



**JOHNS HOPKINS**  
M E D I C I N E



# **Low-risk versus High-risk Prostate Cancer on Multiparametric MRI**

**Katarzyna J. Macura, MD, PhD, FACR**

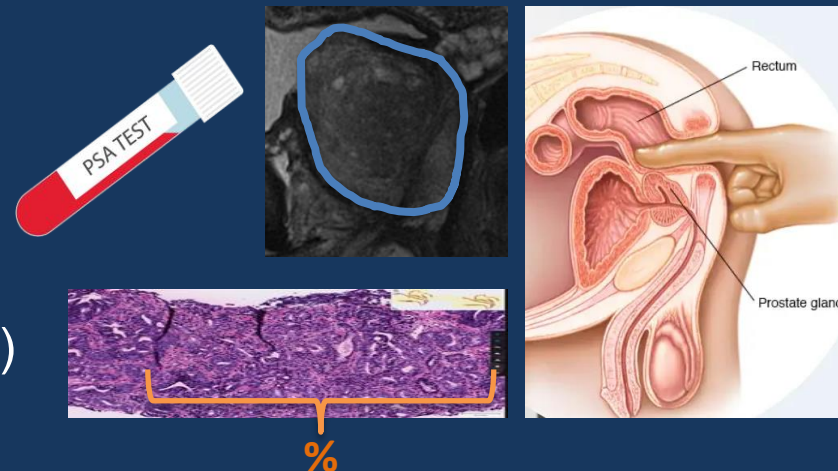
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Radiological Science, Johns Hopkins University  
Baltimore, MD**

# Risk Stratification

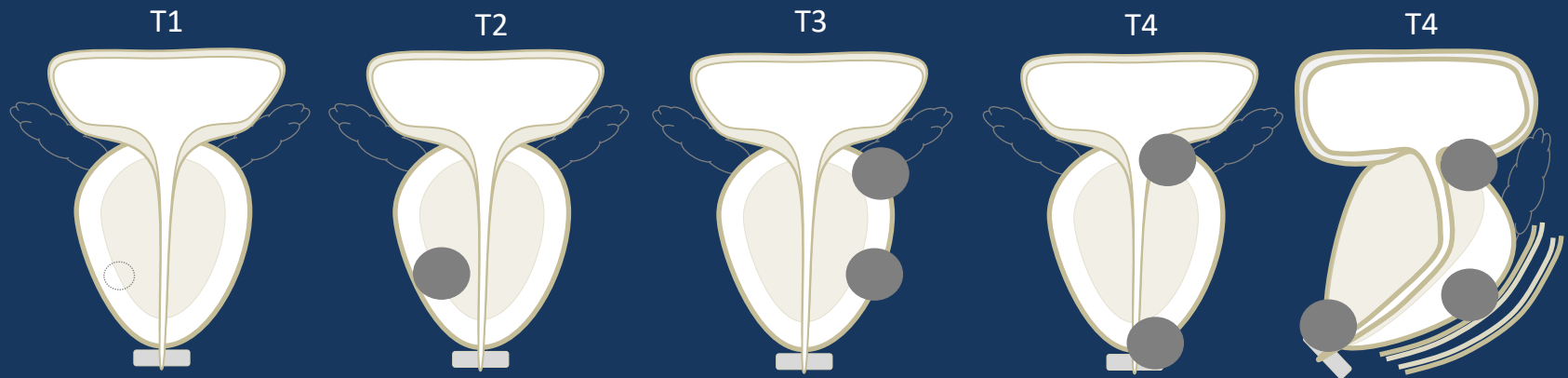
- Biological aggressiveness of prostate cancer and risk of disease progression have management implications
- Clinical classification schemes are based on a combination of:
  - PSA level (normal < 4.0 ng/mL)
  - Gleason score, and
  - T tumor stage
- Factors to select active surveillance vs. radical treatment include:

- Serum PSA
- PSA density → 
$$\frac{\text{Total PSA}}{\text{Prostate Volume}}$$
- Gleason score
- % biopsy core involvement
- Results of DRE (digital rectal exam)



# Risk Stratification

- T stage (size of the tumor on digital rectal exam and/or ultrasound)
  - T1c Tumor identified by needle biopsy (not palpable or seen on imaging)
  - T2a Tumor involves 1/2 of one lobe or less
  - T2b Tumor involves more than 1/2 of one lobe but not both lobes
  - T2c Tumor involves both lobes
  - T3 Tumor extends outside the prostate
    - T3a Extracapsular extension
    - T3b Seminal vesicle invasion
  - T4 Invasion into nearby structures (membranous urethra, bladder, rectum, pelvic wall)



Cancer confined to the prostate

Cancer extends outside of the prostate

# Prognostic Gleason Grade Grouping - GG

**Gleason grade groups** accurately reflect prognosis (JHU - ISUP):

- G score 3+3=6 (well-differentiated) prognostic GG 1
- G score 3+4=7 (moderately differentiated) prognostic GG 2
- G score 4+3=7 (mod-poorly differentiated) prognostic GG 3
- G score 4+4=8 (poorly differentiated) prognostic GG 4
- G score 4+5=9, 5+4=9, 5+5=10 (undifferentiated) prognostic GG 5

## ■ 5-year biochemical free survival rates:

| G Score | 3+3   | 3+4   | 4+3   | 8     | 9-10  |
|---------|-------|-------|-------|-------|-------|
| GG      | 1     | 2     | 3     | 4     | 5     |
| Biopsy  | 94.6% | 82.7% | 65.1% | 63.1% | 34.5% |
| RP      | 96.6% | 88.1% | 69.7% | 63.7% | 34.5% |

p < 0.001

# NCCN

## National Comprehensive Cancer Network

| RISK          | LOW                                                                  | INTERMEDIATE               | HIGH                            |
|---------------|----------------------------------------------------------------------|----------------------------|---------------------------------|
| PSA ng/mL     | ≤10                                                                  | > 10 and ≤ 20              | >20                             |
| Gleason score | 2–6                                                                  | 7                          | 8–10                            |
| T Stage       | T1-T2a<br>not very low-risk                                          | T2b or T2c<br>not low-risk | T3a<br>not very high risk       |
|               | <u>very-low risk</u><br><3 cores+<br>and ≤50% cancer<br>in each core |                            | <b>very high-risk</b> T3b-<br>4 |

# Biomarkers

1<sup>st</sup> Biopsy

Repeat Biopsy

Aggressiveness  
Prognosis

|                                   |                                        |                                                   |                                                            |
|-----------------------------------|----------------------------------------|---------------------------------------------------|------------------------------------------------------------|
| <b>Serum<br/>Plasma<br/>Blood</b> | <b>PSA (PSAD)<br/>PHI<br/>4K Score</b> | <b>PSA (PSAD)<br/>PHI<br/>4K Score</b>            | <b>PSA (PSAD)<br/>N-Glycan<br/>CTCs</b>                    |
| <b>Urine</b>                      | <b>PCA3<br/>ExoDX</b>                  | <b>PCA3<br/>TMPRSS2-ERG<br/>Mi-prostate score</b> | <b>Mi-prostate score<br/>GCNT1 gene</b>                    |
| <b>Tissue</b>                     | <b>N/A</b>                             | <b>N/A</b>                                        | <b>OncotypeDX<br/>ProMark<br/>Prolaris<br/>Decipher GC</b> |

PSA -- Kallikrein-3 enzyme

PHI -- ([2]proPSA/fPSA) √PSA

4K -- 4 Kallikreins: fPSA, tPSA, intact PSA + kallikrein-like peptidase 2 (hK2)

PCA3 -- Prostate Cancer Antigen-3 ncRNA, PCA3 Score PCA3/PSA mRNA ratio x 1000

Mi-Prostate -- Plasma PSA + urinary PCA3 + T2-ERG

TMPRSS2:ERG -- Transmembrane serine protease (TMPRSS2) and ETS transcription factor (ERG) gene fusion (TMPRSS2-ERG fusion gene is the most frequent, present in 40% - 80% of prostate cancers in humans)

ExoDx -- Genomic-based test returns a risk score that determines a patient's risk of clinically significant prostate cancer (Gleason Score ≥7) on prostate biopsy

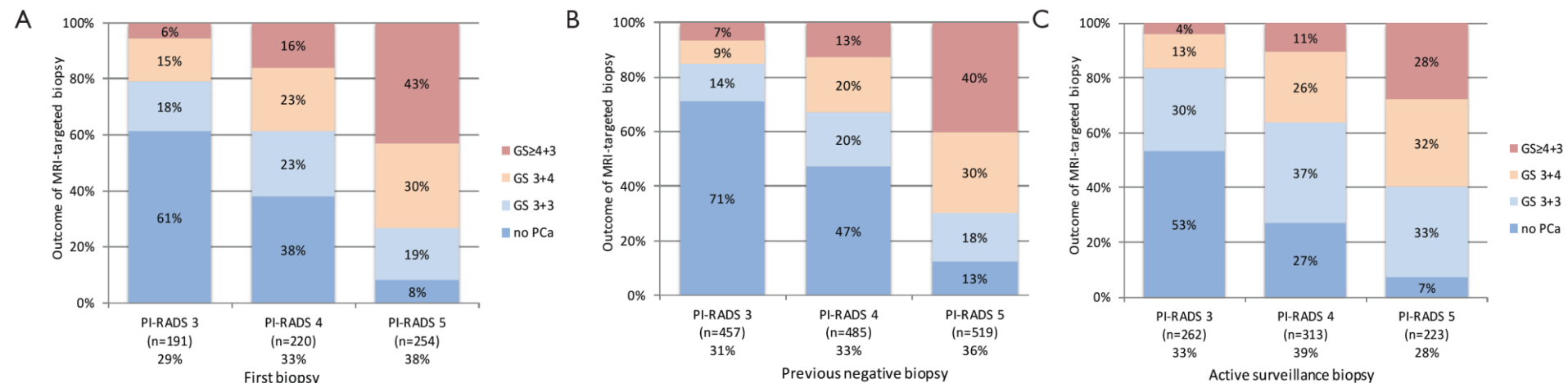
Prolaris -- Genetic test measures tumor cell growth with 10-year disease specific mortality risk

Decipher -- 22-gene genomic classifier (GC) for prognostication after RP into disease phenotypes

## Role of mpMRI

- **19 - 34%** men with low-grade disease on initial biopsy have Gleason upgrading on repeat random extended biopsy → under-sampling by the initial biopsy
- MRI's role in ensuring that the most aggressive tumor is sampled (MR-guided biopsy)
- MRI localizes tumor in atypical locations, i.e. anterior TZ and apex, or small volume aggressive tumors in the peripheral zone

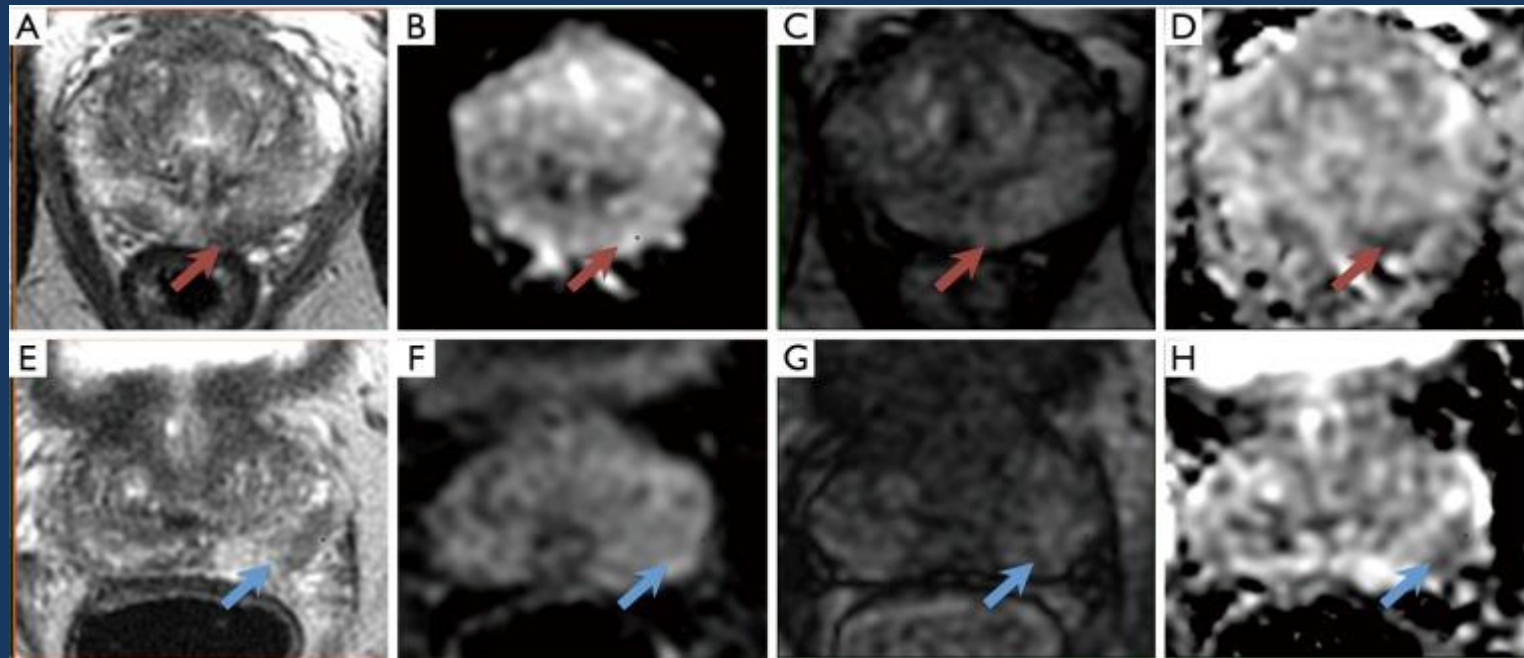
# Indeterminate or equivocal PI-RADS 3 lesions



The prevalence of PI-RADS 3 index lesion in the diagnostic work-up is significant, varying between 1 in 3 (32%) to 1 in 5 (22%) men, depending on patient cohort of first biopsies, previously negative biopsies, and active surveillance biopsies.

# PI-RADS 3 Lesions in PZ

(A) axial T2-weighted image, (B) high-b-value DWI, (C) early DCE time-point, (D) ADC map

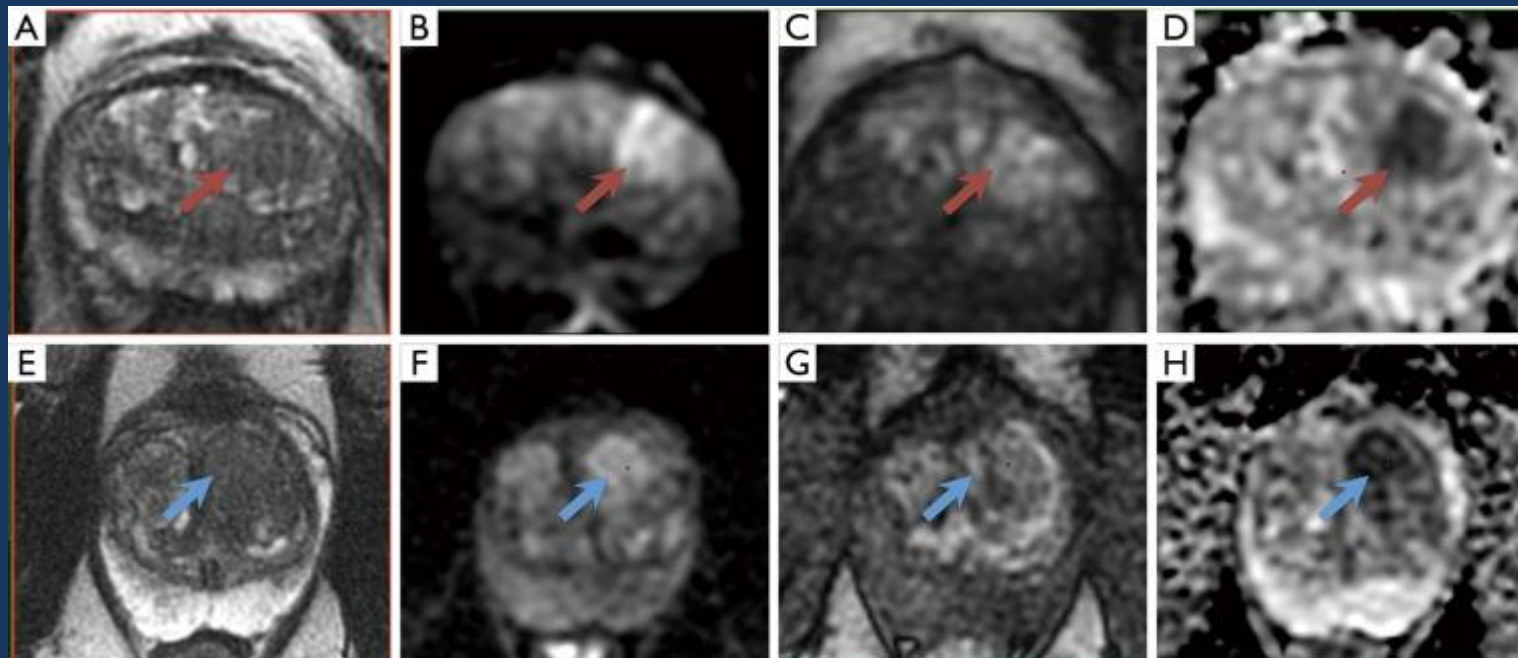


Gleason 3+4  
tumor (red  
arrows)

No prostate  
cancer  
(blue  
arrows).

# PI-RADS 3 Lesions in TZ

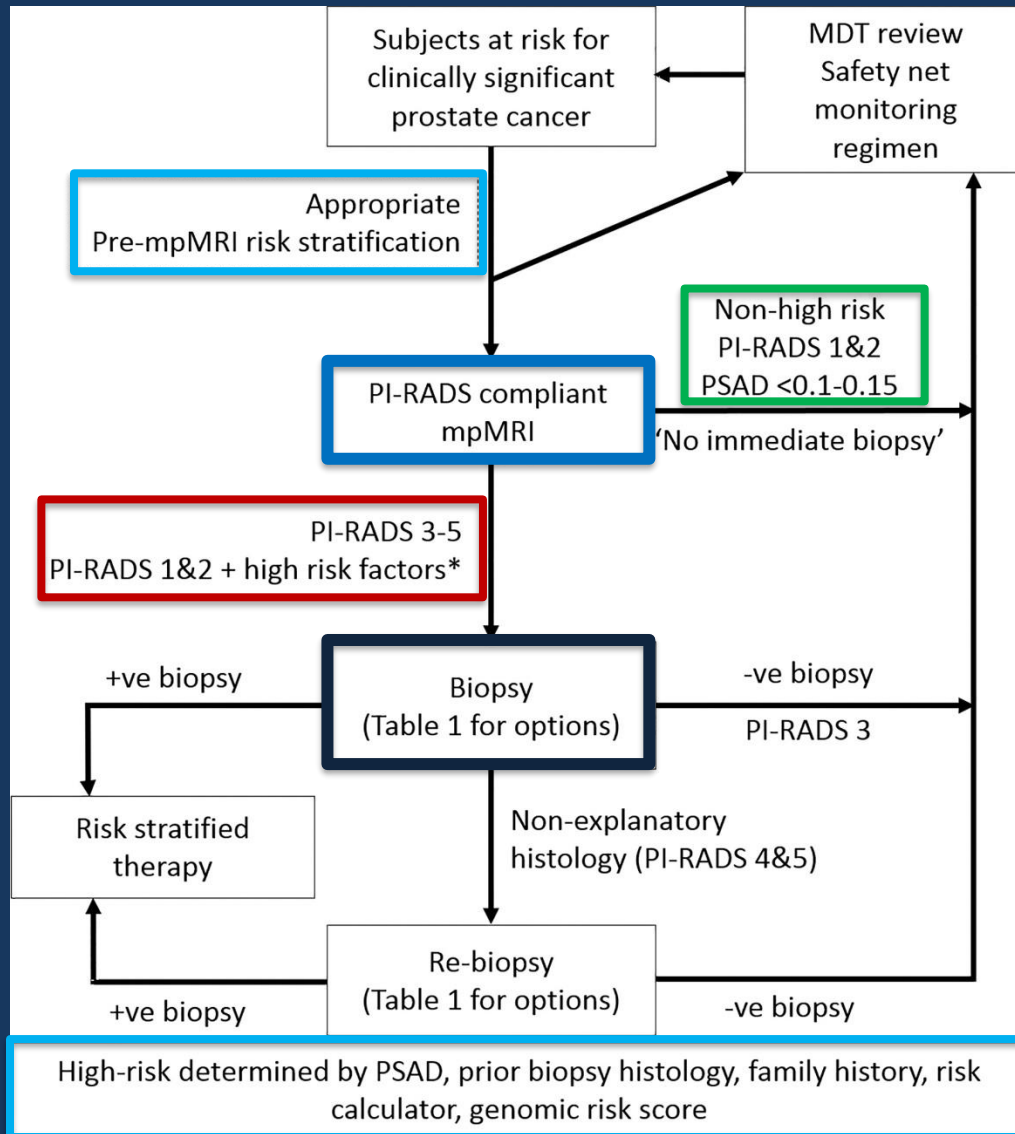
(A) axial T2-weighted image, (B) high-b-value DWI, (C) early DCE time-point, (D) ADC map



Gleason 3+4  
tumor (red  
arrows)

No prostate  
cancer  
(blue  
arrows).

# PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway



For 100 biopsy-naïve men

| PI-RADS 1-2                                                                                                         | PI-RADS 3-5                                                                             |
|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| About 33% (26-41) have PI-RADS 1-2 scans                                                                            | About 67% (57-74) have PI-RADS 3-5 scans                                                |
| No cancer/benign<br>74% (69-81)                                                                                     | * No cancer/benign<br>29% (23-35)                                                       |
| ISUP=1: 18% (14-24)                                                                                                 | ISUP=1: 21% (17-27)                                                                     |
| ISUP≥2: 8% (6-12)                                                                                                   | ISUP=1: 4% (2-7)                                                                        |
| 100 biopsy naïve men with PI-RADS 1-2 MRI undergoing systematic biopsies only                                       | ISUP≥2: 5% (3-8)                                                                        |
| No cancer diagnosed after biopsy.                                                                                   | * ISUP≥2: 44% (39-50)                                                                   |
| Insignificant cancers (ISUP grade = 1) detected by MRI-directed and systematic biopsy.                              | <b>MRI BX + Systematic BX</b>                                                           |
| Proportion of insignificant cancers (ISUP group = 1) found by systematic biopsy cores.                              | 100 biopsy naïve men with PI-RADS 3-5 MRI undergoing MRI-directed and systematic biopsy |
| Significant cancers (ISUP grade ≥ 2) detected by MRI-directed and systematic biopsy.                                |                                                                                         |
| Proportion of significant cancers (ISUP grade ≥ 2) found by systematic biopsy; undetected by MRI-directed biopsies. |                                                                                         |

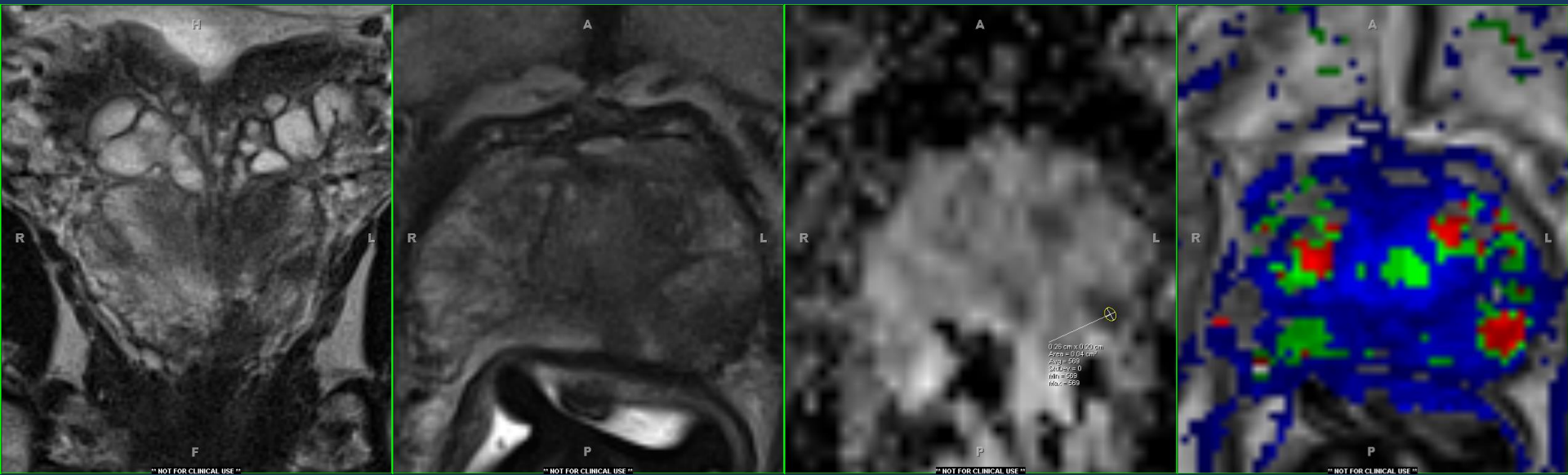
Radiology

Radiology 2019, Vol. 292, No. 2

# Case 1: Candidate for AS

71M with PSA 4.5 ng/mL increased from 3.0, DRE negative.

TRUS BX: 1 core G3+3 (GG1) 5% right base, HPIN right apex, and atypia left apex (T1c). Patient is a candidate for AS, with very low risk prostate cancer. Patient is anxious and opts for MRI before AS.

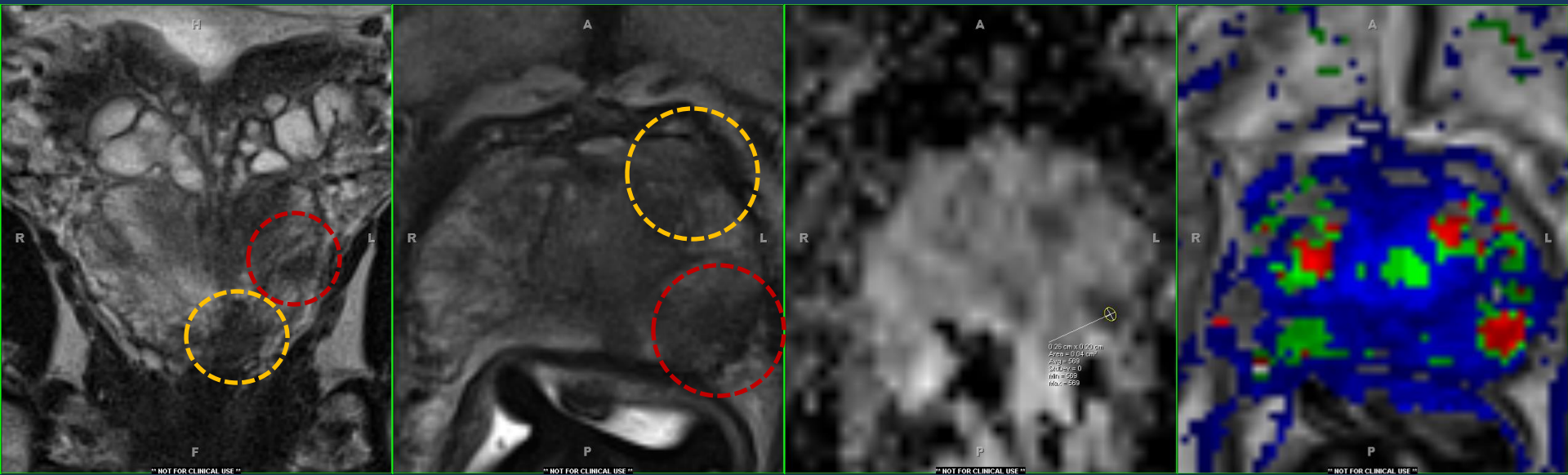


Is prostate cancer visible?  
Where is the dominant nodule?  
Is this patient a candidate for active surveillance?

# Case 1: Candidate for AS

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TRUS BX: 1 core G3+3 (GG1) 5% right base, HPIN right apex, and atypia left apex (T1c). Patient is a candidate for AS, with very low risk prostate cancer. Patient is anxious and opts for MRI before AS.



Is prostate cancer visible? **YES**

Where is the dominant nodule?

**Left Mid PZ Posterior-lateral**

Is this patient a candidate for active surveillance?

**Needs targeted confirmatory biopsy**

PIRADS:

Size 14 mm

T2W score 4

DWI - ADC  $0.600 \times 10^{-3} \text{ mm}^2/\text{s}$  score 4

DCE positive

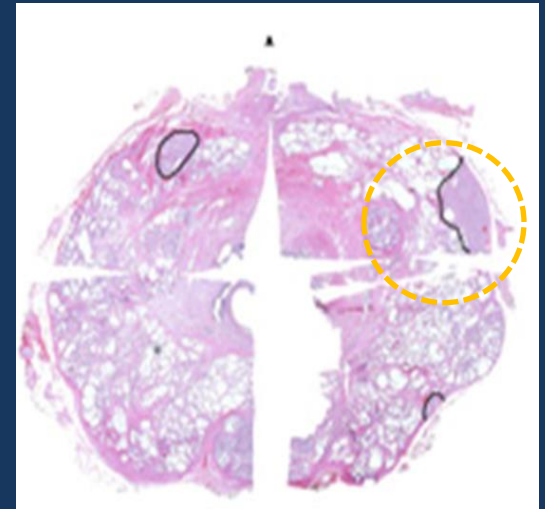
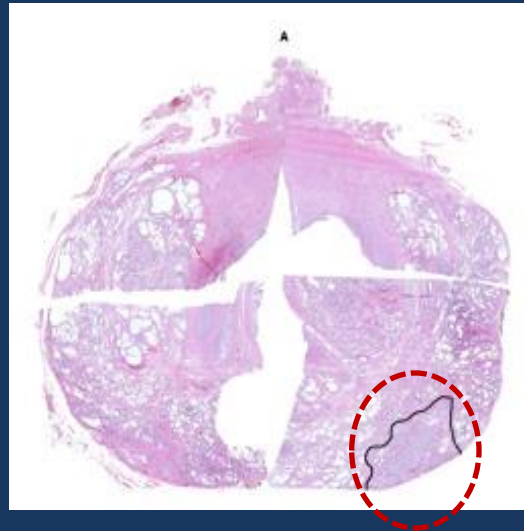
Overall Score 4

## Case 1: (cont.)

Robotic radical prostatectomy, final pathology multifocal disease with a dominant nodule **Gleason 4+3 (GG3) adenocarcinoma in the Left Mid PZ postero-lateral** with **extraprostatic extension**, non-focal pT3a pN0 pM0.

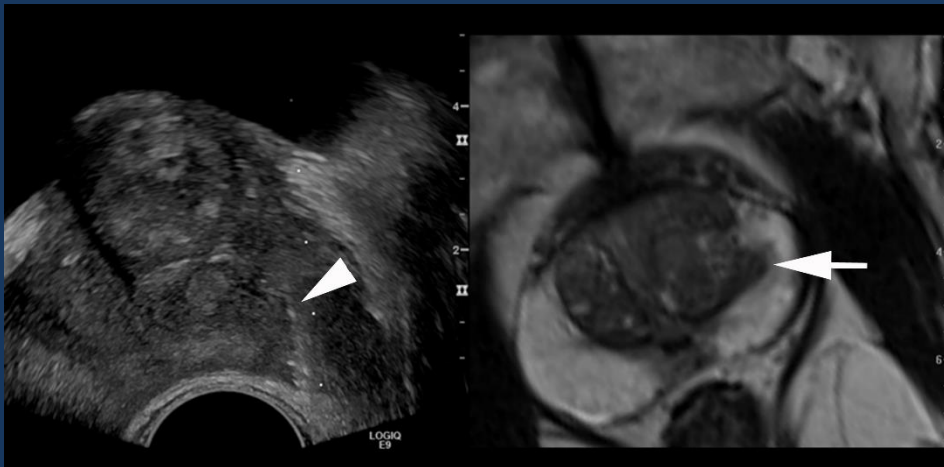
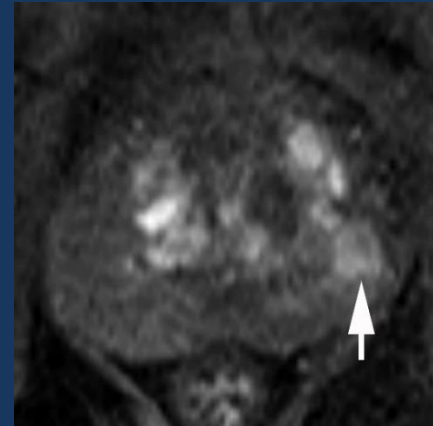
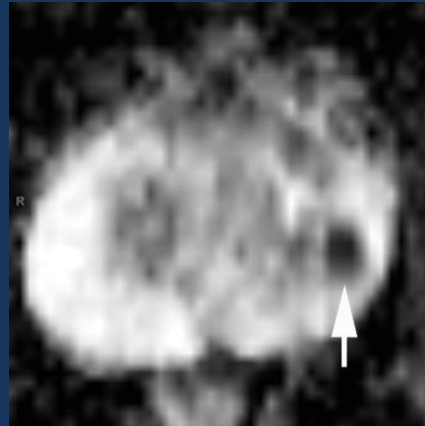


Even cancer located in PZ, that is accessible to TRUS biopsy, may be undetected due to sampling omission



## Case 2: Missed Clinically Significant Cancer on TRUS

71M, PSA 4.83 ng/mL and multiple negative TRUS-guided biopsies



### PIRADS:

Size 10 mm

T2W score 4

DWI - ADC

$0.700 \times 10^{-3} \text{ mm}^2/\text{s}$  score 4

DCE positive

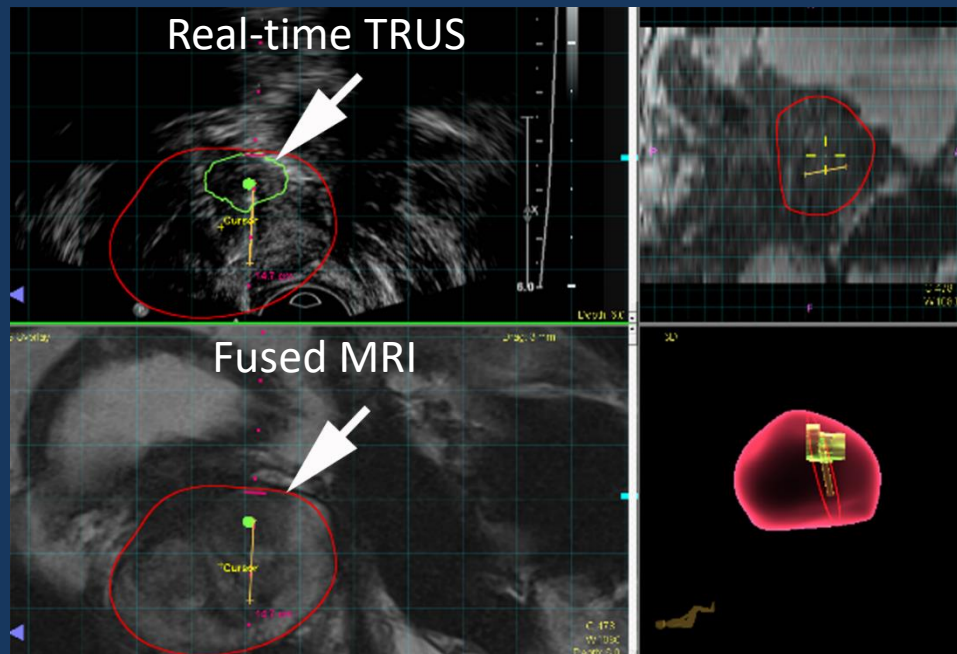
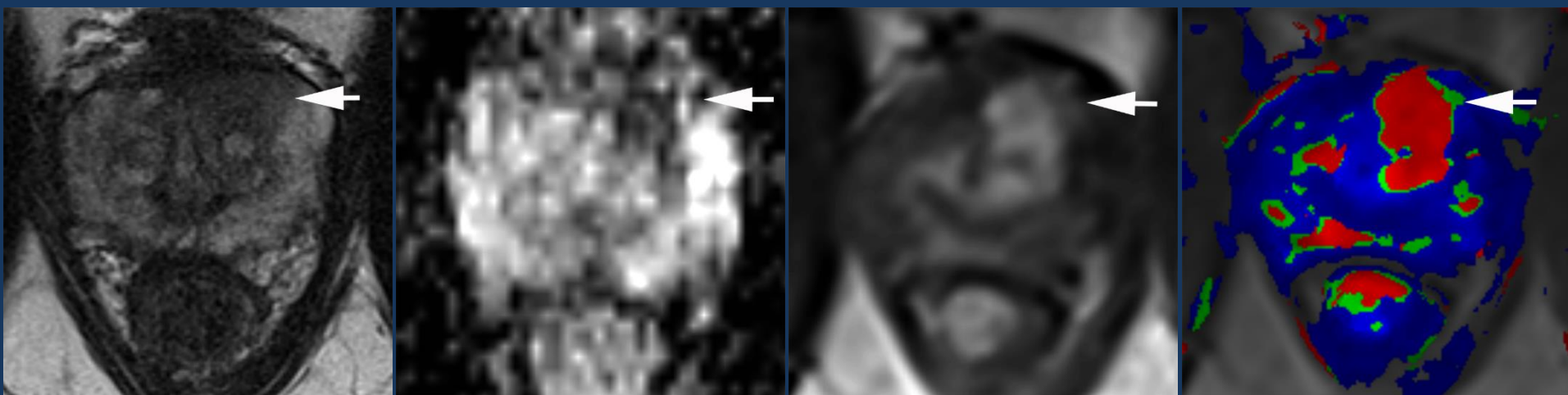
Overall Score 4

**MR-targeted biopsy:**

**Gleason score 4+4=8 (GG4) involving 2 cores (30%, 40%)**

# Case 3: Anterior Transition Zone Cancer

65M with slowly rising PSA over 4 years from 2.98 to 6.95 ng/mL with a Negative TRUS biopsy



## PIRADS:

Size 16 mm

T2W score 5

DWI - ADC

$0.900 \times 10^{-3} \text{ mm}^2/\text{s}$  score 5

DCE positive

Overall Score 5

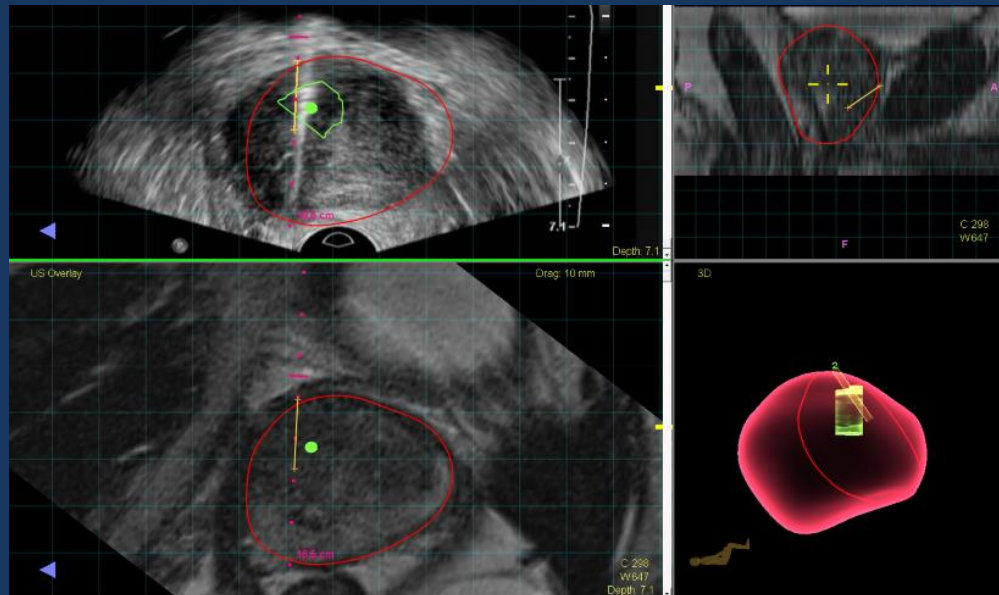
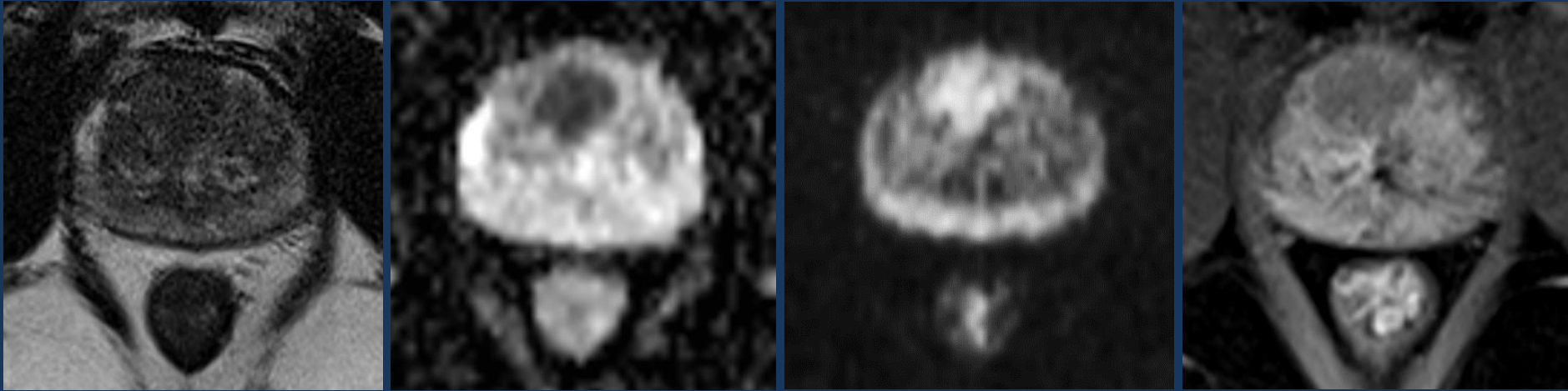
Targeted biopsy:

Gleason score 3+3=6 (GG1)

in 3 cores (100%, 40%, 5%)

# Case 4: Upgrade on Targeted Biopsy

60M, PSA 4.5 ng/mL. Negative prior TRUS biopsy



## Comparison Standard vs. Targeted

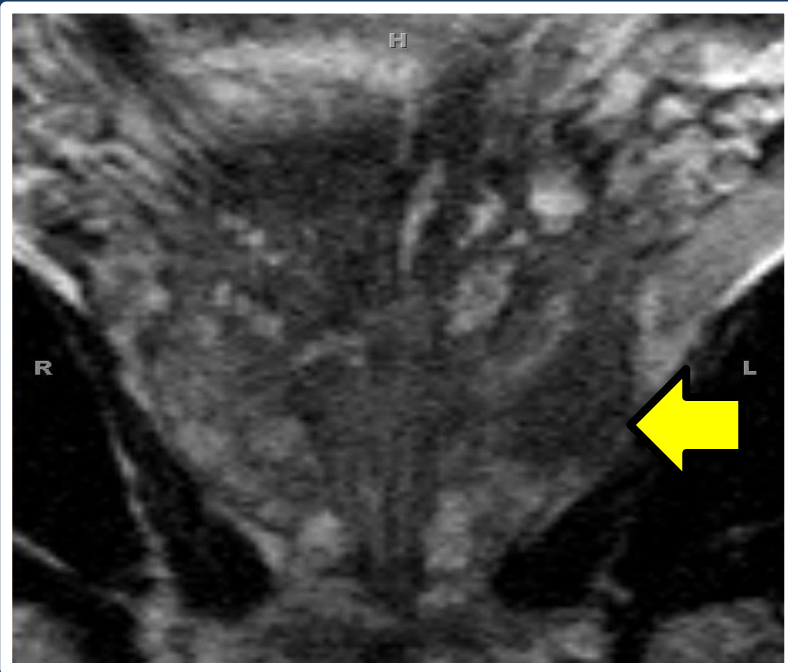
### Standard biopsy

**GLEASON SCORE 3+4=7 (GG 2)**  
**INVOLVING 10% OF 1 CORE (20% GLEASON PATTERN 4)**

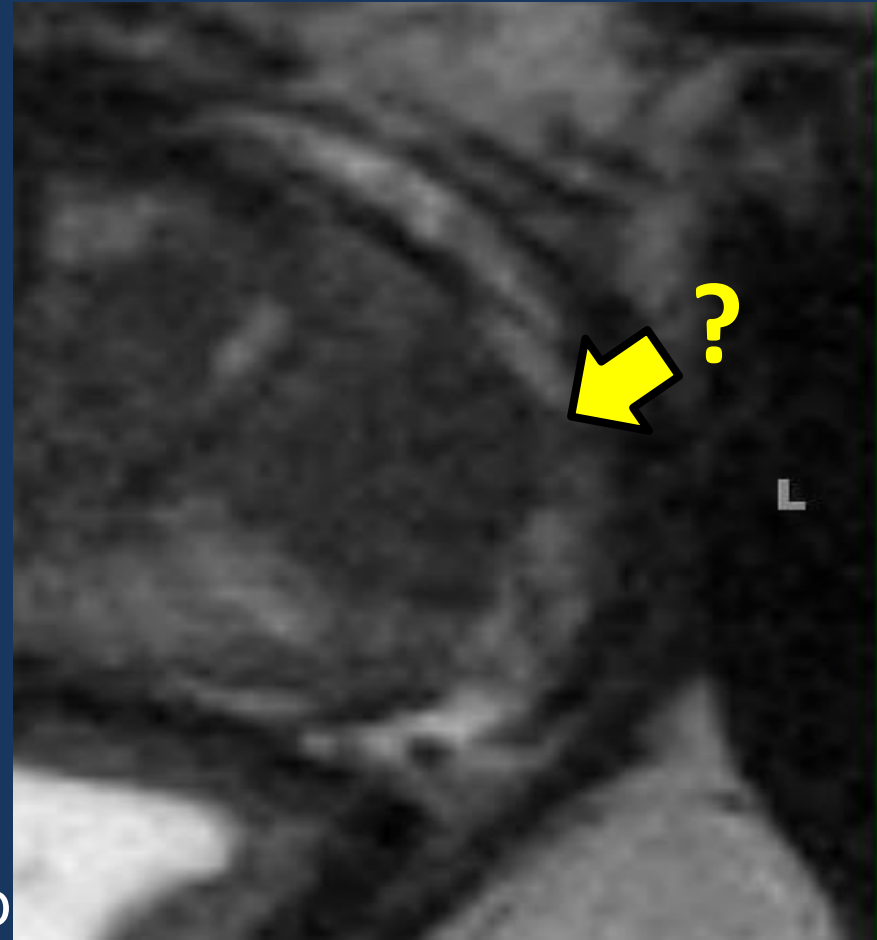
### Targeted biopsy

**GLEASON SCORE 4+3=7 (GG 3)**  
**INVOLVING 4 of 4 CORES (100%, 70%, 30%, 20%).**

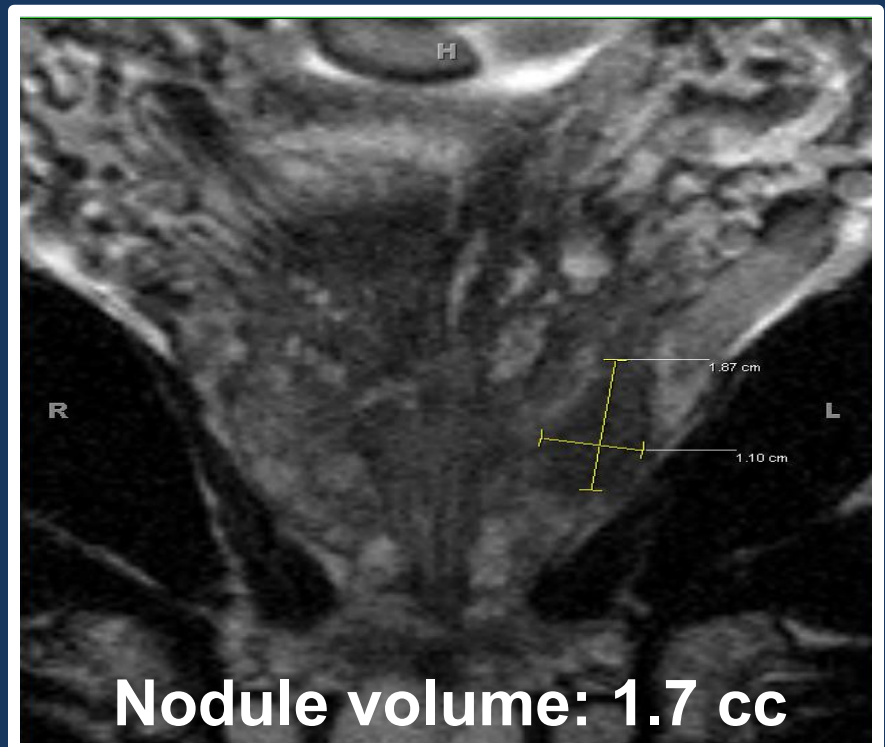
## Extracapsular tumor extension ?



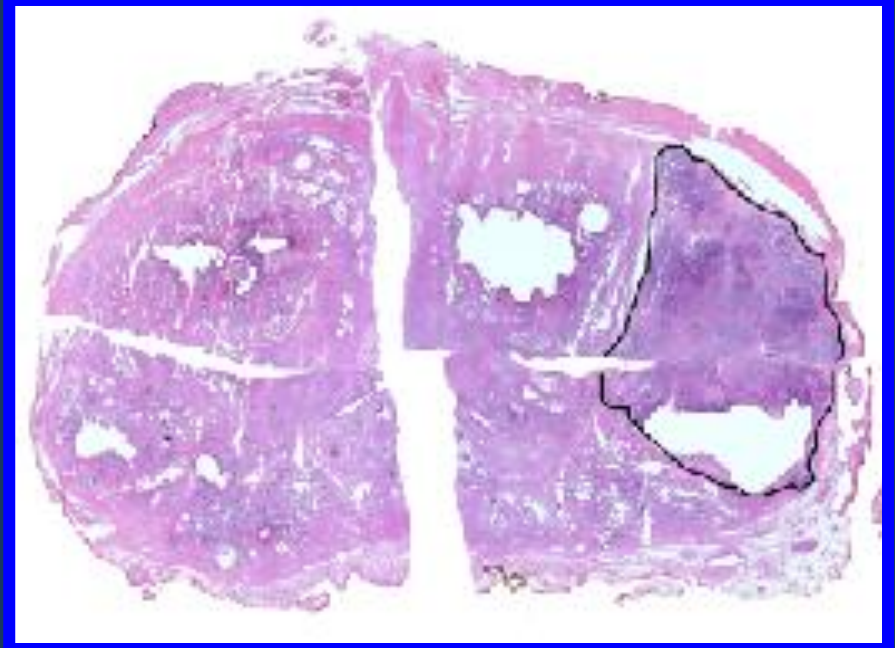
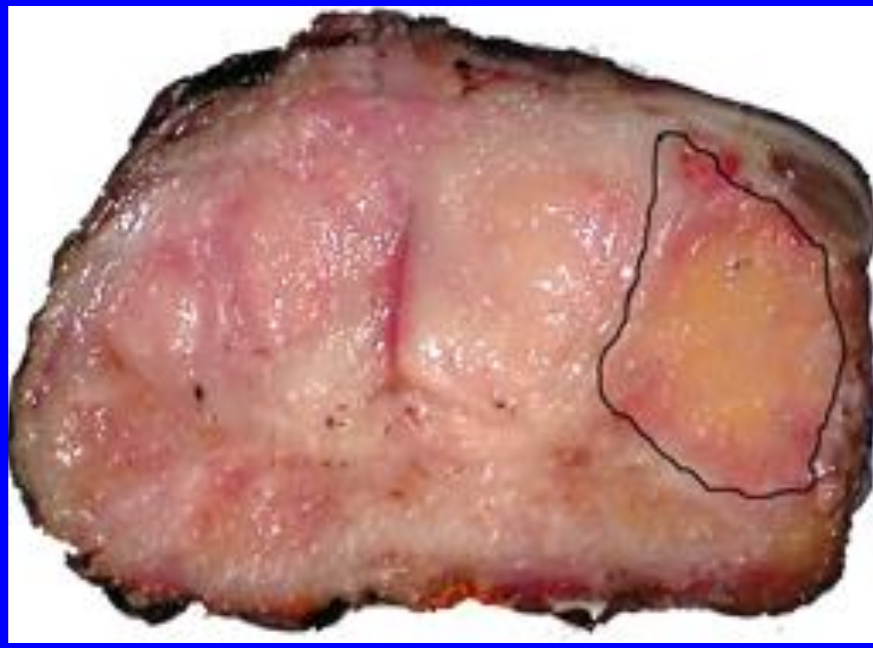
Left Mid lateral gland extra-cap



# The Index Nodule



# Histopathology

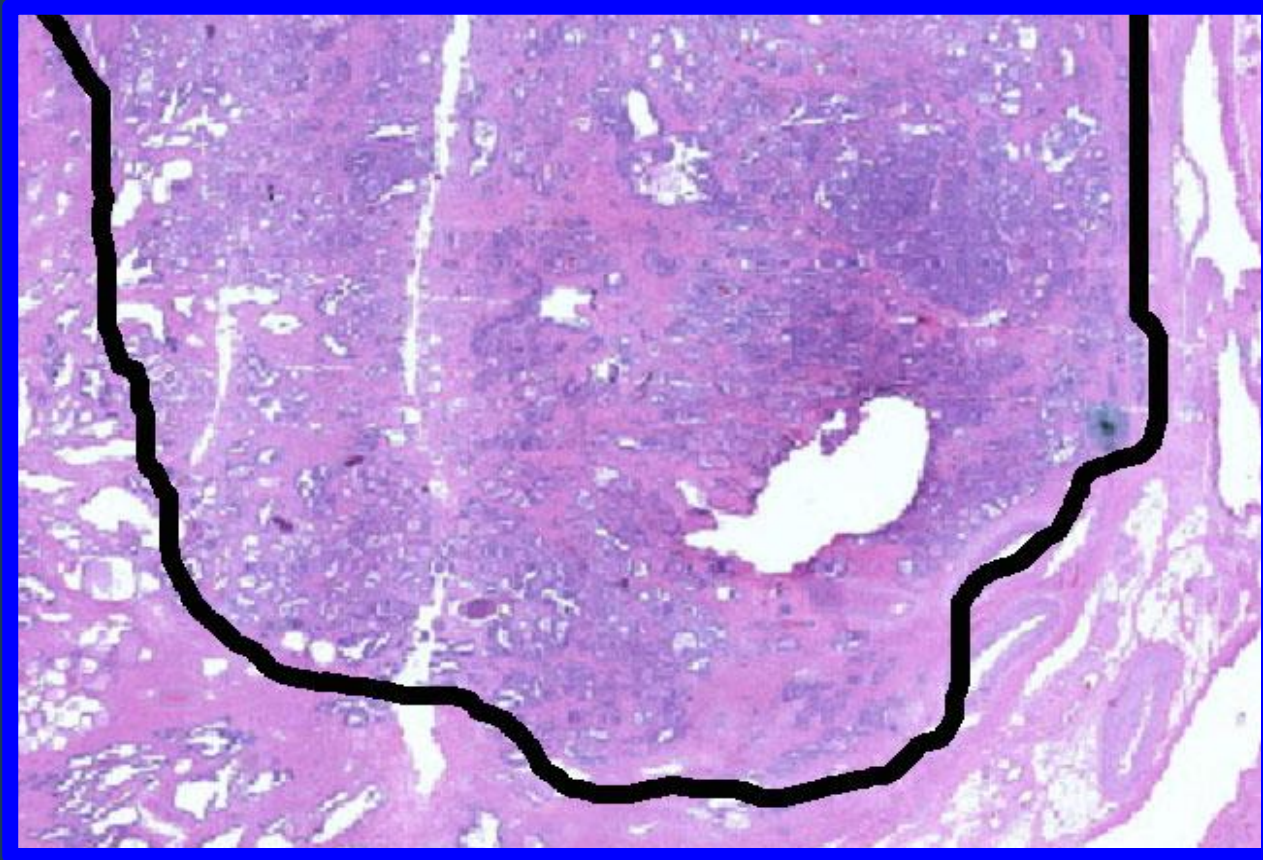


## **DOMINANT NODULE:**

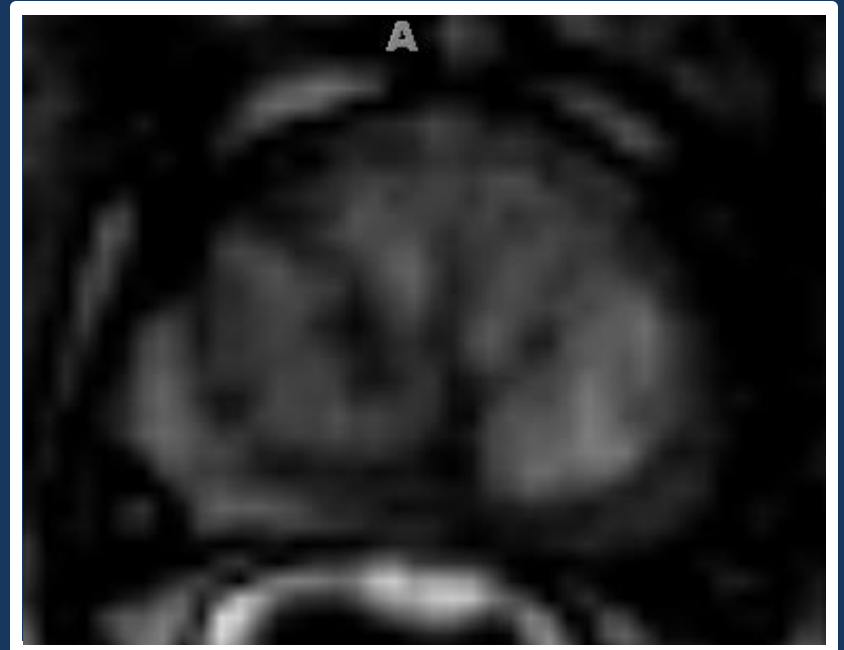
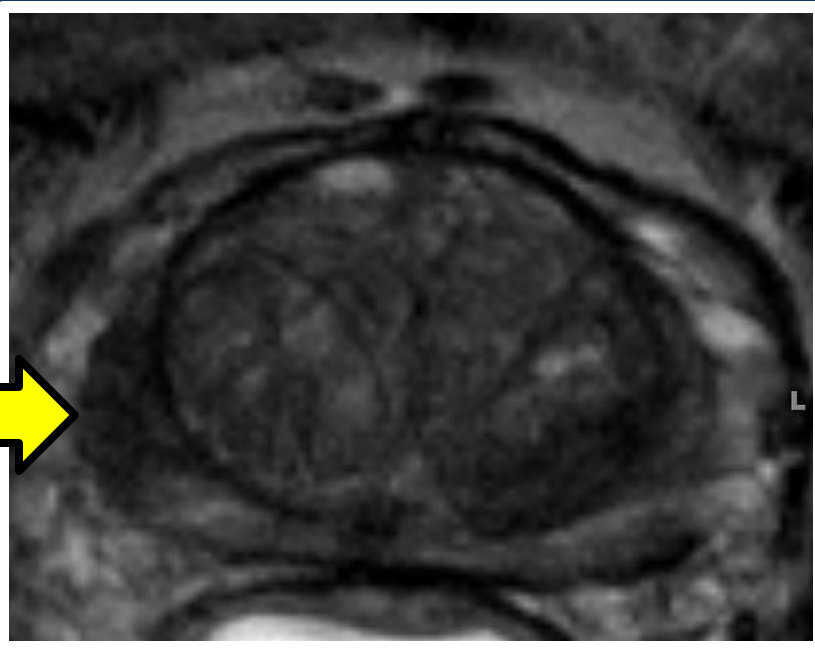
Left, posterolateral, mid, Gleason 4+3=7 with ductal features

Pathology

Organ confined

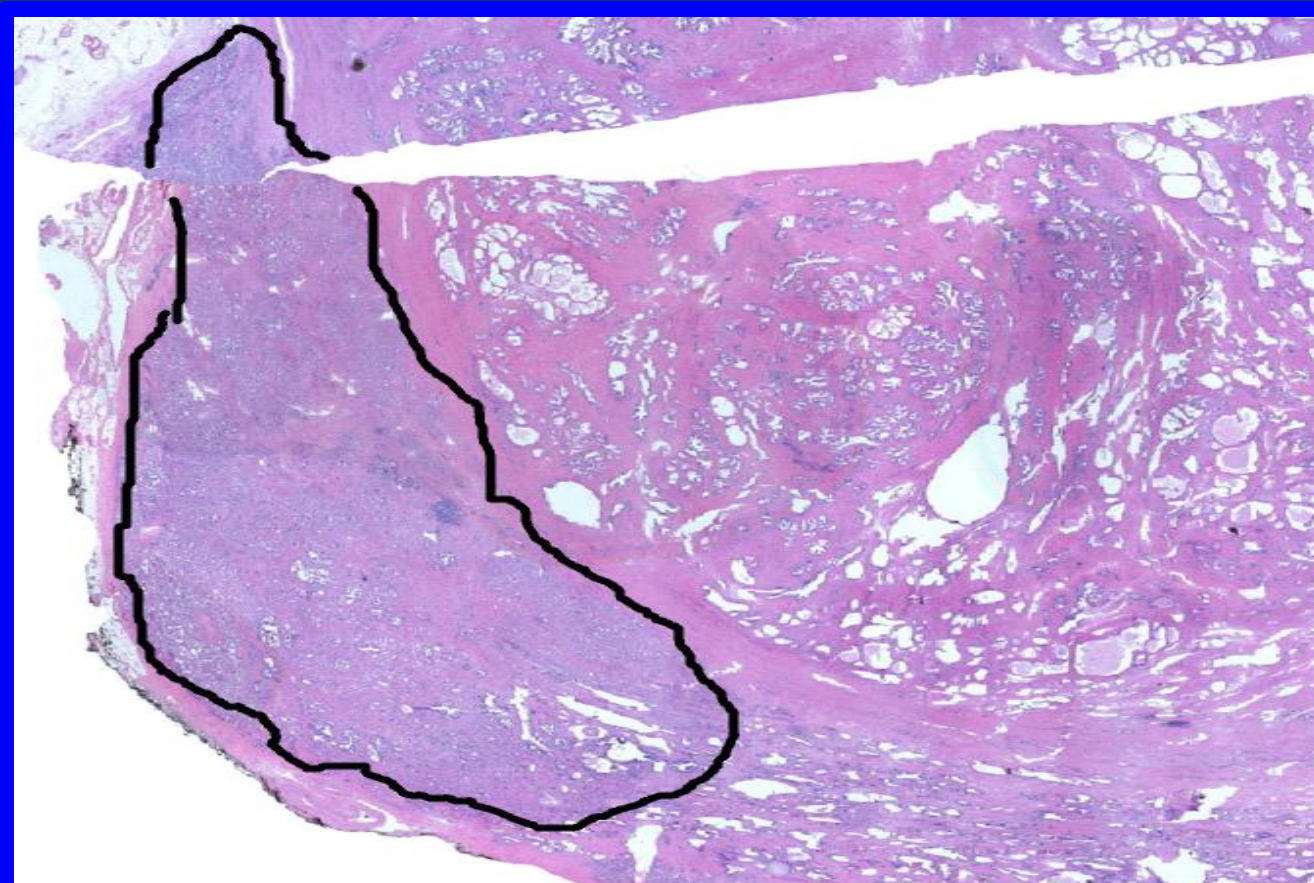


## Extracapsular tumor extension?

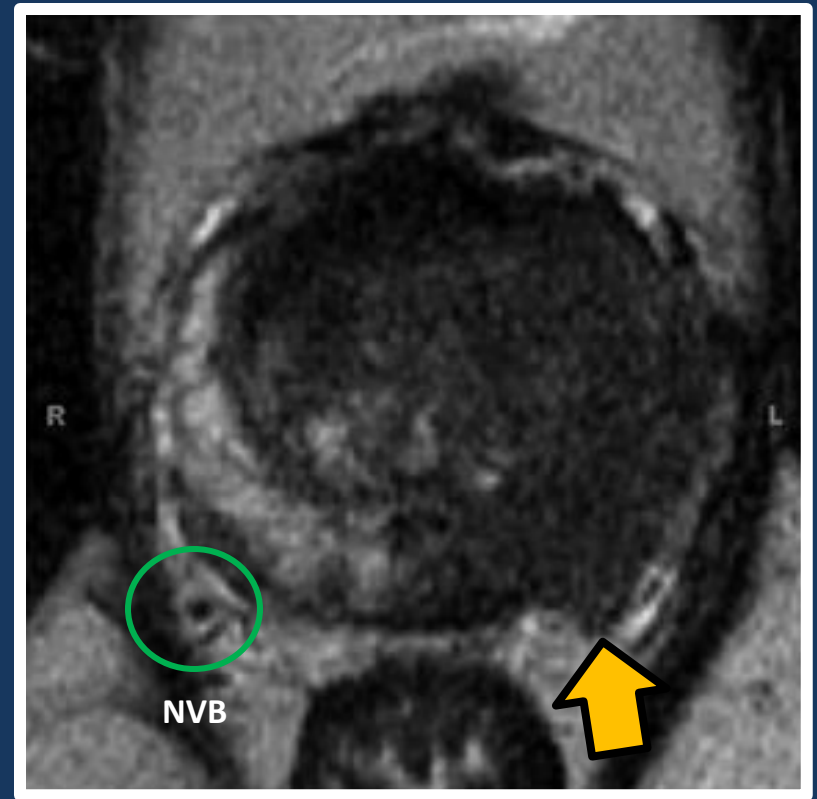
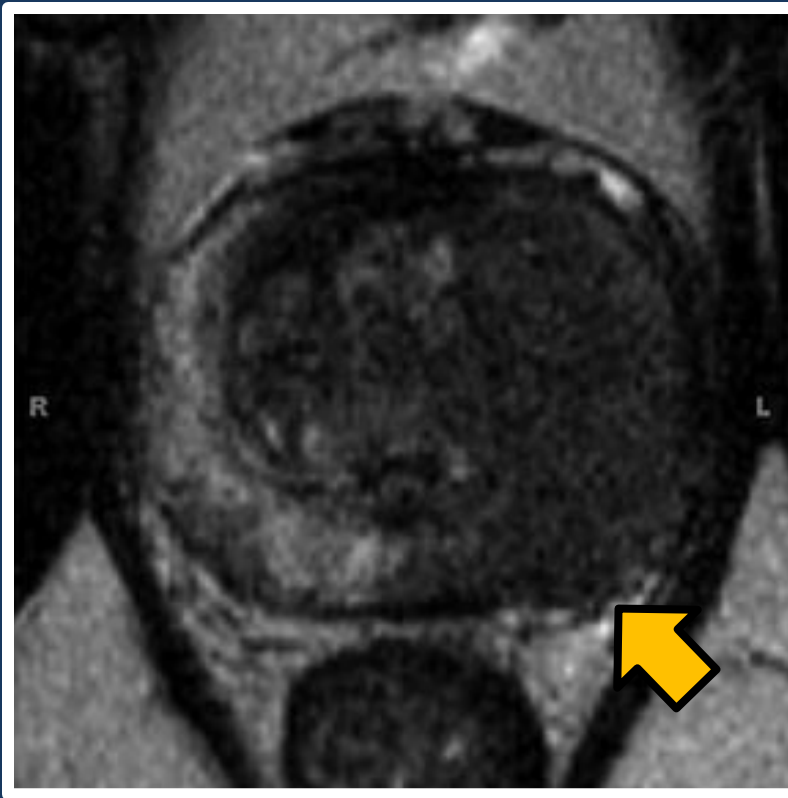


Right Mid lateral gland extra-capsular tumor T3a ?

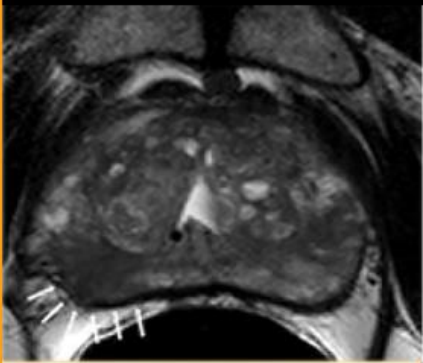
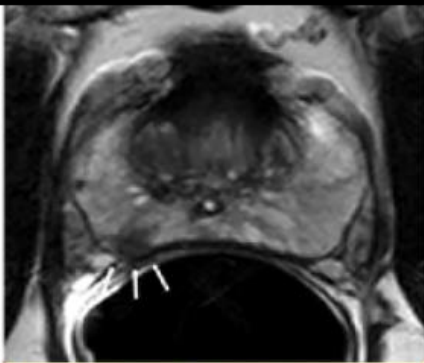
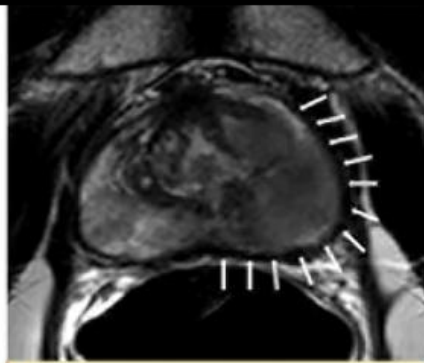
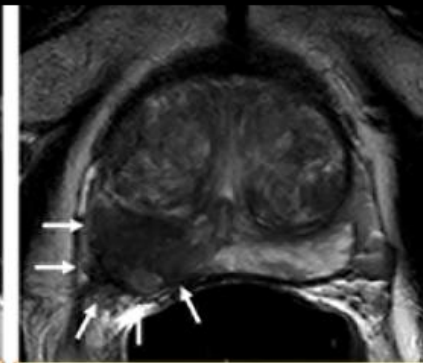
## Extra-prostatic extension Gleason 3+4=7



## Established Extraprostatic Extension T3a

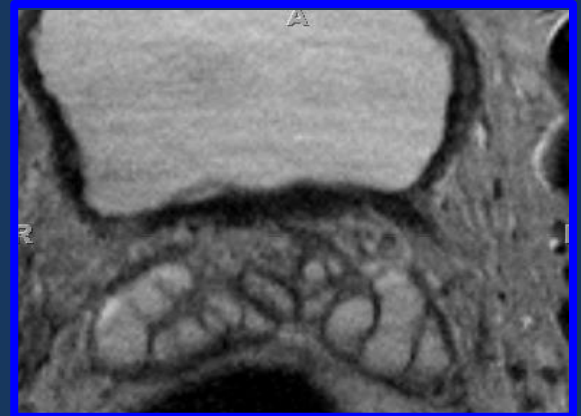
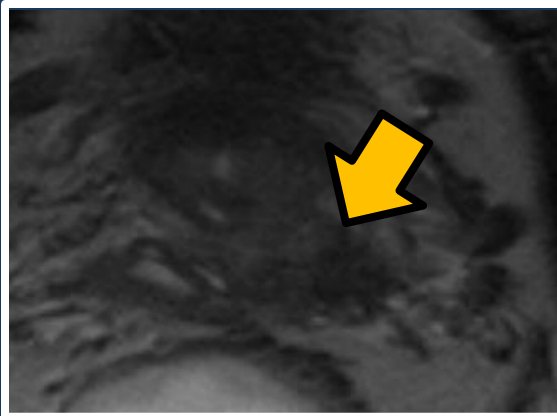
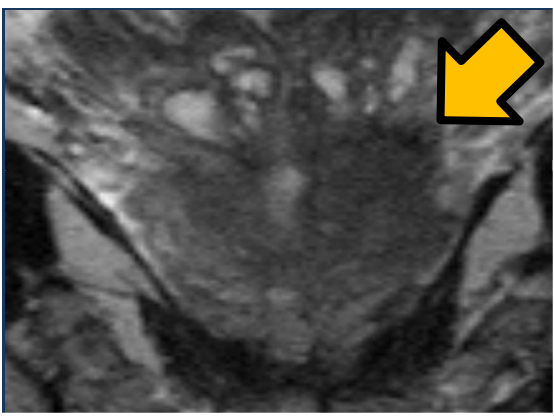


## A Grading System for the Assessment of Risk of Extraprostatic Extension of Prostate Cancer at Multiparametric MRI

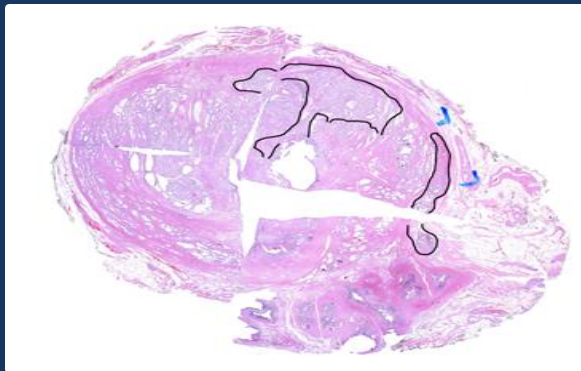
|                                                                                  |                                                                                   |                                                                                    |                                                                                     |
|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|  |  |  |  |
| <u>MRI-Derived<br/>EPE Grade 1</u>                                               | <u>MRI-Derived<br/>EPE Grade 1</u>                                                | <u>MRI-Derived<br/>EPE Grade 2</u>                                                 | <u>MRI-Derived<br/>EPE Grade 3</u>                                                  |
| pEPE Risk<br>24.3%                                                               | pEPE Risk<br>24.3%                                                                | pEPE Risk<br>38.2%                                                                 | pEPE Risk<br>66.1%                                                                  |
| Curvilinear<br>contact length                                                    | Capsular<br>bulge/irregularity                                                    | Curvilinear contact<br>length <u>and</u> capsular<br>bulge/irregularity            | Frank breach of<br>prostatic capsule or<br>invasion of adjacent<br>structures       |

- MRI grade 3 was associated with a 66% positive predictive value and 82% negative predictive value for defining pathologic EPE of prostate cancer

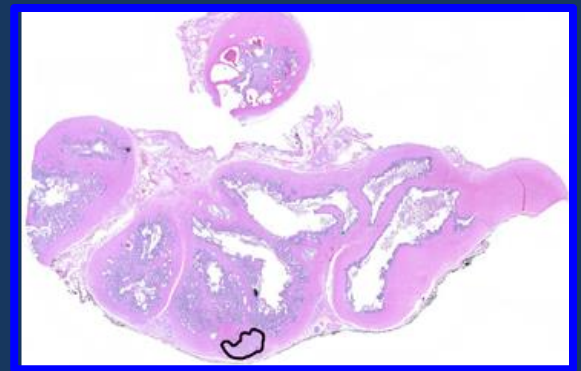
# Seminal Vesicle Invasion T3b?



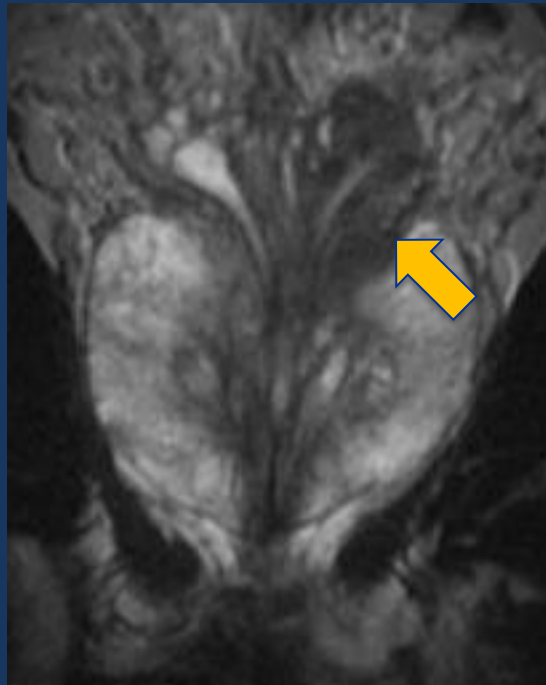
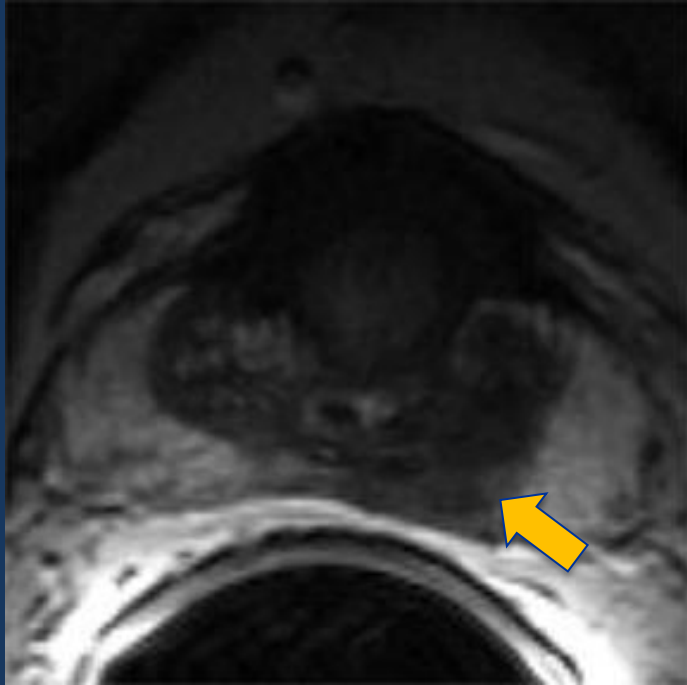
**MRI SVI  
False +**



**MRI SVI  
False -**



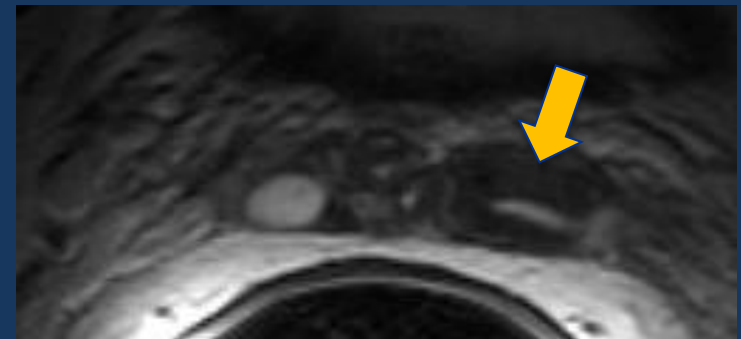
# Case 5: Prostate Cancer in Central Zone



59M PSA < 3.0 ng/mL, RP Gleason 4 + 3 (**GG3**) prostate cancer in the left base with extra-prostatic extension and left seminal vesicle invasion.



Cancers originating in the CZ are uncommon < 5% but significantly more aggressive, with greater risk of ECE, seminal vesicle invasion and positive surgical margins.

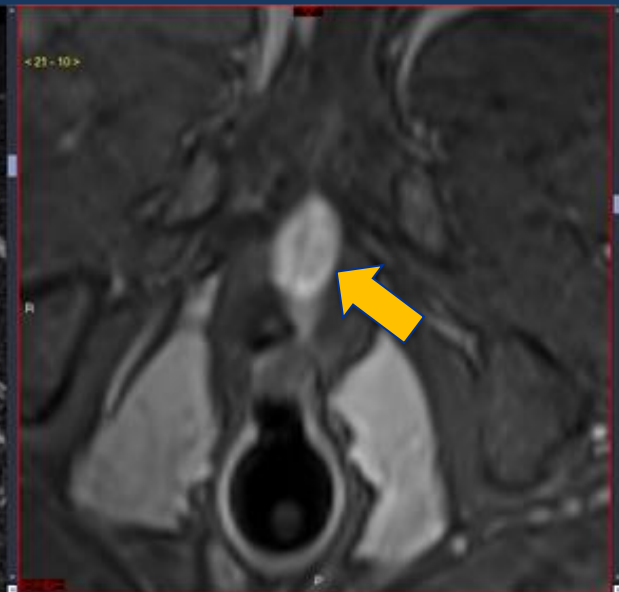
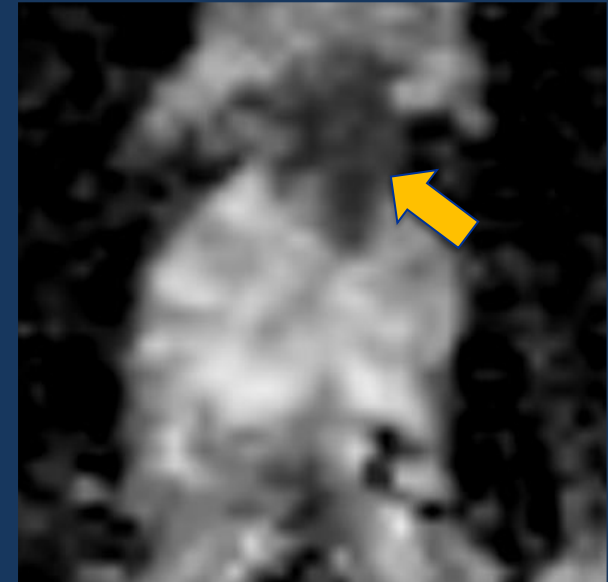
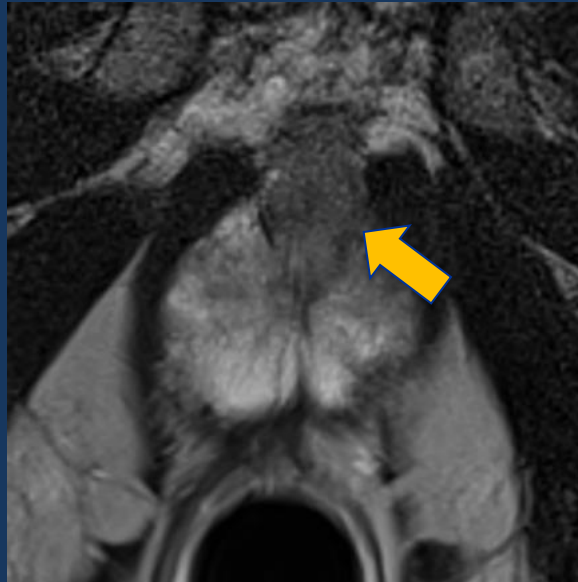


Classic Seminal Vesicle Invasion

# Case 6: Prostate Cancer at Distal Apex and Urethra

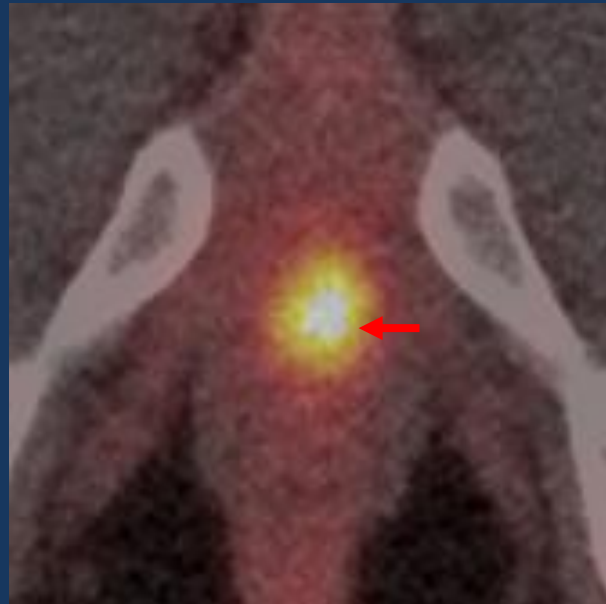
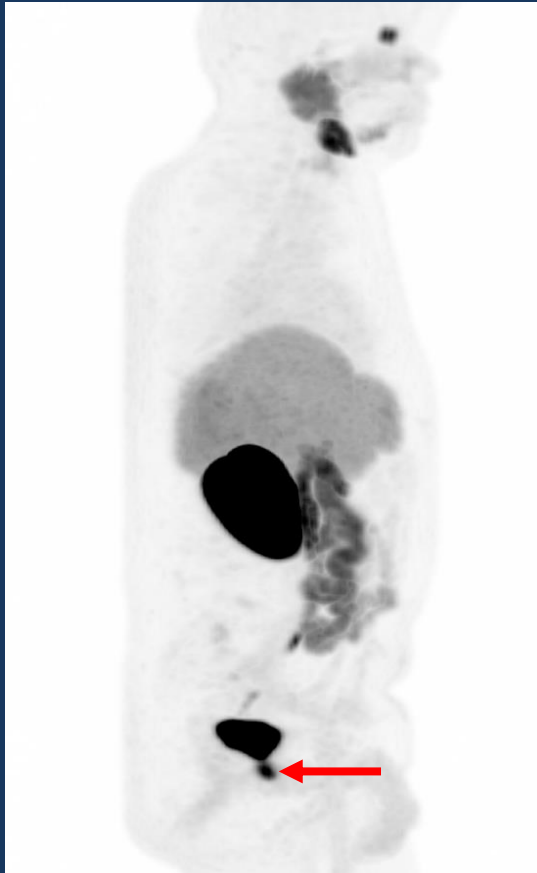
59M pre-op PSA 10.1 ng/mL  
RP: 3+4=7 (**GG 2**) disease  
at the apex with **+margin** at  
the left anterior apex

Initial post-op PSA 4.2  
ng/mL, rising to 6.5 ng/mL 2  
months later, scheduled for  
PSMA-targeted  $^{18}\text{F}$ -DCFPyL  
PET-CT

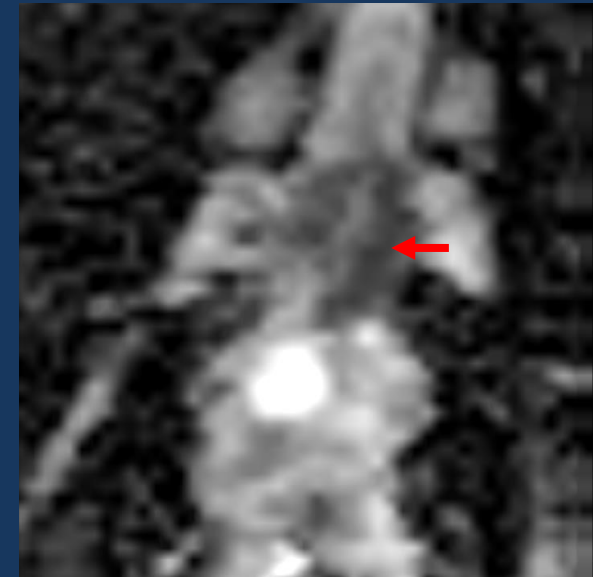
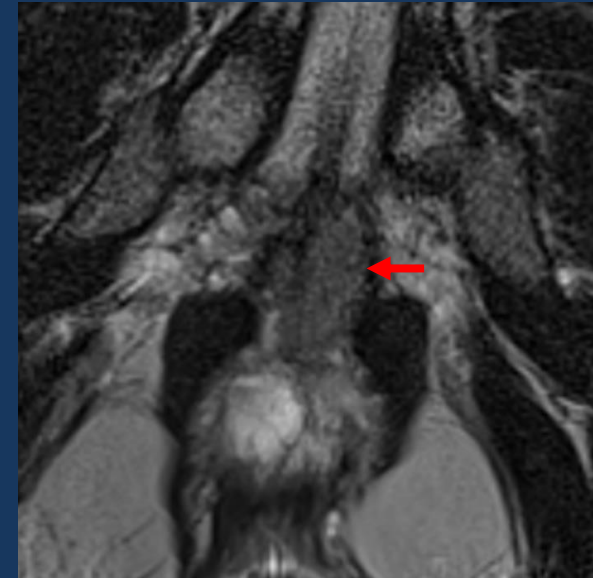


Pre-op MRI

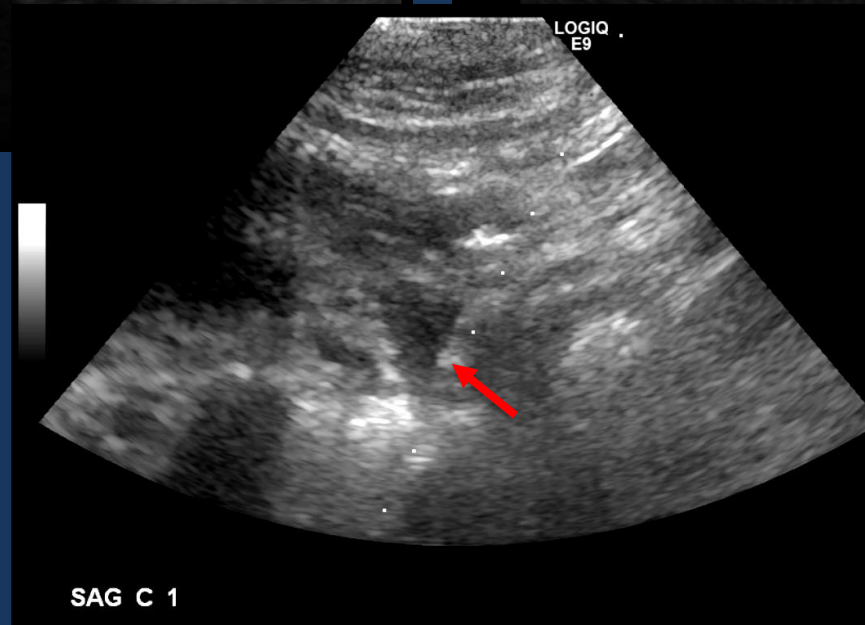
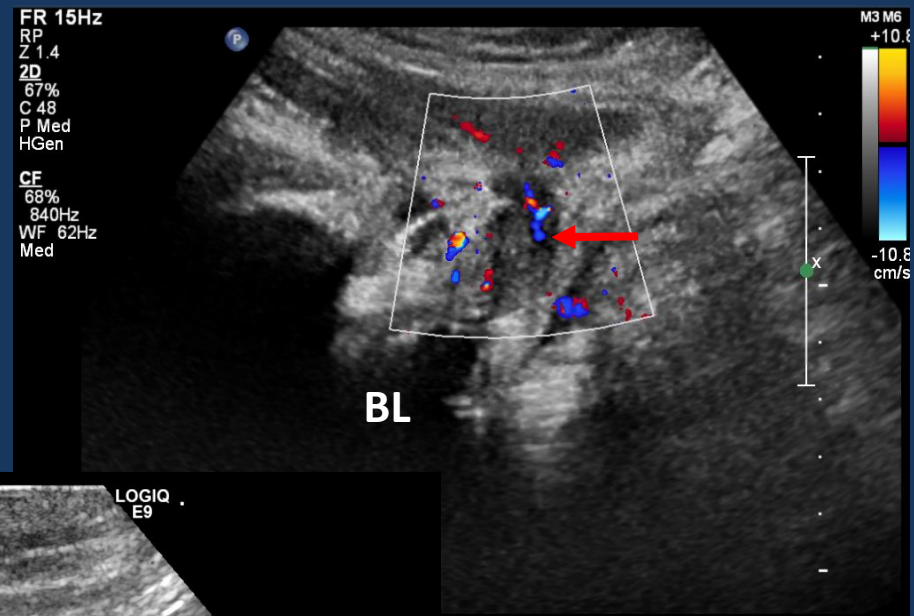
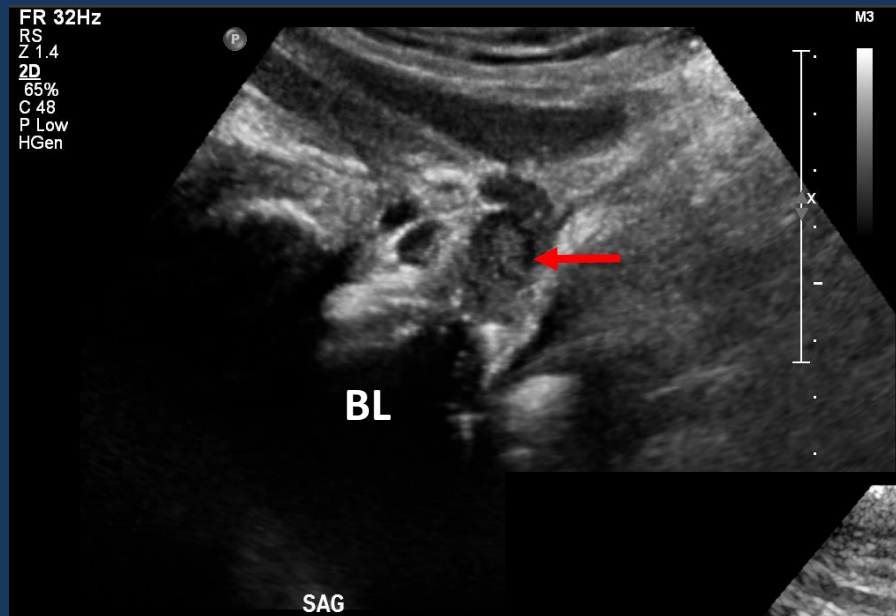
# Post-RP PSMA PET-CT



Pre-op MRI



# Post-RP Trans-perineal US and Biopsy

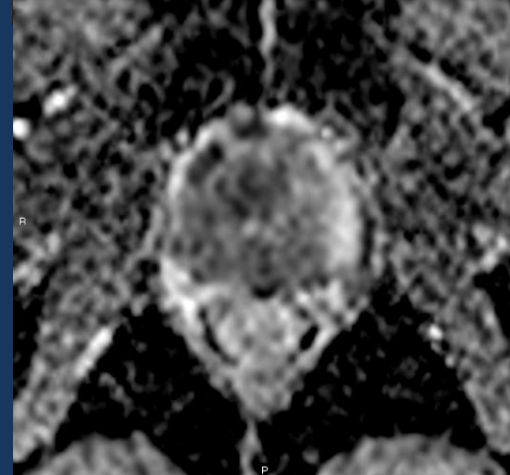
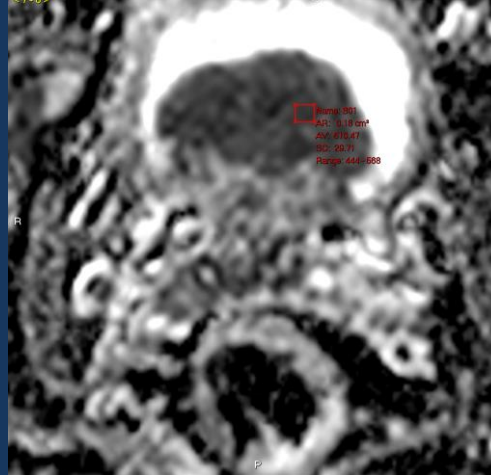
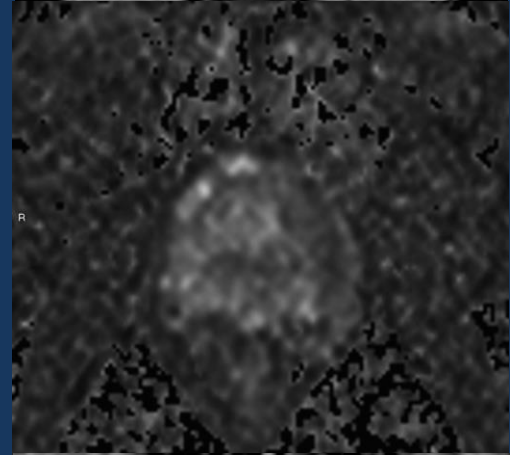
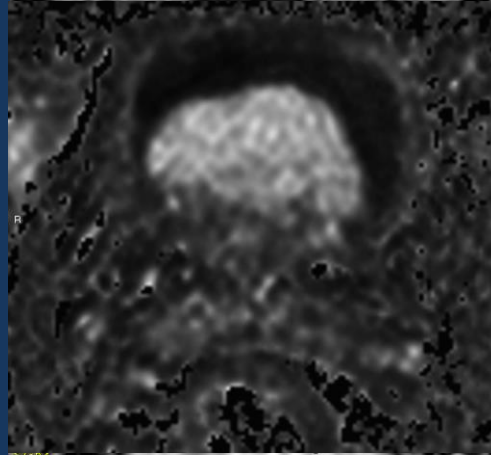
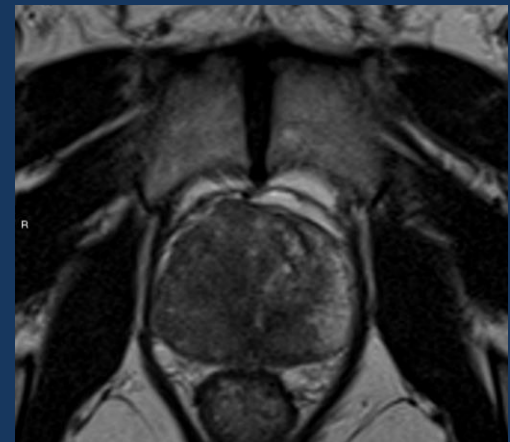
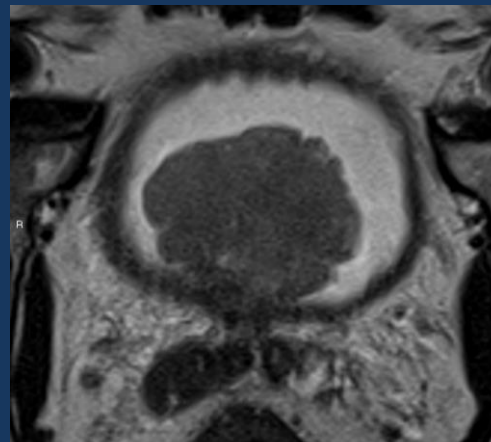
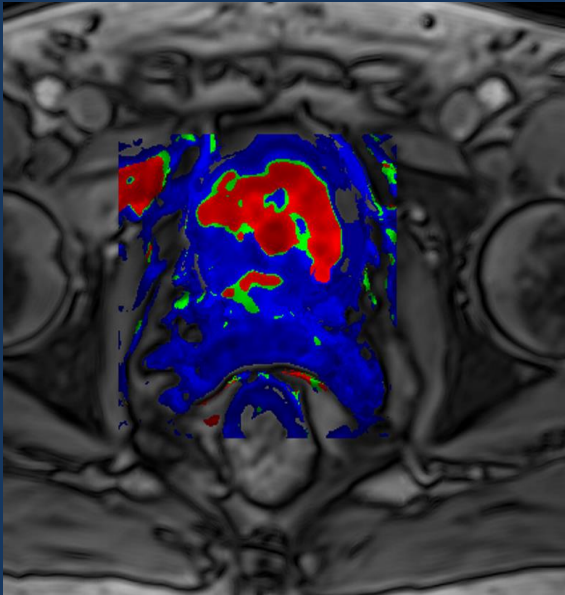


Adenocarcinoma  
Gleason score  
 $3+4=7$  (**GG 2**)

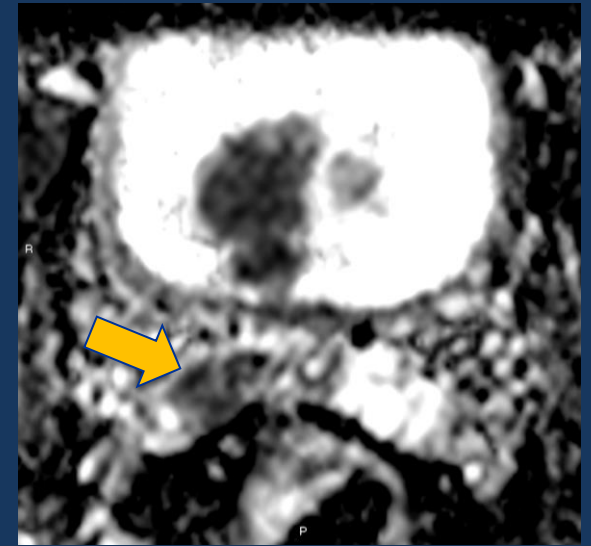
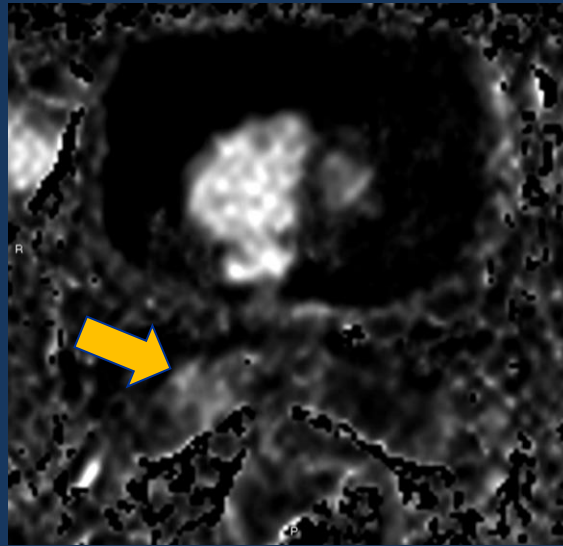
# Case 7: Very High Risk Large Volume Cancer

63M with hematuria and PSA 56.7 ng/mL; PHI: 215

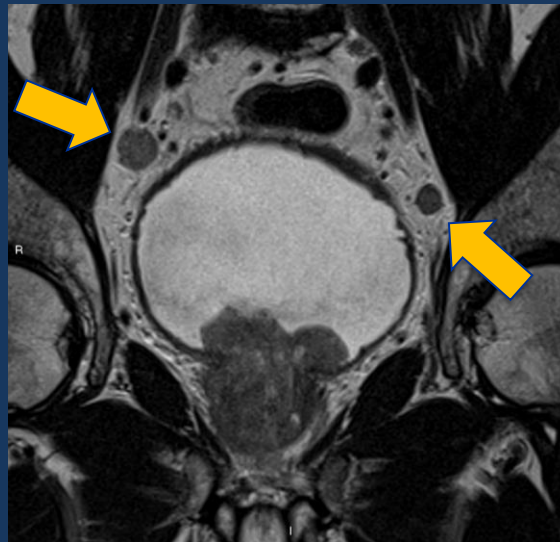
BLADDER TUMOR RESECTION  
TRANSURETHRAL (TURBT)  
Gleason 5+4 = 9 (**GG5**)  
Metastatic, TX → ADT, after 2  
years of ADT, he developed CRPC



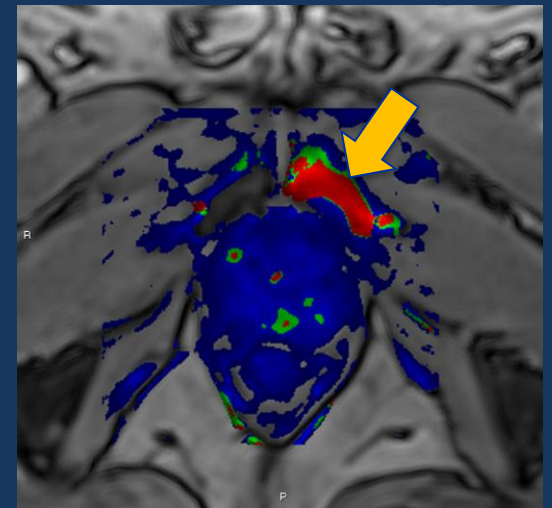
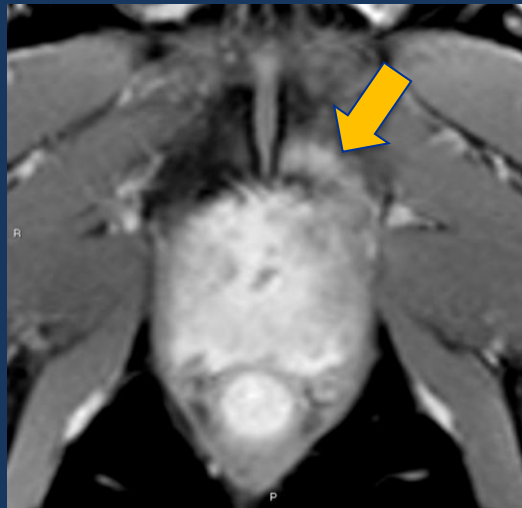
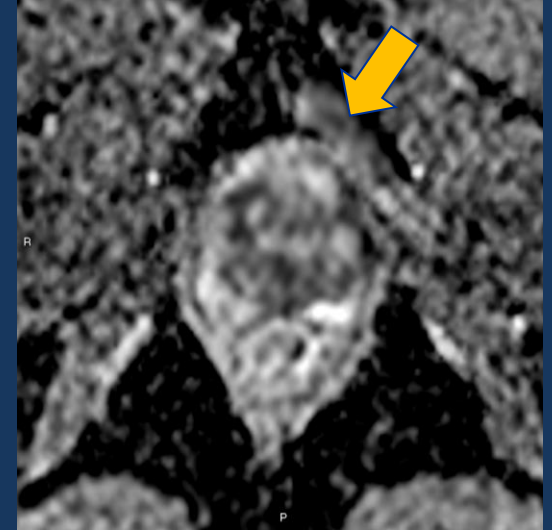
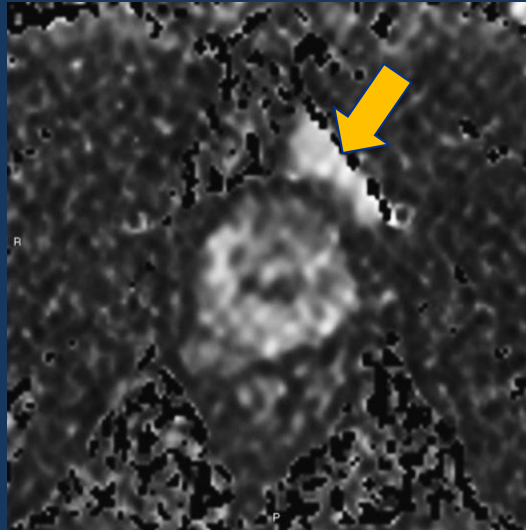
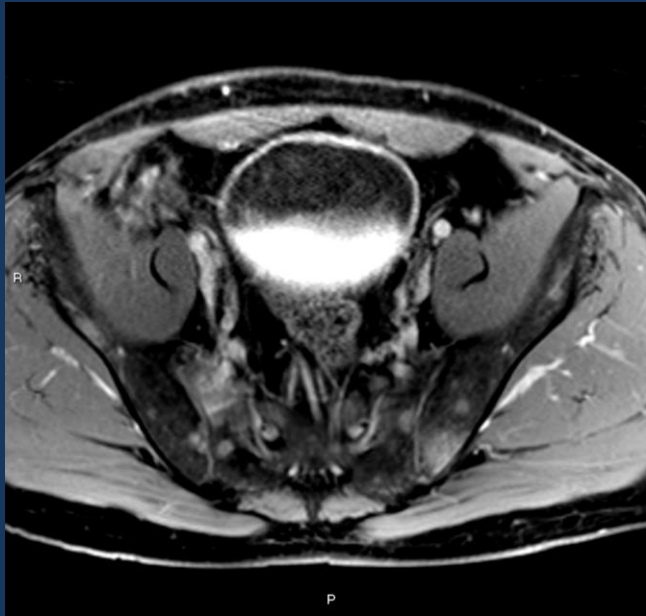
SVI



Nodal  
Metastases



# Bone metastases



# Summary

- **Clinical risk:** age, race/ethnicity, family history
  - 1 in 6 men with prostate cancer has a hereditary genetic variant
  - With metastatic disease, survival of men with BRCA1 or BRCA2 variant is half of men with no genetic variant (16% more men develop metastases with BRCA at 5 years)
  - Lynch Syndrome (hereditary non-polyposis colorectal cancer, or HNPCC)
- **Histopathology - ISUP GG**
- **Biomarker-based risk**
- **Imaging-based risk + MR-guided biopsy**



**Important to incorporate imaging + clinical data**  
**Standardization in image interpretation PI-RADS v2.1**