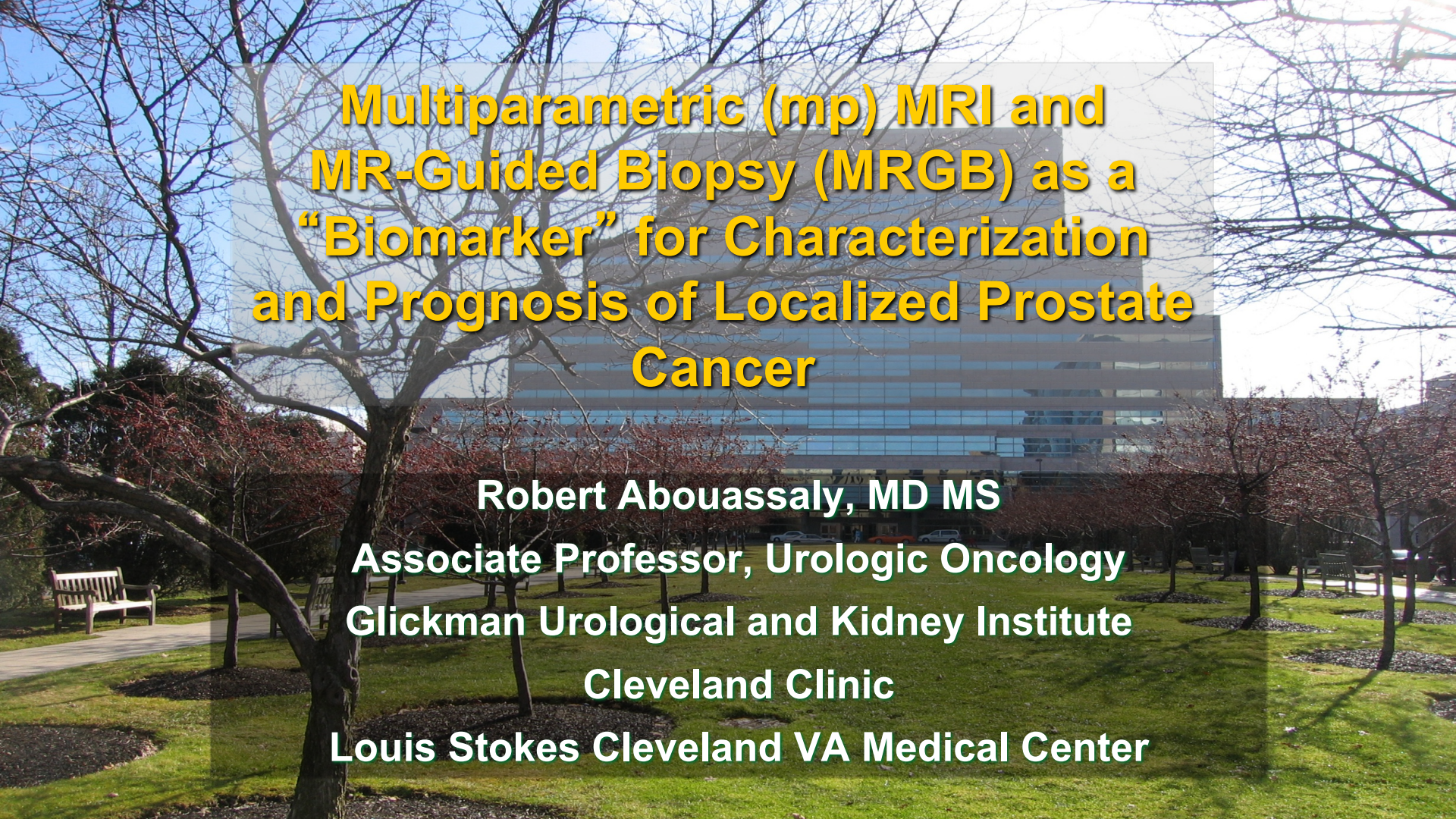

Multiparametric (mp) MRI and MR-Guided Biopsy (MRGB) as a "Biomarker" for Characterization and Prognosis of Localized Prostate Cancer

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Strategies to Reduce Over Diagnosis and Treatment

1. Screening: intelligent use of PSA
2. Improved detection of important cancers and avoidance of unimportant cancers
3. Accurate characterization of cancer's biologic potential
4. Reduce unnecessary biopsy
5. Surveillance for low-risk and select intermediate- and high-risk patients

   Enhanced biopsy strategies may impact #2, #3, #4, and #5

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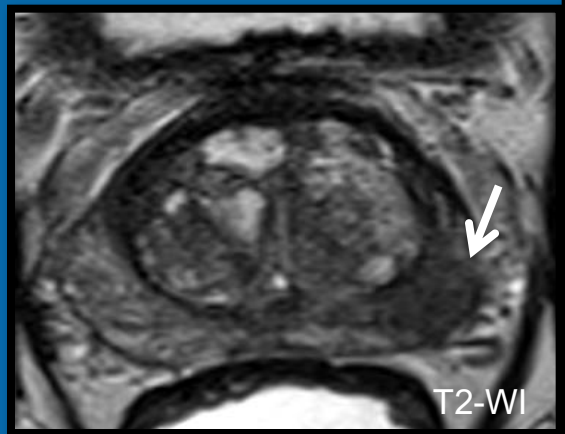
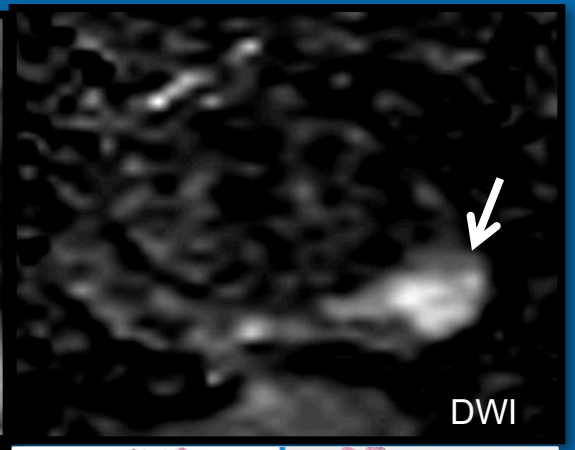
Multiparametric (mp) MRI for Prostate Cancer Detection

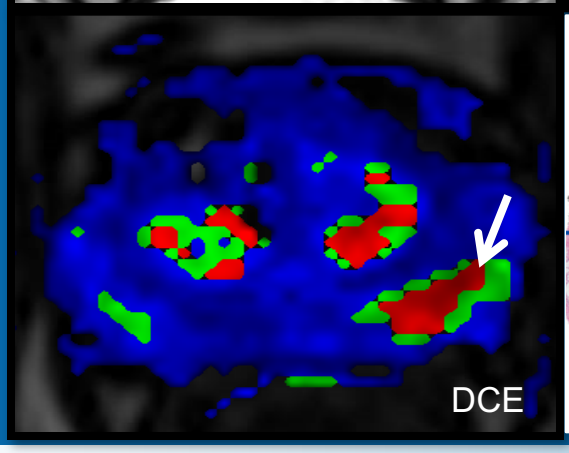
T2-Weighted

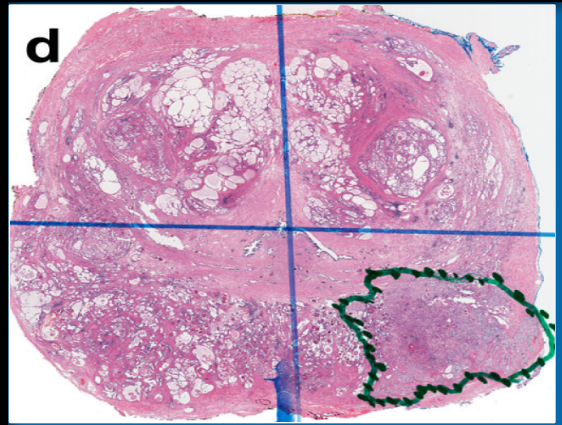




Diffusion-Weighted Images (DWI)

Dynamic Contrast Enhancement (DCE)

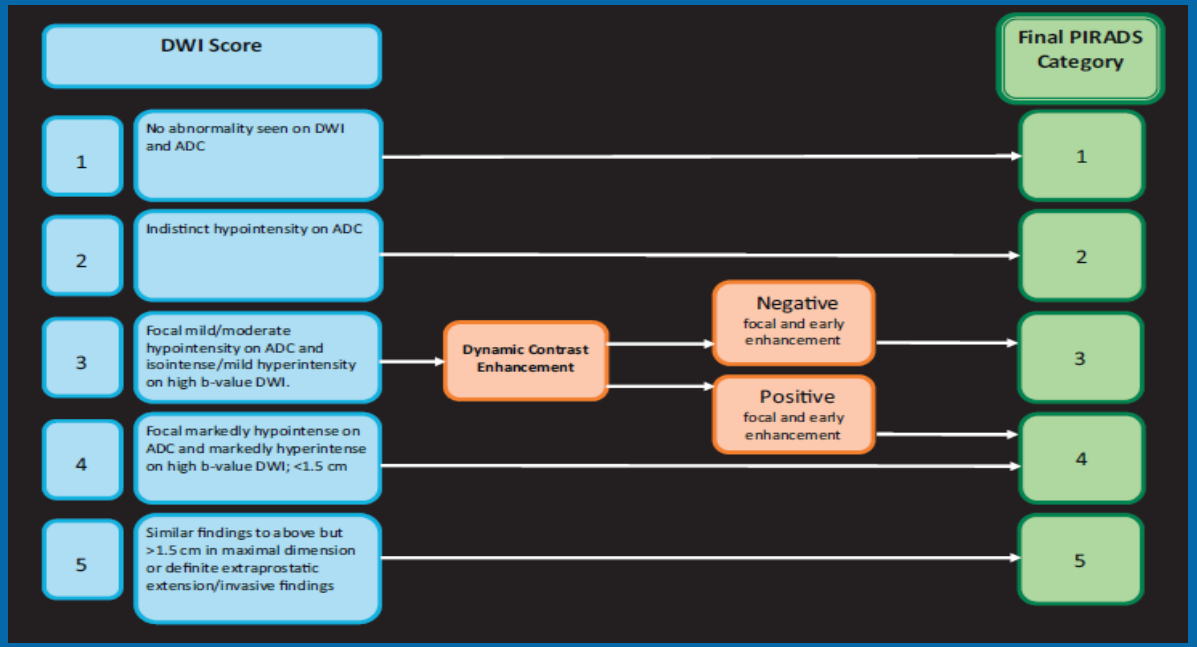




Whole-Mount Specimen

Natarajan et al. *Urol Oncol* 2011

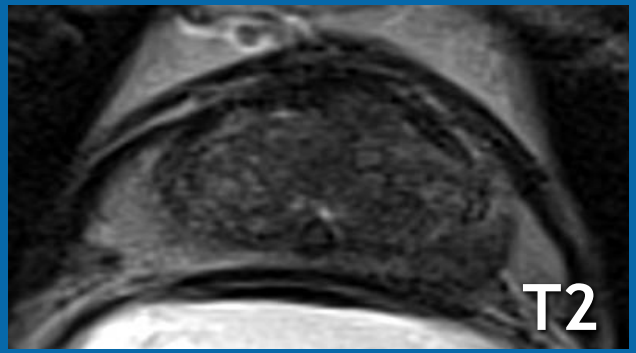
PI-RADS v2 Guidelines: PZ Lesions

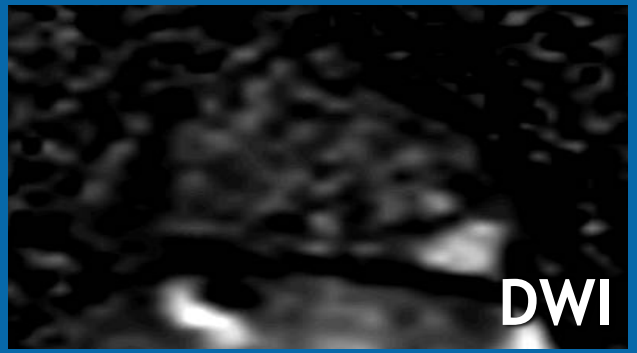


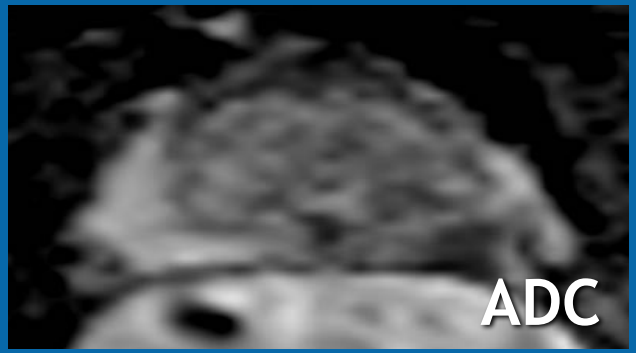
- For PZ lesions, DWI score is the dominant factor
- ADC value is inversely correlated with Gleason score
- Secondary role for DCE sequences among PI-RADS 3 lesions by DWI
- Size > 15 mm used to distinguish between PI-RADS 4 and 5

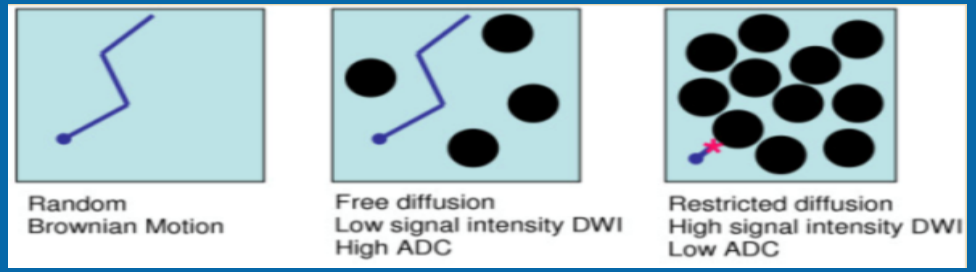
Barentsz JO et al. *Eur Urol* 2016

Multiparametric MRI Sequences: DWI/ADC



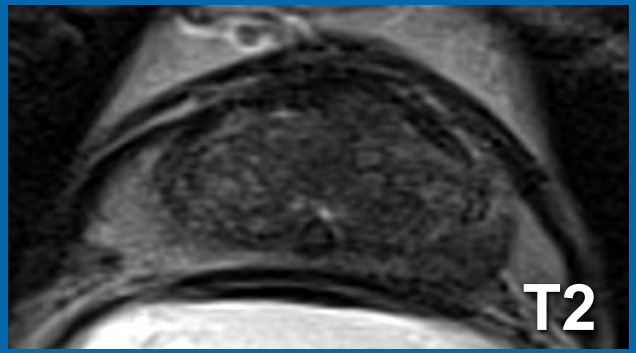


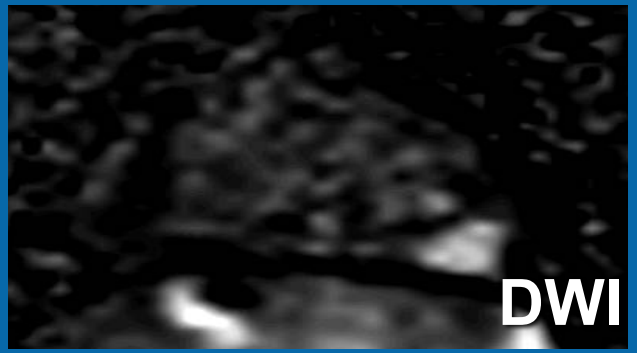


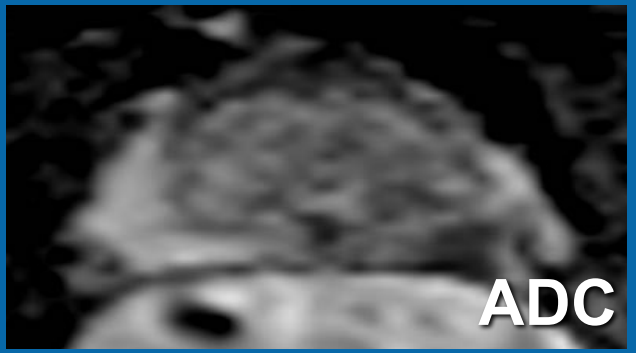


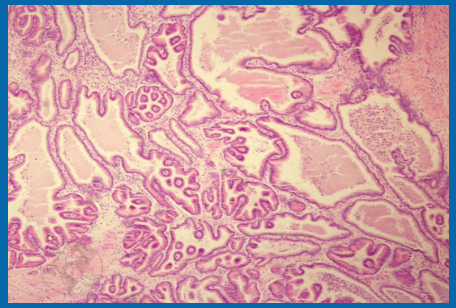
Cancer

Multiparametric MRI Sequences: DWI/ADC

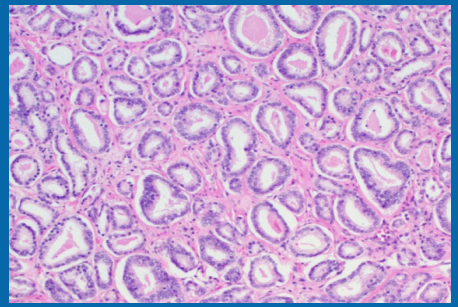




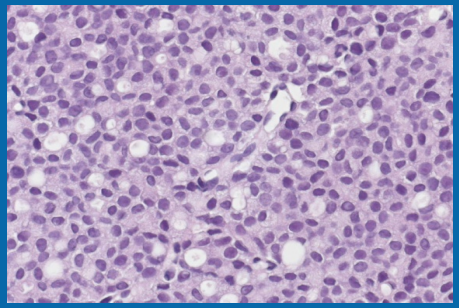




BPH



Gleason 3



Gleason 5

MRGB: Systematic Review

- MRGB for detection of clinically significant cancer
  - Specificity: 23-87%
  - Sensitivity: 58-96%
  - PPV: 34-68%
  - NPV: 63-98%
- “MRGB is substantially better than practice standard”

Fütterer JJ et al. *Eur Urol* 2016

Low-Risk Prostate Cancer: Re-classification

- 2374 RP pts, 1987-2007
- Preoperative low-risk (T1-T2a, PSA < 10, Gleason 6)
- Re-classification:
  - Any upgrading or upstaging: 57%
  - Gleason 4+3 or greater: 4%
  - Gleason 8-9 or SVI or LN+: 3%

Kovac et al. *In preparation*

MRGB for Pathological Staging: Systematic Review

- Analysis of 75 studies (9796 pts) assessing mpMRI for pathological staging (ECE, SVI) using RP path as reference standard

	Extraprostatic Extension	Seminal Vesicle Invasion
Sensitivity (95% CI)	57% (49-64)	58% (47-68)
Specificity (95% CI)	91% (88-93)	96% (95-97)

- MRI has poor sensitivity for advanced pathological features

de Rooji M et al. *Eur Urol* 2016

MRGB vs. Standard Biopsy: RP Pathology

- N = 170 of 1003 (17%) underwent RP, 2007-2014

Table 2. Performance of Different Biopsy Approaches in the Detection of Intermediate- to High-Risk Prostate Cancer on Whole-Gland Prostatectomy Specimen

	Targeted MR/Ultrasound Fusion Biopsy	Standard Extended-Sextant Biopsy	Combined Biopsy
Sensitivity, % (95% CI)	77 (67-84)	53 (43-63)	85 (76-91)
Specificity, % (95% CI)	68 (57-78)	66 (54-76)	49 (37-60)
Negative predictive value, % (95% CI)	70 (58-80)	53 (43-63)	73 (58-84)
Positive predictive value, % (95% CI)	75 (65-83)	66 (54-76)	67 (58-75)
Accuracy, % (95% CI)	73 (70-76)	59 (55-63)	69 (65-72)
AUC (95% CI)	0.73 (0.66-0.79)	0.59 (0.52-0.67)	0.67 (0.60-0.74)
P value of comparison with targeted MR/ultrasound biopsy		.005	.04

Siddiqui MM et al. *Jama* 2015

MRGB: Correlation with RP Pathology

- Accuracy of MRGB for pathological Gleason score

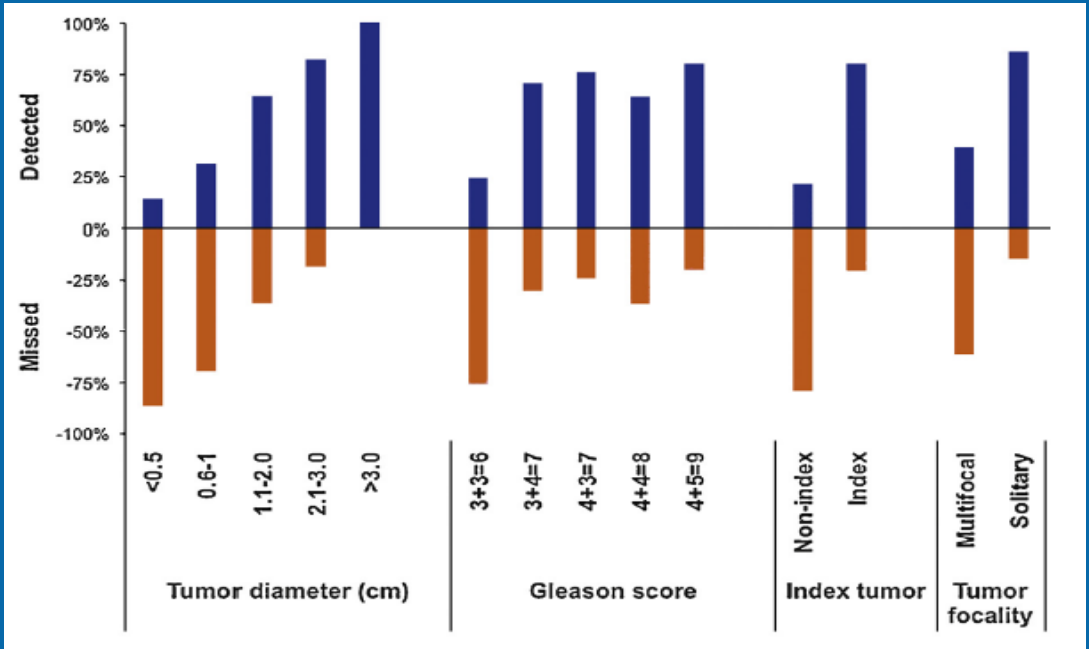
	Per Tumor Foci N = 126
Primary Gleason grade	90%
Secondary Gleason grade	59%
Underestimated Gleason score	29%

- Index lesion detected in all cases
- Highest Gleason grade underestimated in 28%

N = 125, median PSA 7.2 ng/mL, PI-RADS 4-5 74%, median size 14 mm

Lanz C et al. *J Urol* 2016

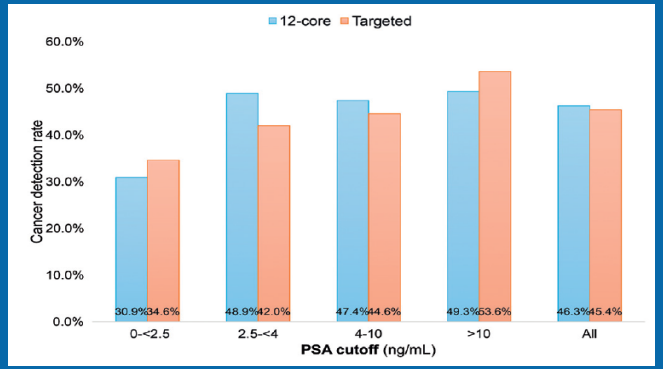
MRGB: Correlation with RP Pathology

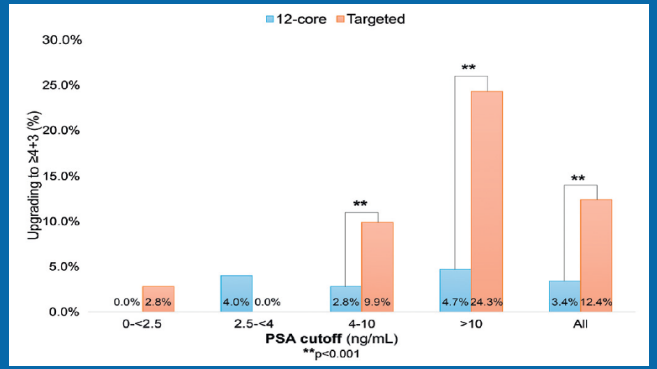


- N = 122, pre-RP mpMRI
- Analysis by tumor foci on RP pathology rather than by patient
- Poor tumor detection for non-index, low-grade, and small tumors
- 68% of clinically significant tumor foci identified by mpMRI (> 1 cm, G≥7, index tumor)
- Sensitivity
  - Gleason ≥ 3+4: 72%
  - Gleason ≥ 4+3: 68%

Le JD et al. *Eur Urol* 2015

mpMRI-US Fusion Targeted Biopsy: Upgrading





Cancer Detection

Gleason Upgrading

- No difference in cancer detection → std vs targeted biopsy
- ↑ Upgrading (G ≥4+3) with targeted biopsy at PSA levels > 4
- ↑ Insignificant cancer (G ≤3+4) with std biopsy at PSA levels < 4

N = 1003, 2007-2014, 19% prior biopsy
Only includes pts with Positive MP-MRI*

Shakir et al. *J Urol* 2014

Index Tumor Characterization: Is MRGB Enough?

- Accuracy of mpMRI, MRGB, standard biopsy for index tumor detection

	Index Tumor Detection
mpMRI	92%
MRGB	80%
Standard Biopsy	92%
MRGB plus Standard Biopsy	96%

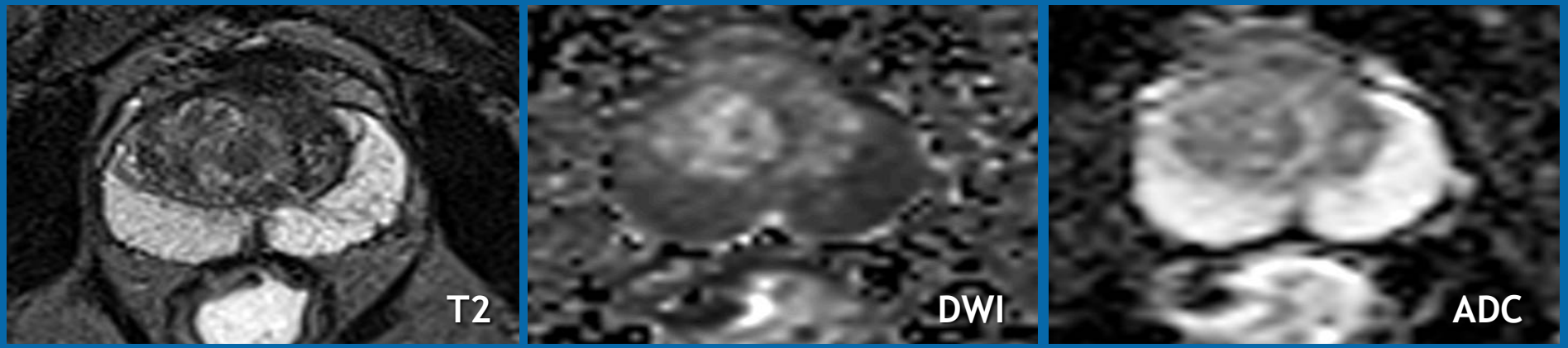
- MRGB and std biopsy detected 97% of all significant prostate cancer foci vs. 85% for mpMRI

Radtke JP et al. *Eur Urol* 2016

Summary: MRGB For Cancer Characterization

- mpMRI performs poorly for pathological staging
- MRGB alone underestimates tumor grade in up to one-third of cases
  - Small high-grade cancers may be missed in up to 75-80% of cases
- MRGB plus standard biopsy best for accurate tumor characterization

Negative MRI: No Clinically Significant Cancer?



Can Biopsy Be Avoided Based on mpMRI?

- Negative mpMRI (PI-RADS 1 ± 2): 19-48%
  - Cancer detection rate: 15-31% → 16-20% of all cancers
  - 25-79% Gleason ≥ 3+4

- NPV 63-98% for significant cancer → Potential for missed significant cancers if patients undergo MRGB without standard biopsy

Pokomy et al. *Eur Urol* 2014; Haffner et al. *BJU Int* 2011; Kuru et al. *J Urol* 2013; Rastinehead et al. *J Urol* 2013; Wysock et al. *Eur Urol* 2014; Sonn et al. *J Urol* 2013

Prostate Cancer Case

- Healthy 57 yo Causasian male, elevated PSA
  - 2017: 6.29 ng/mL (F:T 12%)
  - 2016: 7.40
  - 2015: 3.47 ng/mL
- Family history: father Dx age 64
- Normal DRE
- Minimal LUTS
- Continent, potent

Prostate Cancer Case

- Patient reluctant to undergo biopsy → wanted mpMRI
- Prostate MRI:
  - No visible targets
  - Prostate volume: 50 cc
  - PSA density: 0.13

Prostate Cancer Case

- Prostate biopsy: 3 of 12 cores positive
  - L. mid: Gleason 6, 1 mm
  - L. base: 2/2+, Gleason 3+4, 15 mm, 10% cribiform glands
- RALRP
  - pT3a, established extraprostatic extension
  - Gleason 3+4, cribiform pattern present
  - Tumor volume: 4 cc
  - 0 of 22 lymph nodes positive

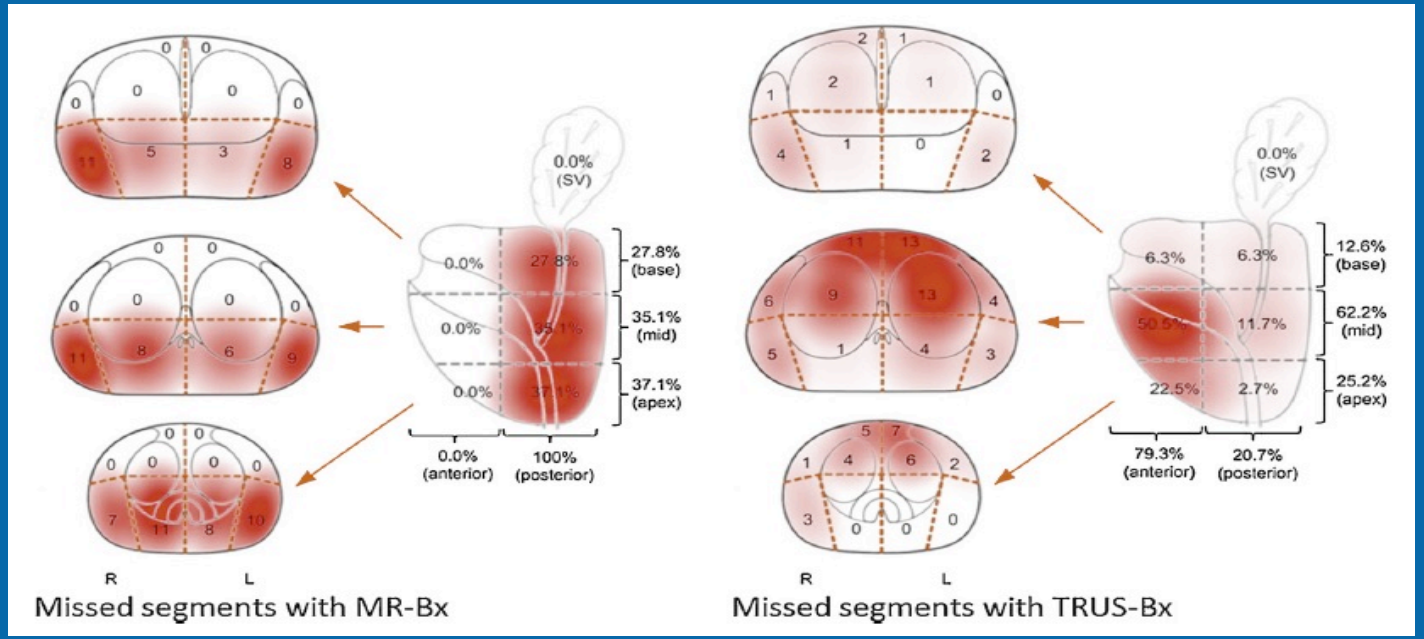
mpMRI PI-RADS v2: Correlation with RP Pathology

- mpMRI: limited accuracy for small, high-grade tumors

	Identification with mpMRI
Tumors > 0.5 mL	
Peripheral zone	94%
Transition zone	95%
Tumors < 0.5 mL and Gleason ≥ 4+3	
Peripheral zone	26%
Transition zone	20%

Vargas HA et al. *Eur Radiol* 2016

Missed Significant Cancers by MRGB



- **Significant Cancer Detection: 74% MRGB vs. 61% Std Bx**

Schouten MG et al. *Eur Urol* 2017

mpMRI and MRGB

- Superior to standard biopsy at characterizing prostate cancer (index tumor) → improved decision-making
- Limitations:
  - Small, high-grade cancers
  - Apical and posterolateral tumors

Vargas HA et al. *Eur Radiol* 2016; Schouten MG et al. *Eur Urol* 2017

- Targeted biopsy operator-dependent
- Substantial cost, inconvenience
- Studies needed to prove value in decision-making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Every life deserves world class care.