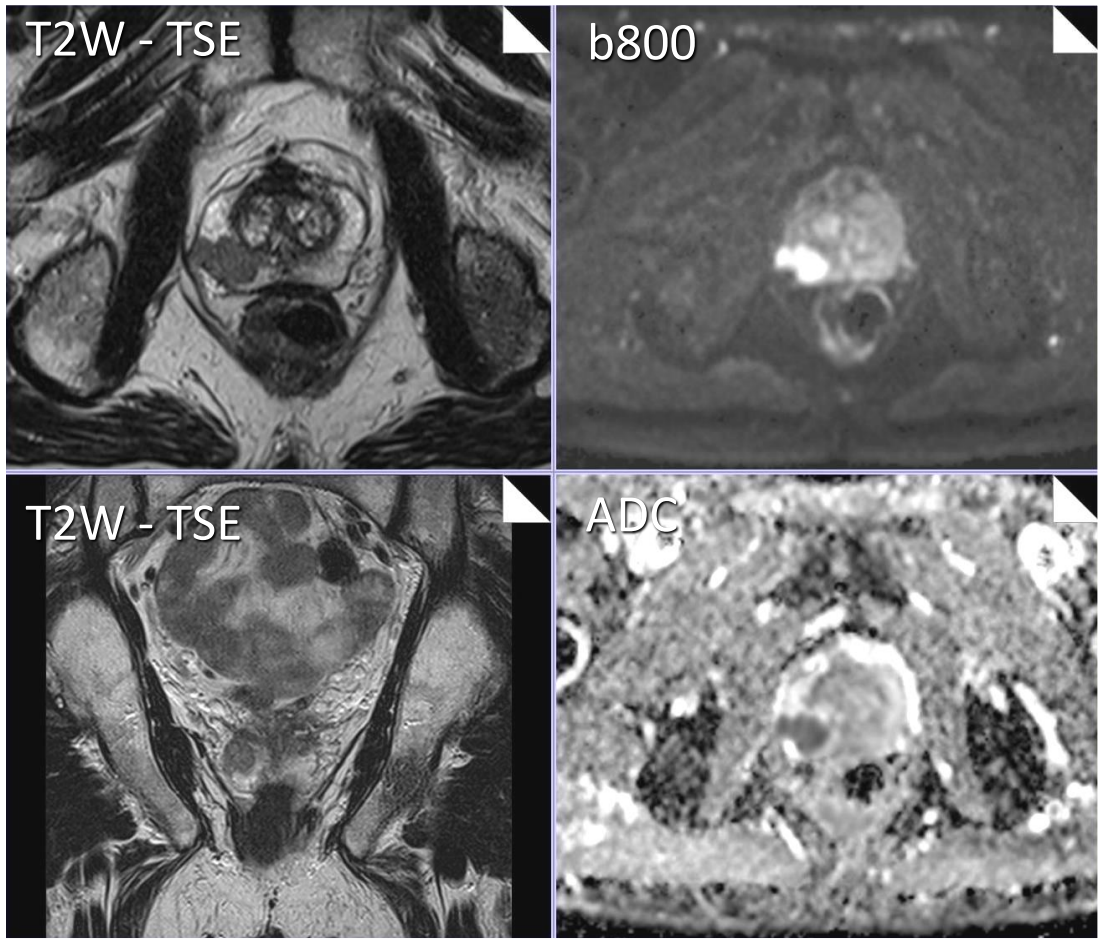
Intermediate risk: impactful MRI features

No adverse features



67yo. GI 3+4; PSA 5.9 ng/ml

Adverse features present



75yo. GI 4+3; PSA 18 ng/ml

Intermediate risk: impactful MRI features

Non-adverse MRI

- Non-visible lesion (PI-RADS 1-2)
- ADC >1000 $\mu m^2/s$
- Tumor contact length $\leq$10mm
- Intraprostatic lesion with no capsule abutment
- Tumor away from capsule and sphincter
- No SVI/EPE

Adverse MRI

- Higher PI-RADS scores ((3)4-5)
- Low ADC <800 $\mu m^2/s$
- Tumor capsule contact length >15mm
- SVI/EPE +
- Posterior-lateral lesions – large lesions against the capsule
- Tumor proximity to sphincter
- Multiple lesions, and >2 adverse features

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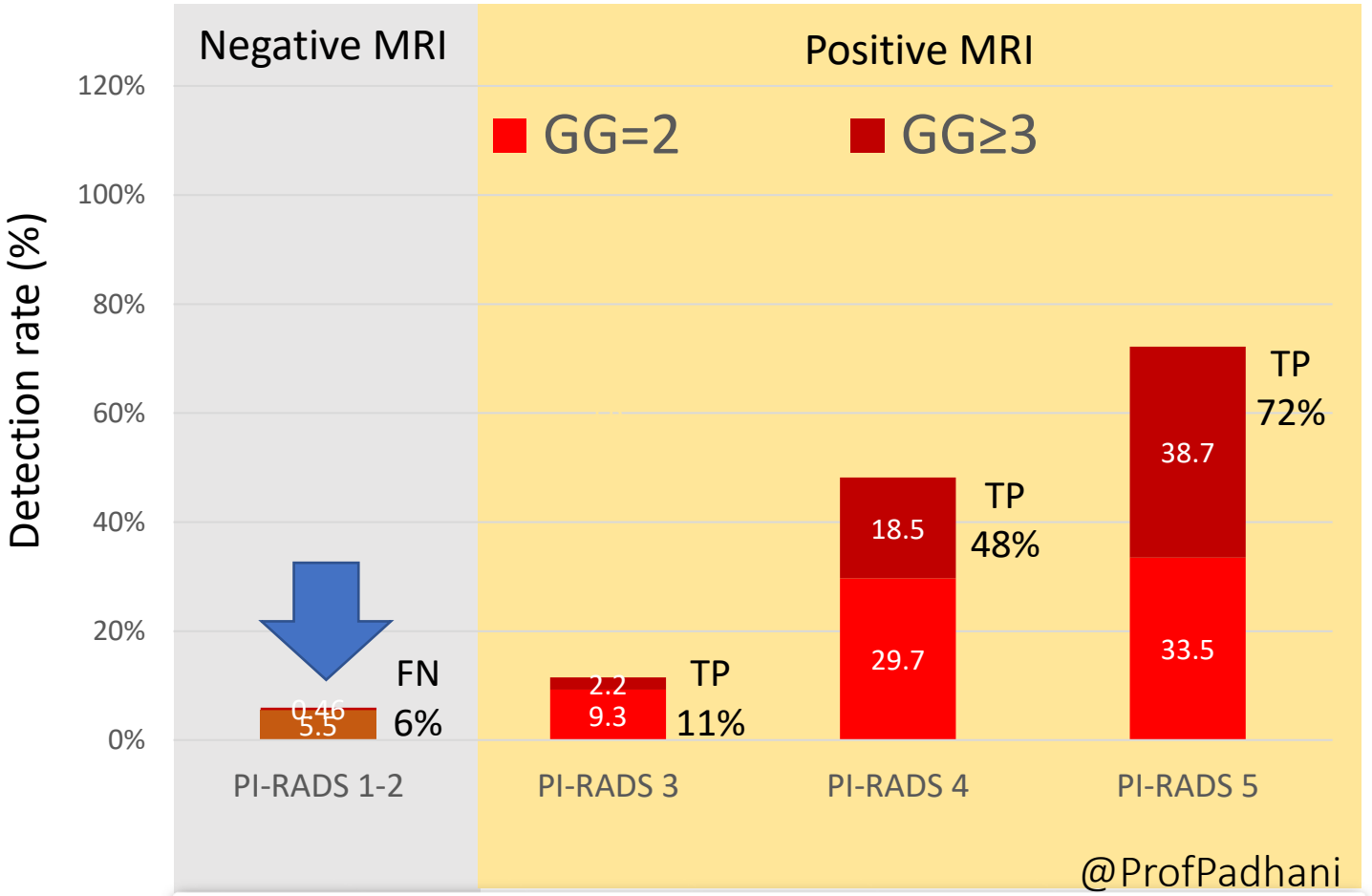
Detection rates of significant cancers (GG ≥2) according to PI-RADS v2 lesion categories

Lesion-based analysis

13 studies 1738 patients
mixed population
including AS
2462 lesions on bp/mp studies

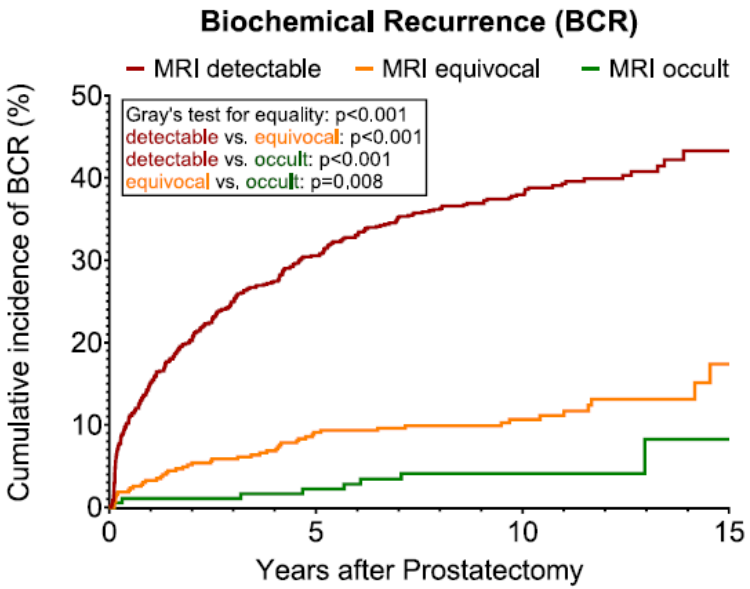
Barkovich EJ, et al. A Systematic Review of the PI-RADSv2 Literature and Subset Meta-Analysis of PI-RADSv2 Categories Stratified by Gleason Scores. AJR Am J Roentgenol. 2019; 212(4):847-854.

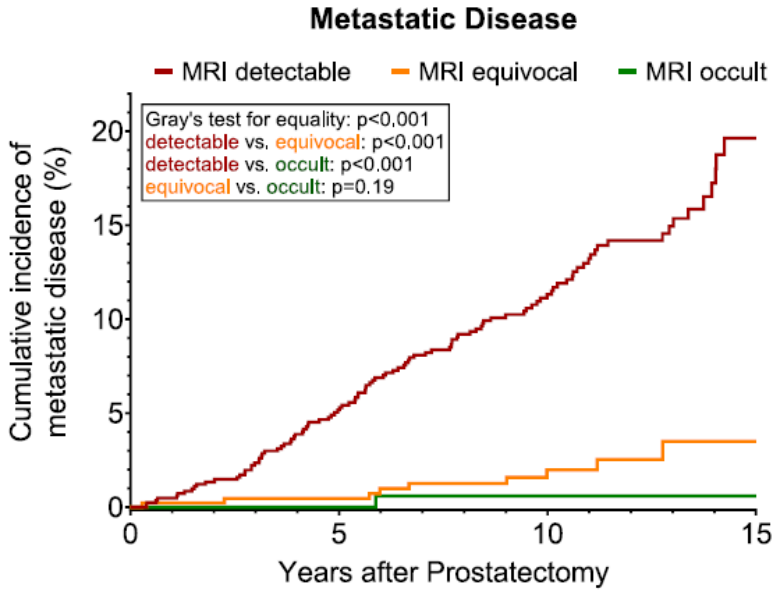
Men with negative MRI 0.5% prevalence of having undiagnosed GG≥3

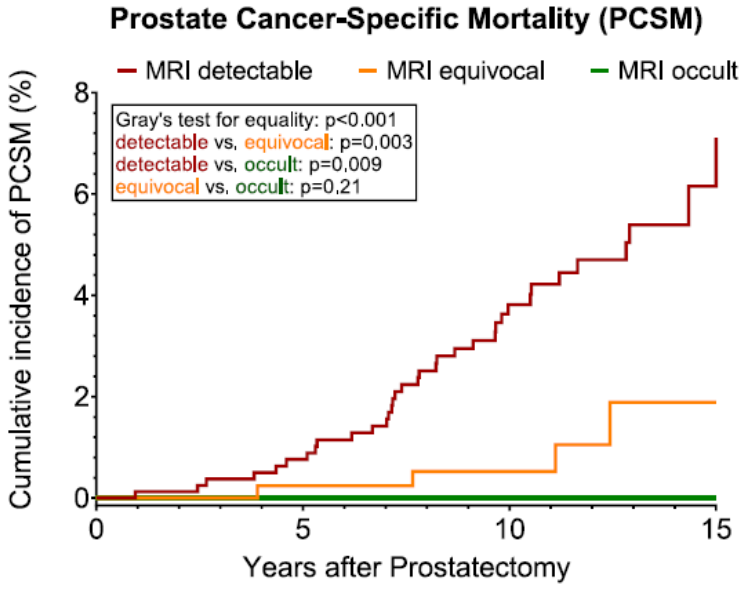


PI-RADS category is a diagnostic BM for csPCa (GG≥2) and potential prognostic BM (GG≥3)

•. 2022 Aug;20(4):319-325.







T2W-MRI occult cancers are less likely to recur biochemically (8% vs. 43%, P < .001), metastasize (0.6% vs. 20%, P < .001), or lead to prostate cancer mortality (0% vs. 7%, P < .001) than MRI-detectable cancers

PI-RADS T2W category a prognostic biomarker for localized prostate cancer undergoing prostatectomy

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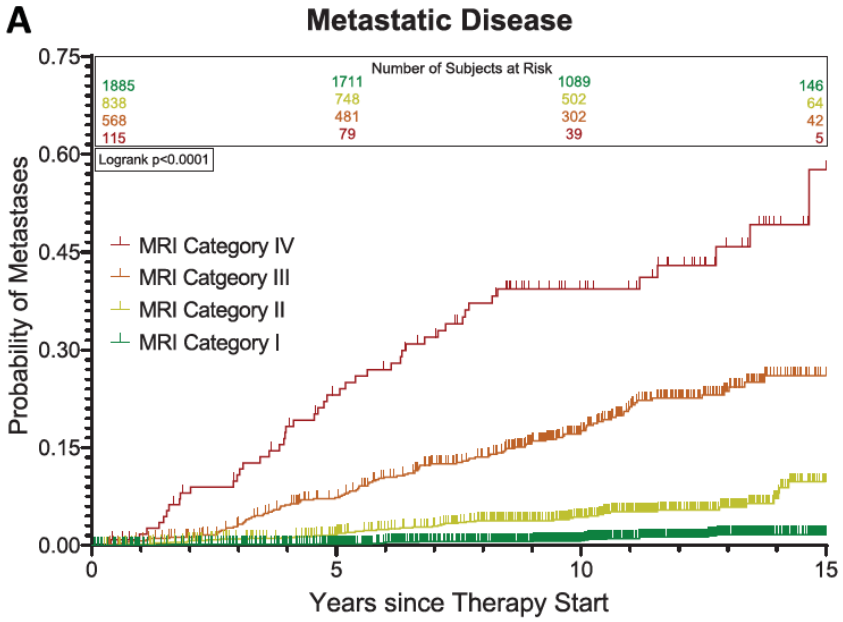
Wibmer AG, et al. MRI-Detectability of Clinically Significant Prostate Cancer Relates to Oncologic Outcomes After Prostatectomy. Clin Genitourin Cancer. 2022 Apr 14: Clin Genitourin Cancer 2022 Aug;20(4):319-325.



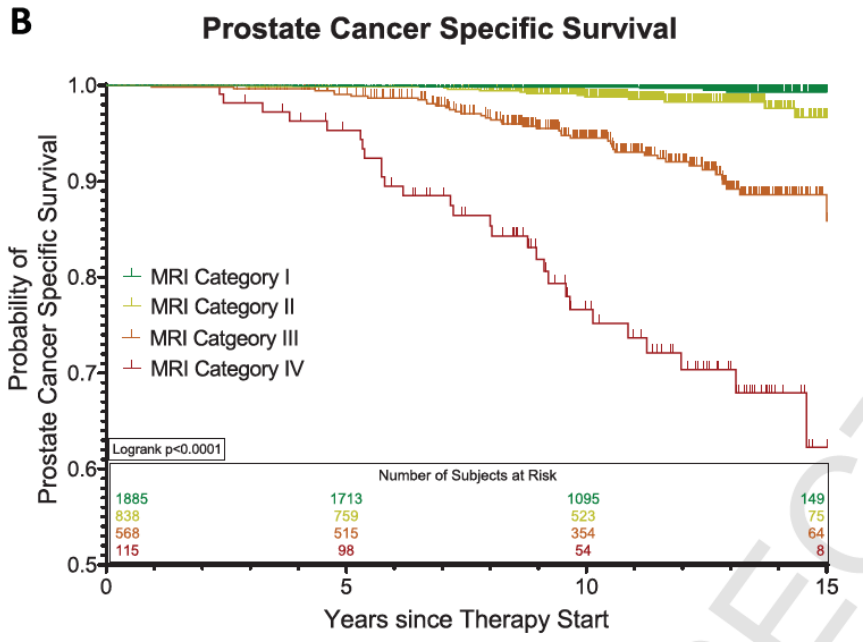


Table 1. *Description of the four MRI categories*

MRI Category	Description
I	No focal suspicious lesion
II	Organ-confined suspicious lesion
III	Suspicious lesion with EPE, no SVI
IV	Suspicious lesion with EPE and SVI

In men with localised intermediate & high-risk disease, the visibility of cancer signifies a more aggressive phenotype, as does extra-prostate disease for both surgical and radiation-treated patients

Morphological MRI is a prognostic biomarker for localized IR/HR prostate cancer undergoing radical Rx

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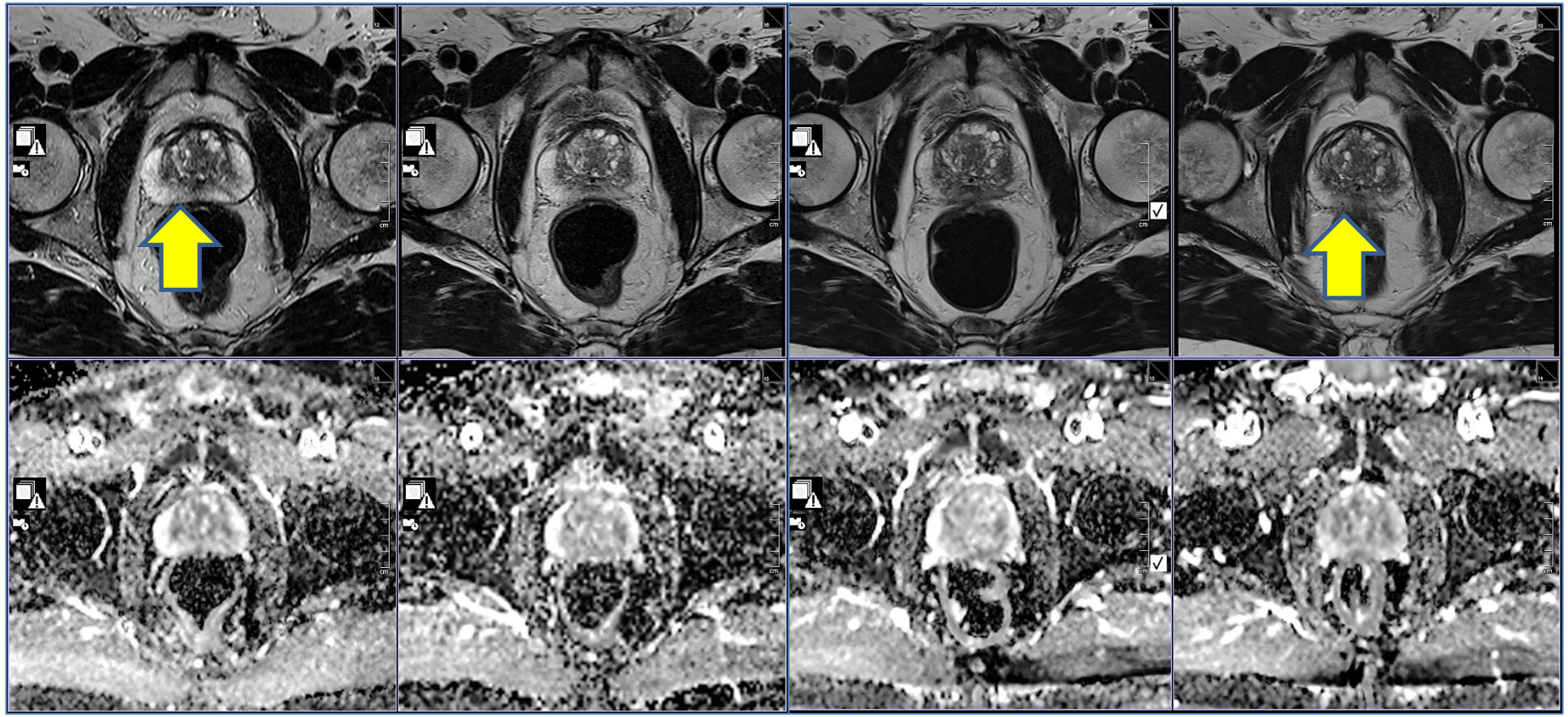
Wibmer AG, et al. Oncologic Outcomes after Localized Prostate Cancer Treatment: Associations with Pretreatment Prostate MRI Findings. J Urol. 2021; 205(4):1055-1062

Intermediate risk because of high PSA & bilateral disease: suitable for an initial trial of AS?



12Jun13
19 ng/ml
GG=1 (Rt+Lt)

19Nov14
16 ng/ml

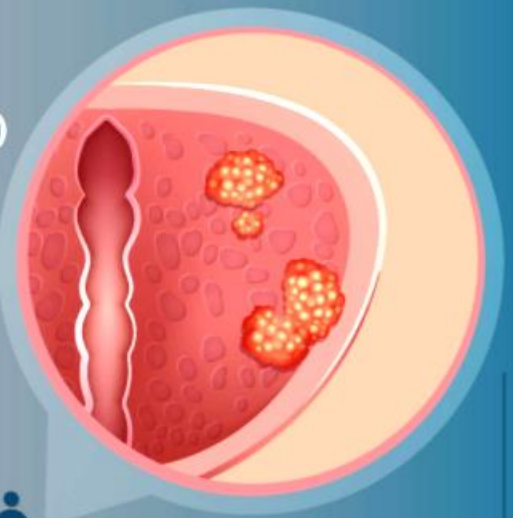
26Nov16
21.7 ng/ml

25Jan17
24.9 ng/ml
GG=2 (Rt & Lt)

→ HDR brachytherapy

Can Magnetic Resonance Imaging Play a Role in Selecting Patients for Active Surveillance in Favorable Risk Prostate Cancer?

Men diagnosed with favorable risk Grade Group 2 (GG2) prostate cancer are considered candidates for active surveillance (AS)



However, identifying patients with GG2 prostate cancer who can be safely managed with AS is controversial

To aid selection for AS, this study evaluated the association of multiparametric magnetic resonance imaging (mpMRI) with adverse pathology results in favorable risk GG2 disease

Retrospective cohort study

1,117 men with favorable risk GG2 disease who underwent radical prostatectomy (RP)

- Preoperative mpMRI (Predictor)
- Pathology assessment on RP tissue sample (Outcome)

→ Multivariable logistic regression modelling

Positive mpMRI

- T3a/b LN+ → Higher rates of adverse pathology (Odds ratio 2.55)
- GG≥3 → Disease upgrading (Odds ratio 3.89)

Adding mpMRI results to prediction model → Benefit on decision curve analysis

Addition of mpMRI increases the prediction accuracy of prostate cancer risk in patients with favorable GG2 disease

Stonier T, et al. Selecting Patients with Favorable Risk, Grade Group 2 Prostate Cancer for Active Surveillance-Does MRI Have a Role? J Urol. 2021; 205(4):1063-1068.

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Can Magnetic Resonance Imaging Play a Role in Selecting Patients for Active Surveillance in Favorable Risk Prostate Cancer?

For men with GG2 MRI 'visible' or 'not visible' is important

(1) Absence of index lesion on MRI in GG2 patients allows identification of a subgroup (8-12%) who become downgraded to GG1 at prostatectomy (Gondo 2014)

(2) GG2 patients with PI-RADS 4 or PI-RADS 5 lesions should not undergo an initial trial of Active Surveillance (Woo 2016, Perera 2017; Faiena 2019, Stonier 2021)

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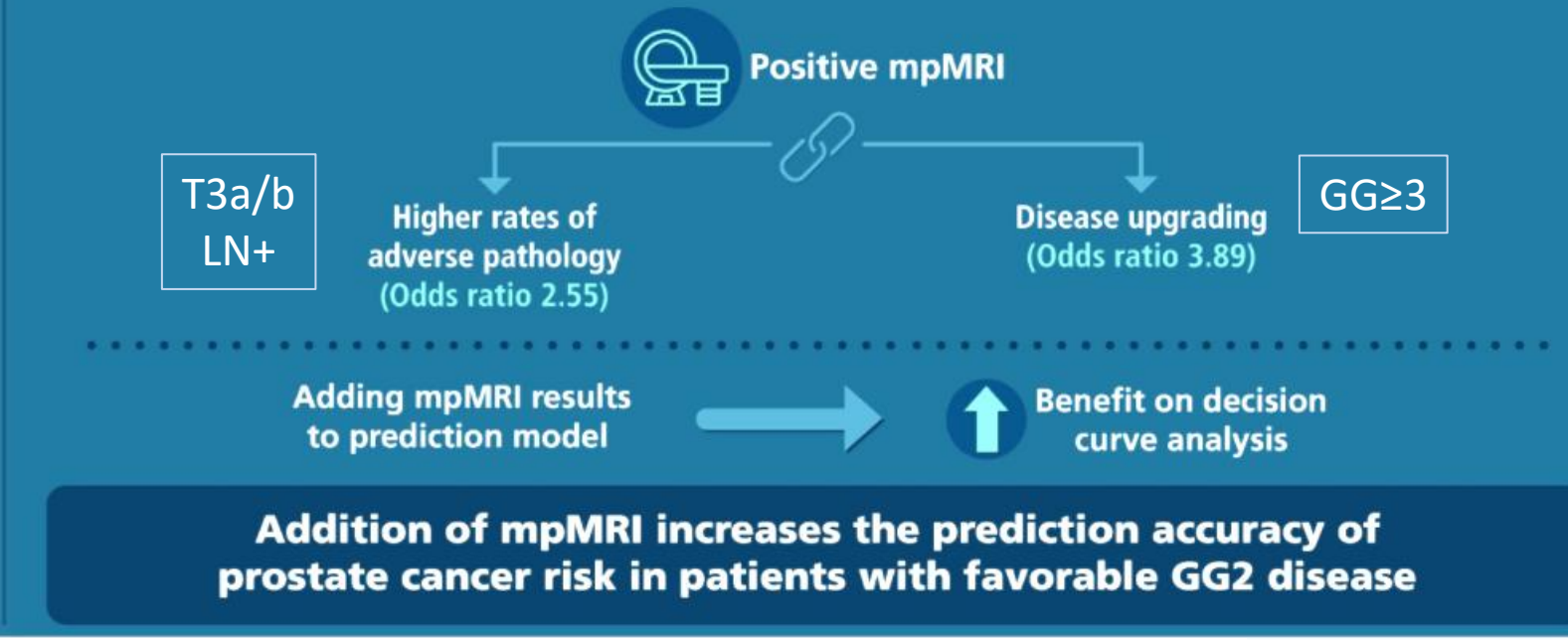

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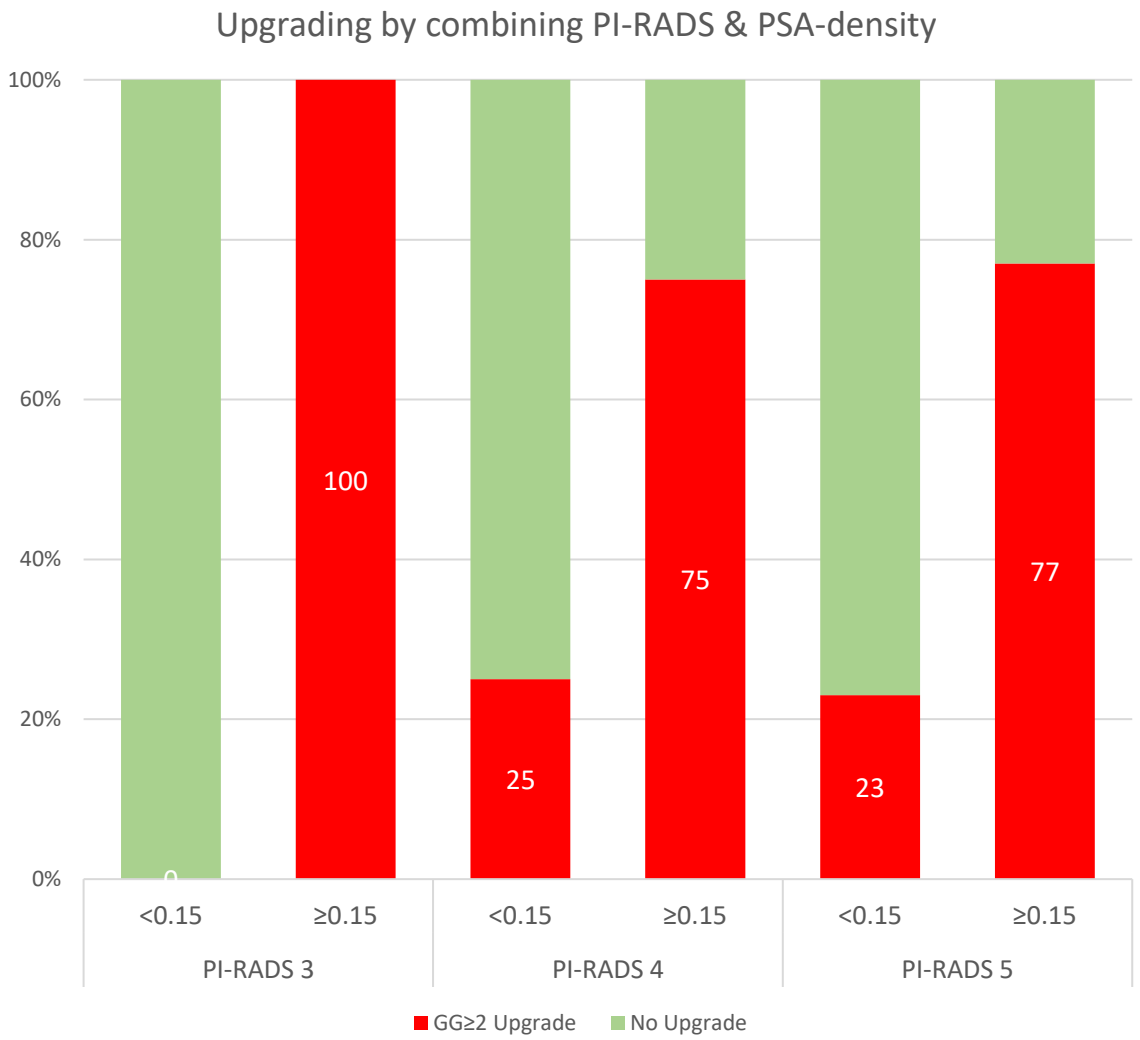
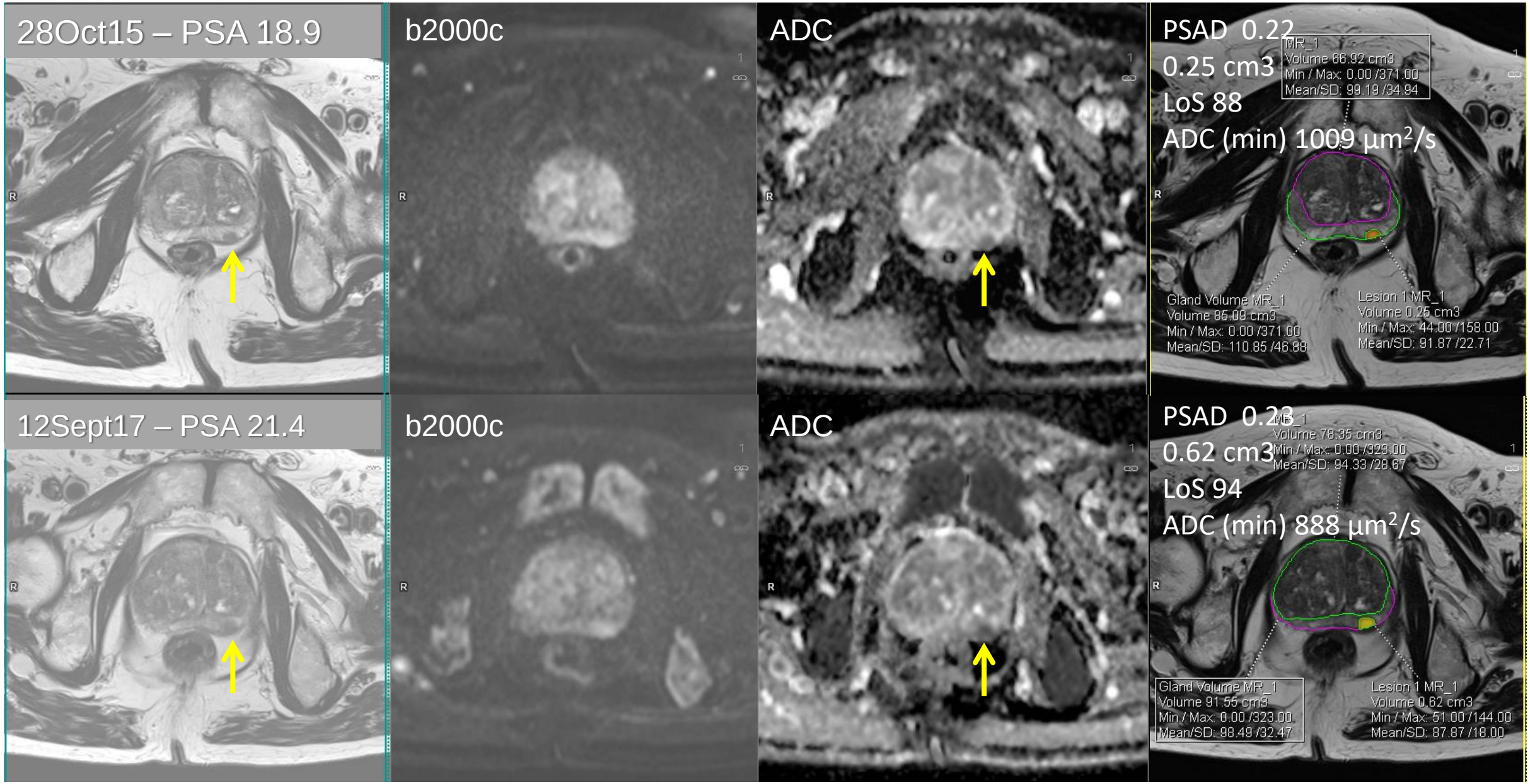
Most AS patients with positive MRI and high PSAD are upgraded by MRI-directed biopsy

- Prospective MRI-PRIAS study in TRUS diagnosed low risk-men
- 60% (198/331) had PI-RADS 3-5 lesions
  - 41% of positive MRI upgraded by MR-directed biopsy
- Upgrading by PI-RADS: P3 = 30%; P4 = 34%; P5 = 66%
- Upgrading by PSAD: <0.15 = 20%; ≥0.15 = 80%
- PI-RADS 3 lesions with PSAD <0.15 did not have any upgrades



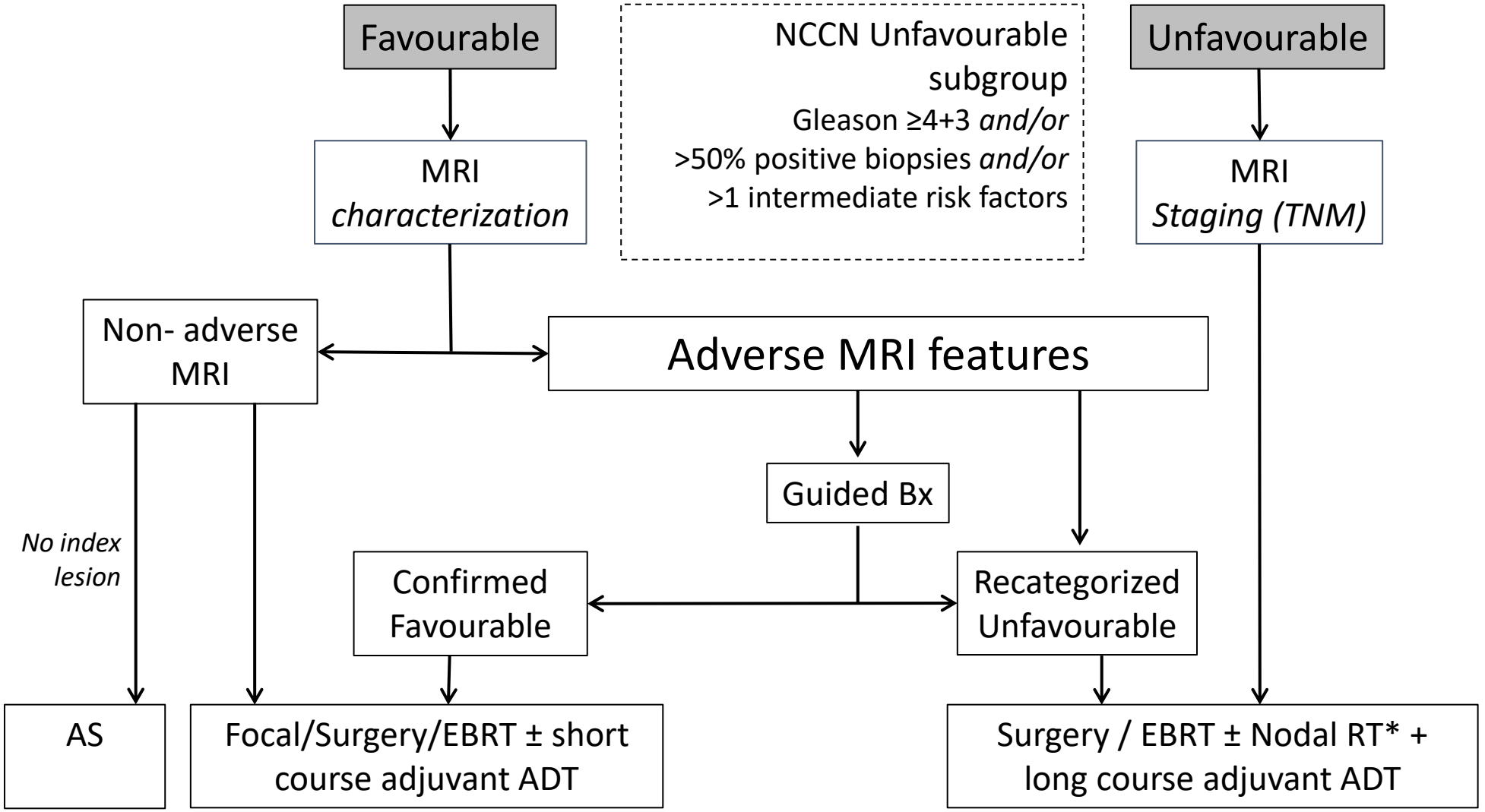
Schoots IG, et al. Reduction of MRI-targeted biopsies in men with low-risk prostate cancer on active surveillance by stratifying to PI-RADS and PSA-density, with different thresholds for significant disease. Transl Androl Urol. 2018; 7(1):132-144.

66 yrs. intermediate-risk on AS. TRUS biopsy Lt: GG=2 in 1/7 core; Rt: 0/6



Personalizing Rx of intermediate risk patients with MRI

*(*PSA 10–20 ng/mL, *and/or* Gleason score 7, *and/or* clinical stage T2b or T2c*)*



Adverse MRI

- High PI-RADS scores
- Low ADC <800 $\mu m^2/s$
- Tumor capsule contact length >15mm
- SVI+/EPE+
- Posterior-lateral lesions – large lesions against the capsule
- Tumor approximating to sphincter
- Multiple (>2) adverse features

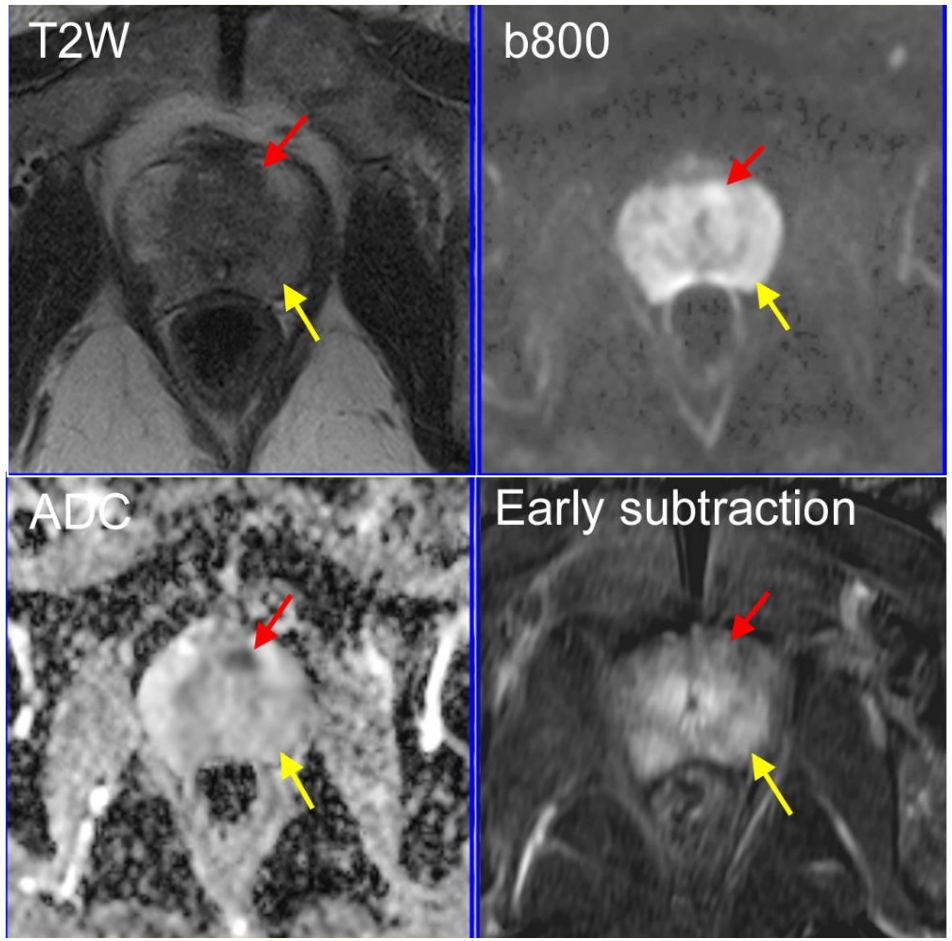
Non-adverse MRI

- Low PI-RADS scores (1-3)
- ADC >1000 $\mu m^2/s$
- Tumor contact length ≤10mm
- No SVI/EPE
- Intraprostatic lesion with no capsule abutment
- Tumor away from capsule and sphincters

D'Amico AV. Euro Urol 2013; 64:903-4; *use of nodal irradiation depends on risk of nodal disease

Intermediate risk: impactful MRI features

No adverse features



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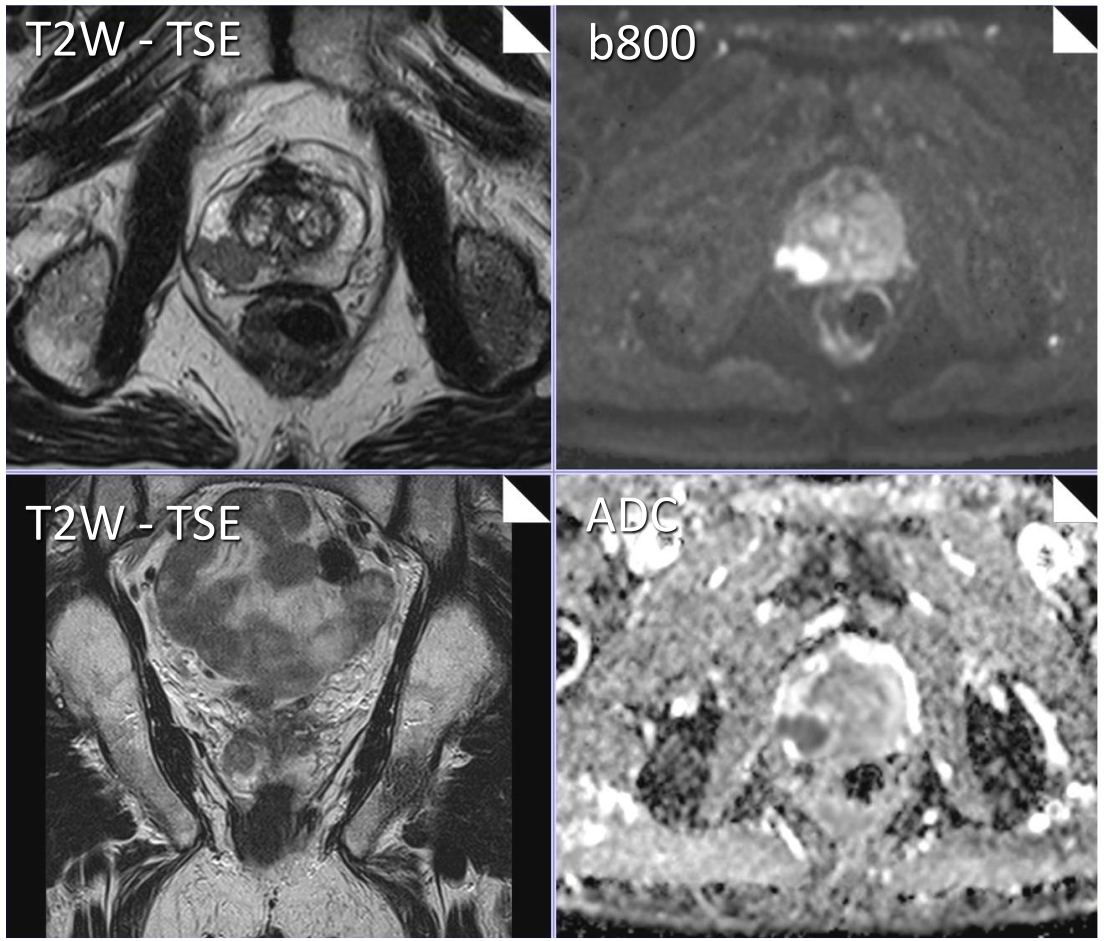
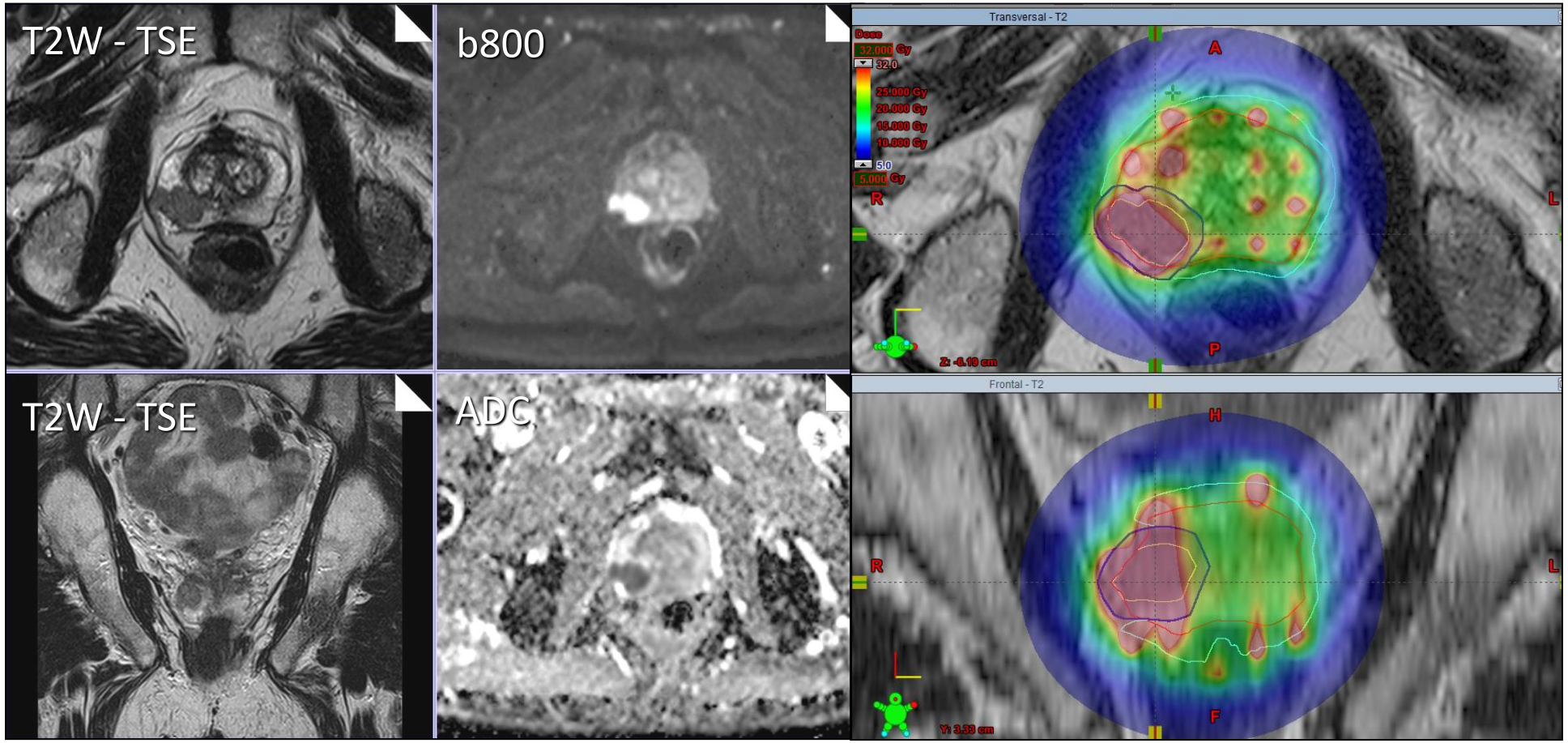


75yo. GI 4+3; PSA 18 ng/ml

HDR brachytherapy with boost + 6/12 of ADT (Intermediate risk: unfavorable group with adverse MRI)



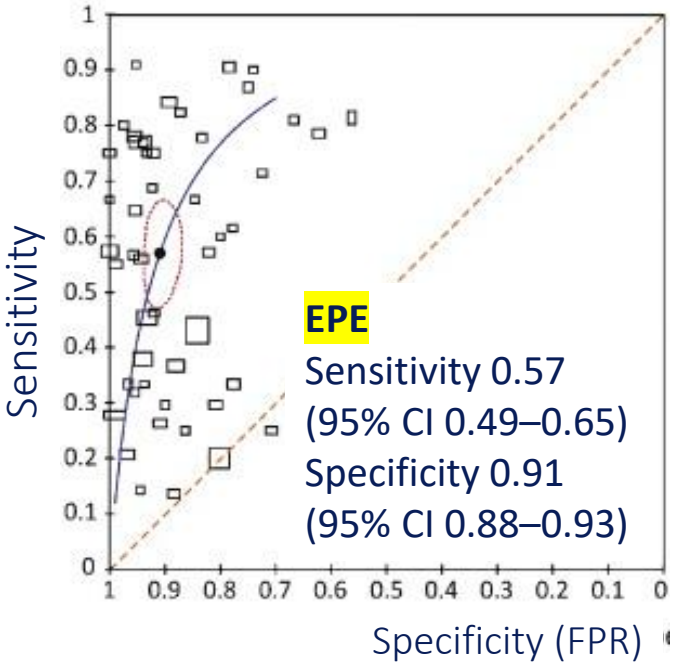
75yo. Gl 4+3; PSA18; N0; M0

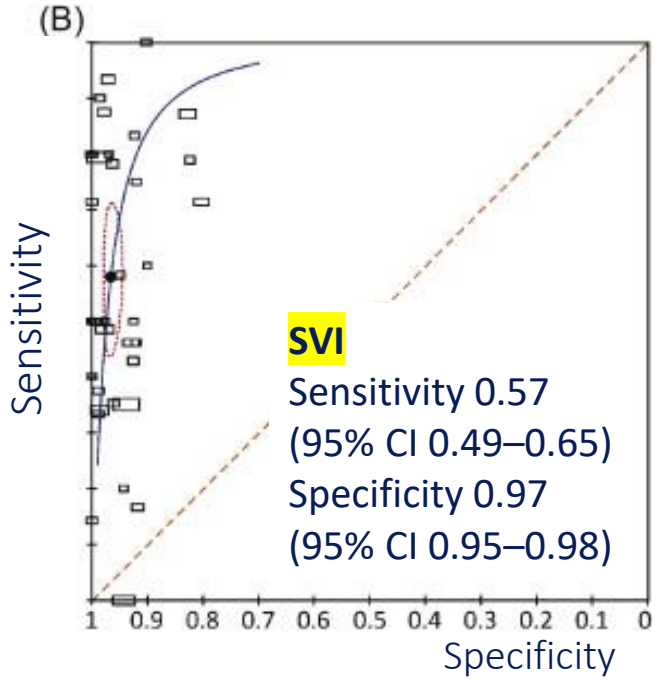
Courtesy of Roberto Alonzi, MVCC, London

	Known cancer
	Intermediate risk
Clinical state	PSA 10-20 or GS 7 (GG2 or GG3) or cT2b Favorable subgroup: GG2 patients with < 10% pattern 4, PSA <10 ng/mL, <cT2a, low disease extent on MRI and low biopsy extent* Unfavorable subgroup: Gleason GG3 and/or >50% positive biopsies and/or >1 intermediate risk factors
Role of imaging in promoting therapy	Define adverse/non-adverse features that allow appropriate Rx If initial AS is considered, then it is important not to underestimate tumor grade/volume/stage For EBRT, the presence of unfavorable disease affects duration of adjuvant hormonal Rx For focal therapy, index lesion localization/volume is needed **For surgery, accurate staging enables curative treatment with negative margins & nerve sparing if possible**

Extraprostatic disease, what's the MRI performance?

- When an average radiologist says that EPE is present; they are very likely to be correct (high-specificity), and the information should be acted on accordingly
- When an average radiologist says that there is no EPE; viewed this with some doubt (microscopic disease not seen). Act on according to the radiologist's expertise & the management plan





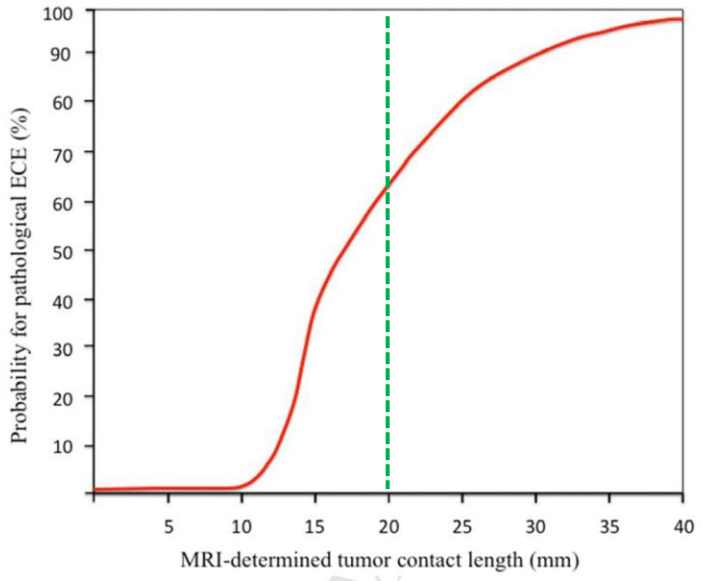
de Rooij M, et al. Accuracy of MRI for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol. 2016; 70:233-45
Padhani AR, at el. Finding Minimal Extraprostatic Disease: Who Cares? Eur Urol. 2016; 70:246-7

Improving MRI performance for EPE

- Additional MRI features
  - Tumor-capsule contact length*
  - PI-RADS scores
  - ESUR EPE feature score
  - NCI EPE score
- Multivariate models
  - Multiple MRI features
  - Combined clinical and MRI features
- LIKERT impressions

*Kim TH, et al The Diagnostic Performance of the Length of Tumor Capsular Contact on MRI for Detecting Prostate Cancer Extraprostatic Extension: A Systematic Review and Meta-Analysis. Korean J Radiol. 2020 Jun;21(6):684-694. doi:

- MRI tumor contact length (TCL) good at predicting microscopic EPE
  - TCL ≥20 mm > conventional MRI criteria for predicting microscopic EPE (82% versus 67%, p=0.015) [3]



Baco, E, et al. J Urology 2015; 193:466-72;

Tumor capsule contact length - prognosis

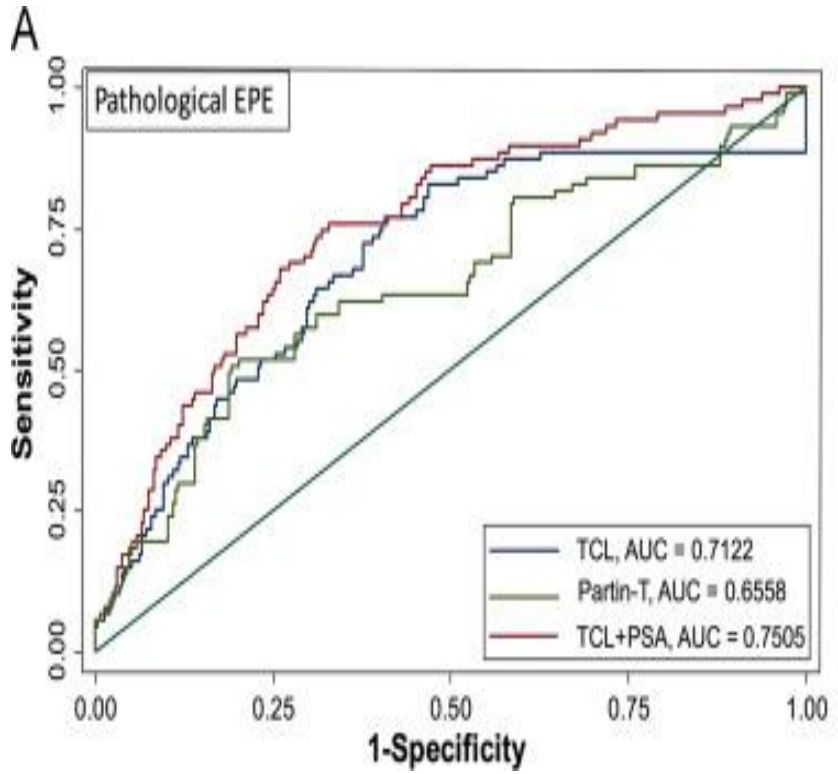


Fig. 2. Receiver operating characteristics (ROCs) curves and areas under the curves (AUCs) of Partin tables (Partin-T), MRI determined tumor contact length (MRI-TCL), and MRI-TCL+PSA to predict the presence of pathological extraprostatic extension

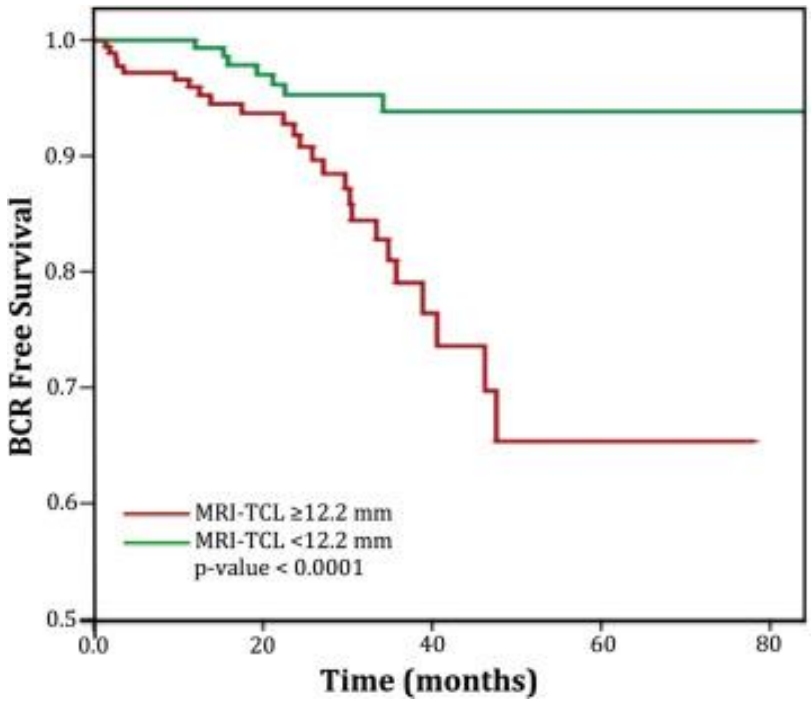
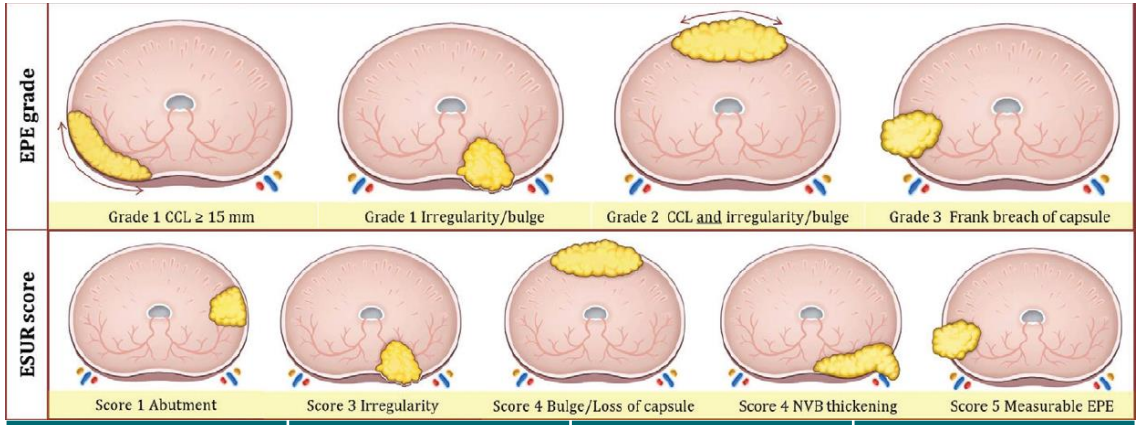


Fig. 3. Kaplan-Meir curves showing biochemical recurrence (BCR)–free survival between 2 groups of patients separated by the median tumor contact length (12.2 mm) of BCR cohort.

Kongnyuy M, et al. Tumor contact with prostate capsule on MRI: A potential biomarker for staging and prognosis. Urol Oncol. 2017 Jan;35(1):30.e1-30.e8..

Efforts to improve T staging by MRI

- 301 pts, MRI & RP[1]
  - Four MRI-based criteria
    - Only relying on imaging
      - SE ↑ but SP↓
    - SE & SP analyses
      - Not clinically meaningful
- Urologists & radiation oncologists
  - Want to know a patient's likelihood of having EPE before prostatectomy or RT on *individual basis*
  - More interesting in predictive values which depend on risk category!



		SE (%)	SP (%)
EPE grade	Reader 1	77.5	70.9
	Reader 2	79.8	75.0
ESUR score	Reader 1	75.2	75.6
	Reader 2	70.5	76.2
Likert scale	Reader 1	68.2	76.2
	Reader 2	72.1	76.2
CCL	Reader 1	73.6	75.6
	Reader 2	82.2	76.7

1. Park KJ et al. Radiology. 2020 Jul;296(1):87-95.

Adverse pathology by risk groups

- Low risk (n=1454), favorable IR (n=250) and unfavorable IR (n=1362) underwent radical prostatectomy
- Adverse pathology defined as ISUP Grade Group III-V, EPE, nodal disease was found in
  - Low-risk (14.8%)
  - Favorable IR (27.4%)
  - Unfavorable IR (48.5%) p <0.001

Nerve sparing surgery

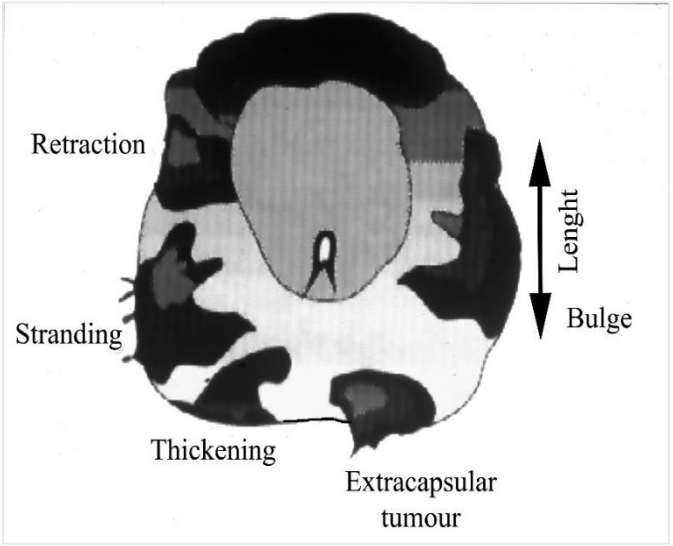
R0 resection; NS if possible

Aghazadeh MA, et al. NCCN Favorable Intermediate Risk Prostate Cancer Patients: Is Active Surveillance AppropriateJ Urol. 2018 May;199(5):1196-1201

Surgery for intermediate risk (unfavourable) disease

- Surgical strategy: negative margins with nerve sparing (if possible)
- EPE prevalence: 30-50%
- Use less strict criteria on index lesion - in order to reduce margin positive rates[2]
- Per-operative MRI index lesion localization and staging alone may not be enough to decrease positive margins in larger volume disease[3]

ESUR (2012) criteria for T3a disease		
Criteria	Findings	Score
EPE; T3a	Abutment	1
	Irregularity of capsule	3
	Neurovascular bundle thickening	4
	Bulge, loss of capsular outline	4
	Measurable extra-capsular disease	5



[1]Somford DM, J Urol 2013; 190:1728-34; Barentsz JO, Eur Radiol. 2012; 22:746-57; [2]Cornud F, Curr Urol Rep. 2012; 13:82-92; [3]Rud E, et al. Euro Urol 2015; 68:487-496.

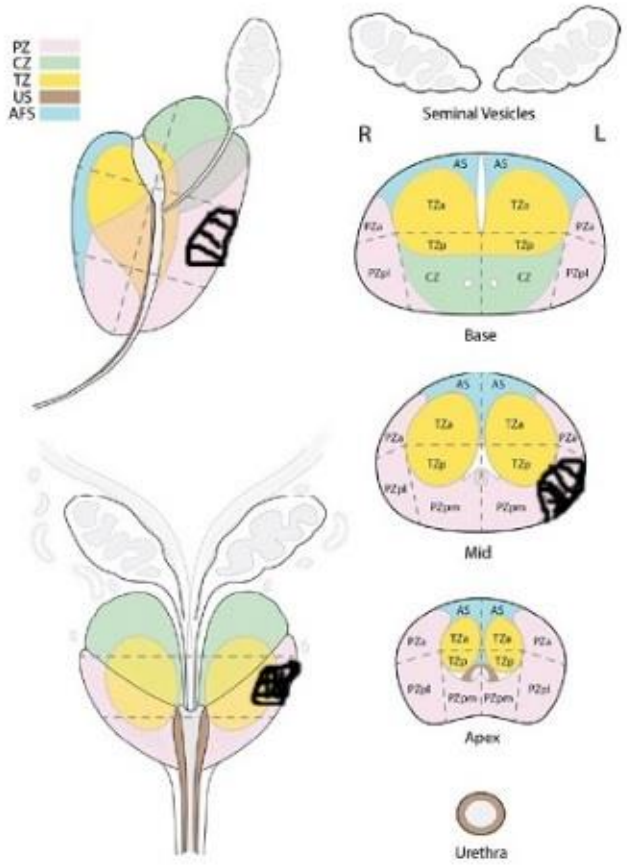
Does MRI result in better nerve sparing @ robotic prostate surgery?

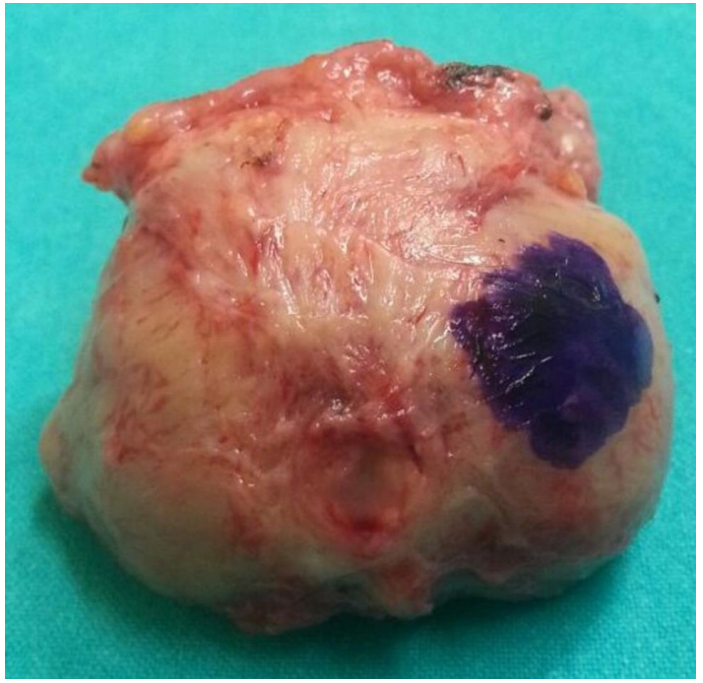
	Rud 2015		Petralia 2015	
	Randomized control study		Case control study	
	No MRI	MRI	No MRI No IFS	MRI+ IFS
Patients	216	222		
PSM	23%	19%		
NS procedures	144	140	134	134
PSM	19.4%	15%	18.7%	7.5%

DWI = diffusion MRI, IFS = intra-operative frozen section analysis at location of MRI index lesion location with re-resections of surgical positive margins, PSM = positive surgical margins, NS = unilateral or bilateral nerve sparing

Rud E. et al. Eur Urol 2015; 68:487-496
Petralia G. et al. Radiology. 2015; 274:434-444

MRI-directed intra-operative frozen section analysis to ensure R0 resections





IEO procedure

- Gross examination, inking and sampling

- Specimen orientation, inclusion and freezing

- 268 pts nerve sparing robotic assisted radical prostatectomy
  - 134 MRI + intra-operative frozen section evaluations
  - 134 controls
- PSM rate from 18.7% to 7.5% (P=.01)

Petralia G. et al. Radiology. 2015 Feb;274(2):434-44

Summary: MRI supports patient management in favorable and unfavorable intermediate-risk disease

MANAGEMENT PLAN	MRI FAVORABLE IR GROUP	MRI UNFAVORABLE IR/HR GROUP
Watchful waiting	Helps identify complications	Helps identify complications
Active surveillance	Confirms deferred Rx option*	Not recommended
Prostatectomy		
• Strategy	Promotes NS + R0	Enables R0 ± NS if possible
• PLND (5% risk threshold)**	If low risk; negative nodal MRI can help avoid surgery	Encourages limited → extended PLND if suspicious on MRI
Radiotherapy		
• Adjuvant ADT***	Supports absent or short course	Supports long course Rx
• Pelvic nodal RT (15% risk threshold)[$]	Standard fields if N0 on MRI	Encourage boost RT to regions at higher risk
Focal therapy	Organ sparing - e.g., HIFU	Whole organ RT ± focal boost

Take home points

MRI directs patient management by contributing to staging assessments

MRI identifies adverse features helping to improve AS patient selections by minimizing the inclusion of higher-risk patients

EPE assessments are impaired in low-volume disease because MRI does not see microscopic disease

Imaging staging accuracy can be improved with knowledge of the likelihood of EPE involvement (prevalence is risk group dependent)

MRI interpretations need to be aligned with clinical management plans (MDT discussions)

Effective communication of imaging findings/ uncertainties can improve the outcomes for men with intermediate-risk prostate cancer

Twitter: @Profpadhani
Youtube: anwar padhani

Be impartial → take an unbiased view of the facts and avoid the pitfalls of group thinking, railroading, filtering, compromising

Innovate → work together to introduce new creative thinking to address challenges and make changes for the betterment of patients

Insightful → develop more accurate and deeper understanding, based on analyses of the facts, experience and intuition, that sees things beyond the present