MRI Ultrasound Fusion Targeted Prostate Biopsy In Prostate Cancer Localization, Risk Assessment, And Focal Therapy

Marc A. Bjurlin, DO, MSc
Associate Professor
Department of Urology
Lineberger Comprehensive Cancer Center

UNC
LINEBERGER

Problems with Current Detection Paradigm

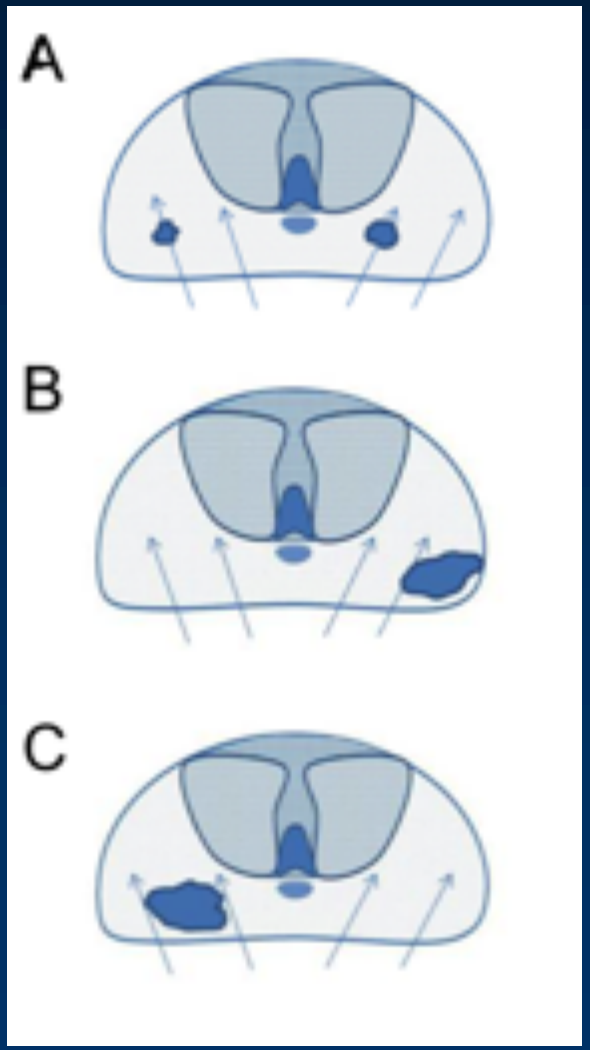
- PSA sensitivity is set by threshold, but specificity is poor at all threshold
- No ability of PSA to distinguish aggressive disease
- Huge number of biopsies
  - Repeat biopsies for men with cancer
  - Repeat biopsies for men without cancer
- Resulting over-detection leading to over-treatment leading to criticism of our field

What is the problem?

- The biomarker
- The response to the biomarker
- The biopsy
- The response to the biopsy

We can probably do better with all of the above.

Current Limitations of Prostate Biopsy



Clinically insignificant cancers are identified by chance

Important cancers are incorrectly risk stratified

Clinically significant tumors are missed

(Bjurlin, et al, J Urol, 2014; adapted from H Ahmed, UCL)

Definition of Biopsy Optimization

- Detection of potentially lethal prostate cancer
- Avoidance of “over-detection” of clinically insignificant cancer
- Generation of clinically useful data
  - accurate depiction of risk and cancer location
- Maintenance of cost effectiveness
  - Avoidance of repetitive biopsy
  - Cost effective specimen handling

Taneja, et al, AUA White Paper: Optimization of Prostate Biopsy and Specimen Handling, 2013
Bjurlin, et al, J Urol, 2013

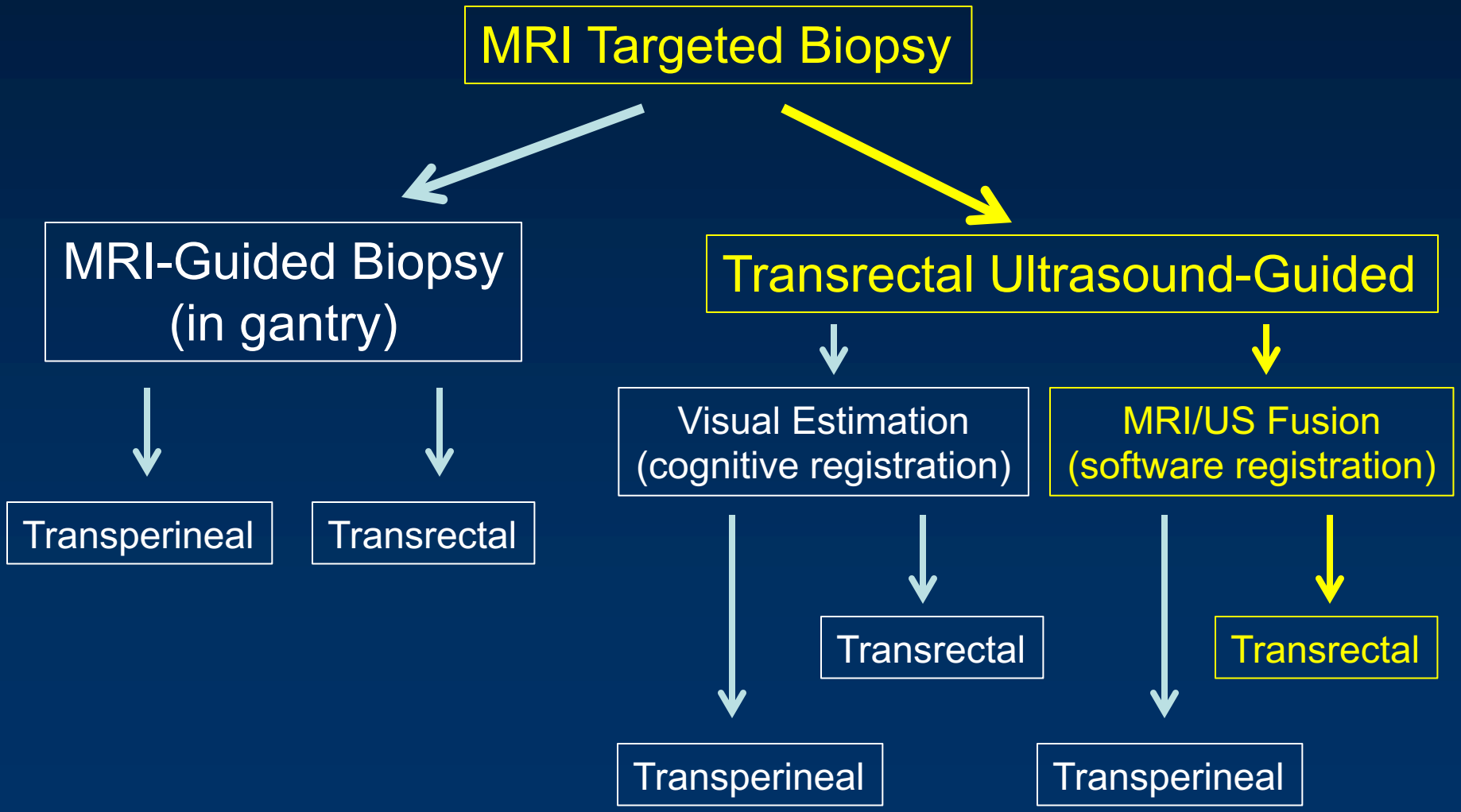
Options for Improving The Biopsy Paradigm

- Better candidate selection
  - Biomarkers: PCA3, PHI, 4k score
  - Nomograms: PCPT calculator, Vienna nomogram
- Saturation techniques
  - Overcome sampling error through excessive sampling
- Targeted biopsy/Imaging
  - Use of imaging to guide biopsy
  - Use of imaging to stratify risk

MRI Could Correct All the Limitations of Systematic Biopsy

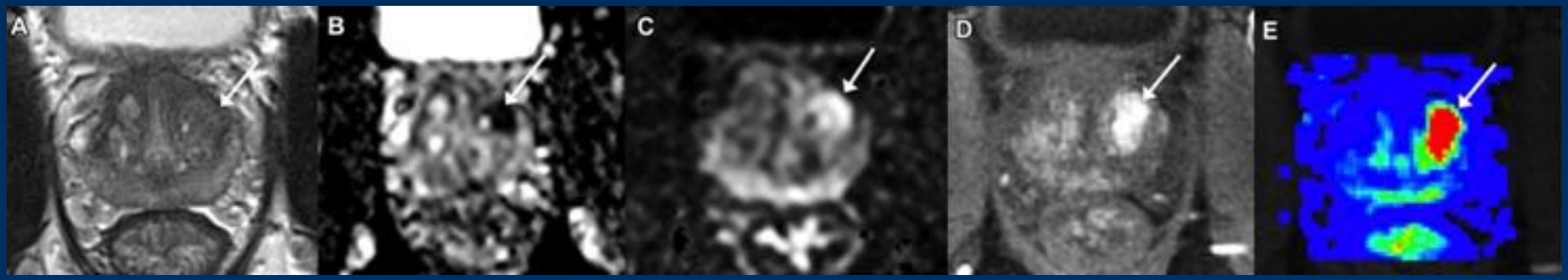
- Targeting of patients with MR detected abnormality
  - fewer false negatives
    - fewer repeat biopsies
  - more accurate cancer classification
    - greater cancer core length
    - better grade concordance
    - better patient selection for AS/therapy
- No biopsy for MRI normal patients
  - avoidance of over-detection of indolent tumors

MRI Targeted Biopsy Approach



Multiparametric MRI of the Prostate

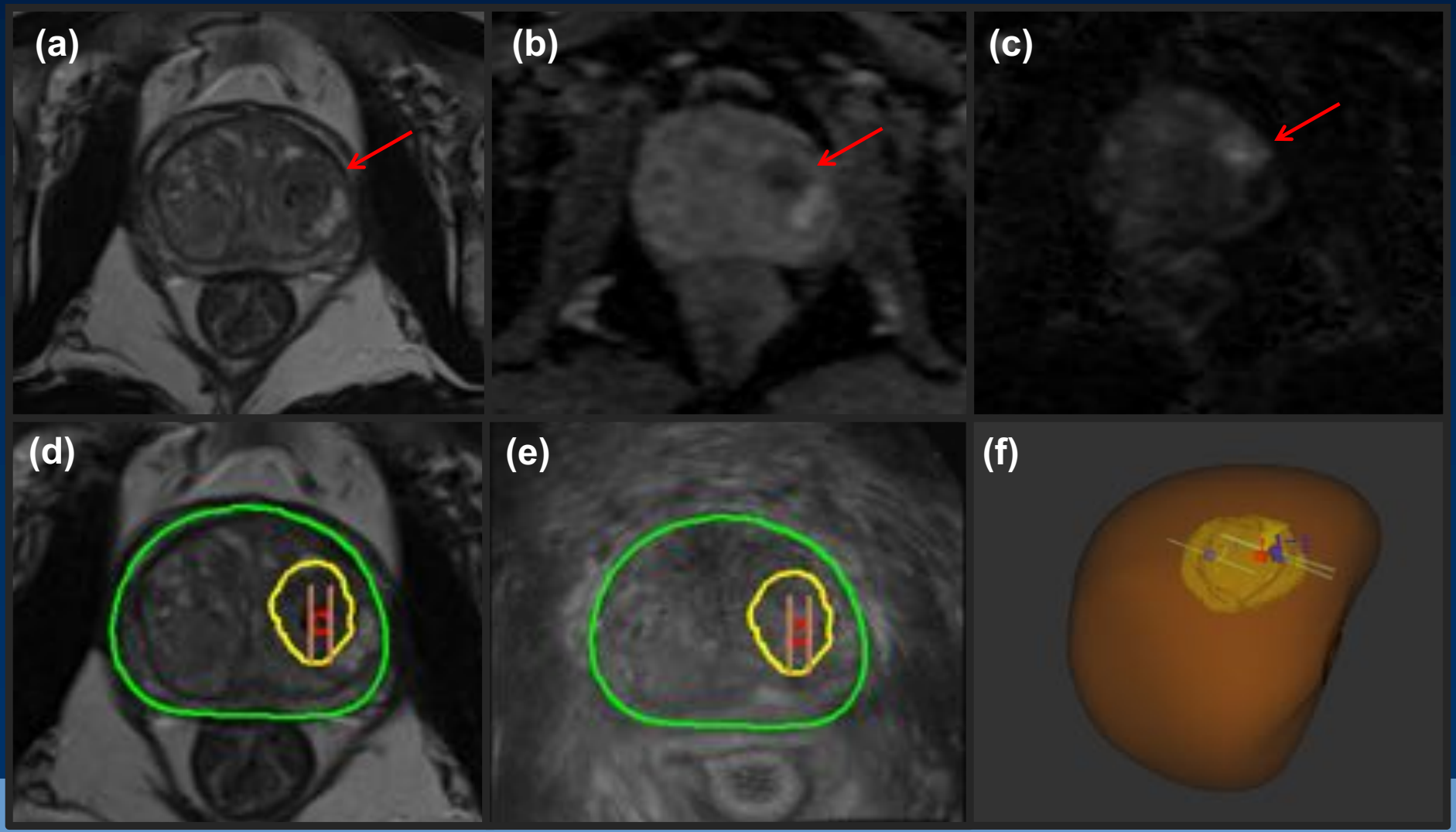
- Pre-biopsy 3T multi-parametric MRI
  - Identify areas of suspicion for sampling
  - Predicts likelihood of prostate cancer through MRI suspicion score (PI-RADS)
  - Selection of patients for biopsy



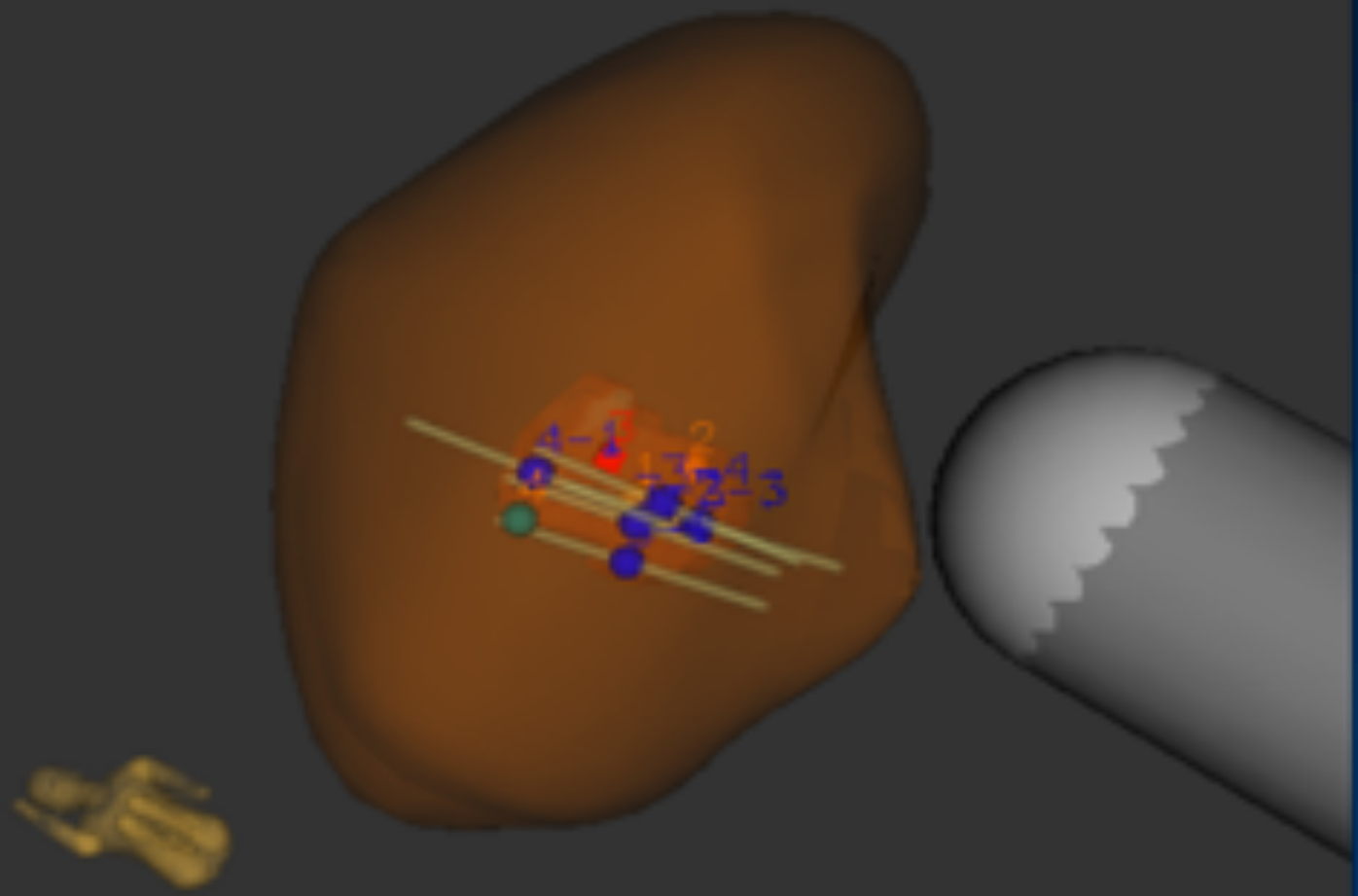
T2WI ADC DWI DCE Perfusion Map

Bjurlin, et al, J Urol, 2013

MRI-targeted fusion biopsy

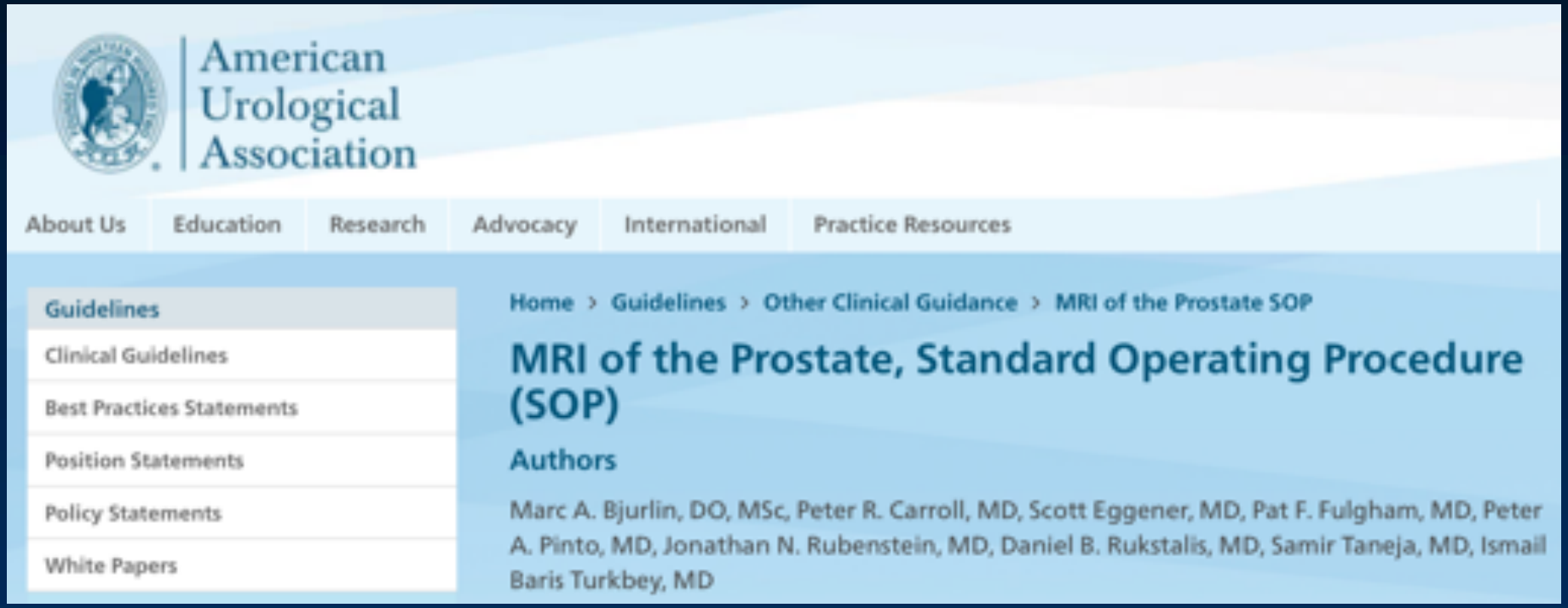


MRI-US Fusion-Targeted Biopsy



Clinical Applications of Pre-biopsy MRI Prior to Targeted Biopsy

- Previous negative biopsy
  - Finding missed disease
- Active surveillance/ known cancer
  - Localizing dominant disease
  - Accurate classification of disease risk
- **No previous biopsy**
  - Goal of finding lethal disease while missing non-lethal disease
  - Reduction of over-detection



- **2017**: Purpose of this paper is to evaluate the available evidence and make practical recommendations

Evaluation of Biopsy Naïve Patients Utilizing mpMRI (2017)

- **Keypoint:** The *clinical impact of mpMRI-targeted biopsy in men with no previous history of prostate biopsy remains controversial*, due to an unclear magnitude of clinical impact relative to cost. In considering its use, quality of mpMRI, experience of interpreting radiologist, cost of mpMRI, and availability of alternate biomarkers should be considered.

Evaluation of Biopsy Naïve Patients Utilizing mpMRI (2017)

- **<u>Keypoint:</u>** *There is insufficient data to recommend routine MRI in every biopsy naïve patient under consideration for prostate biopsy*. Its use may be considered in men for whom clinical indications for biopsy are uncertain (minimal PSA increase, abnormal DRE with normal PSA, or very young or old patients).

Changing the Biopsy-Naïve Paradigm

- **PROMIS** - Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study – *Lancet* 2017

- **PRECISION** - MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis – *NEJM* 2018

- **MRI-FIRST** - Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study – *Lancet* 2019

PROMIS

- Multicenter, paired-cohort, confirmatory study to compare the diagnostic accuracy of MRI and TRUS-guided systematic biopsy against a reference template prostate mapping biopsy

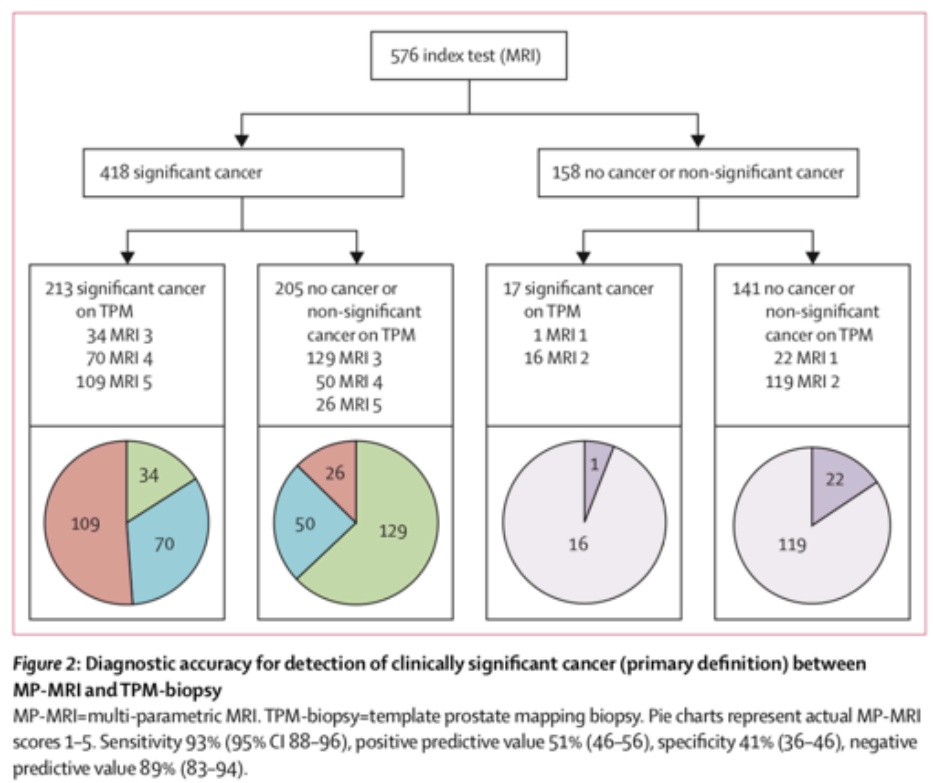


Figure 2: **Diagnostic accuracy for detection of clinically significant cancer (primary definition) between MP-MRI and TPM-biopsy**
MP-MRI=multi-parametric MRI. TPM-biopsy=template prostate mapping biopsy. Pie charts represent actual MP-MRI scores 1–5. Sensitivity 93% (95% CI 88–96), positive predictive value 51% (46–56), specificity 41% (36–46), negative predictive value 89% (83–94).

- MRI: more sensitive for clinically significant cancer (defined as GS ≥4+3) than TRUS biopsy (93% vs 48%) and less specific (41% vs 96%
- MRI triage: allow 27% to avoid a biopsy, 5% fewer clinically insignificant cancers detected
- NPV of 89% for low suspicion MRI, (using 4+3) but for 3+4, the NPV decreased to 74%

PRECISON

- Multicenter randomized, noninferiority trial, assigning men with a clinical suspicion of prostate cancer who had not undergone biopsy previously to undergo MRI, with or without targeted biopsy, or standard TRUS biopsy

Table 2. Comparison of Cancer Detection between Groups.*

Outcome	MRI-Targeted Biopsy Group (N=252)	Standard-Biopsy Group (N=248)	Difference†	P Value
Biopsy outcome — no. (%)			—	—
No biopsy because of negative result on MRI	71 (28)	0		
Benign tissue	52 (21)	98 (40)		
Atypical small acinar proliferation	0	5 (2)		
High-grade prostatic intraepithelial neoplasia	4 (2)	10 (4)		
Gleason score				
3+3	23 (9)	55 (22)		
3+4	52 (21)	35 (14)		
3+5	2 (1)	1 (<1)		
4+3	18 (7)	19 (8)		
4+4	13 (5)	6 (2)		
4+5	7 (3)	2 (1)		
5+5	3 (1)	1 (<1)		
No biopsy‡	4 (2)	3 (1)		
Withdrawal from trial§	3 (1)	13 (5)		
Clinically significant cancer¶				
Intention-to-treat analysis — no. (%)	95 (38)	64 (26)	12 (4 to 20)	0.005
Modified intention-to-treat analysis — no./total no. (%)	95/245 (39)	64/235 (27)	12 (3 to 20)	0.007
Per-protocol analysis — no./total no. (%)	92/235 (39)	62/227 (27)	12 (3 to 20)	0.007
Clinically insignificant cancer — no. (%)	23 (9)	55 (22)	−13 (−19 to −7)	<0.001
Maximum cancer core length — mm	7.8±4.1	6.5±4.5	1.0 (0.0 to 2.1)	0.053
Core positive for cancer — no./total no. of cores (%)	422/967 (44)	515/2788 (18)	—	—
Men who did not undergo biopsy — no. (%)‖	78 (31)	16 (6)	—	—

- 71 of 252 men (28%) had PI-RADS 1-2 = No biopsy
- ≥Gleason 3+4: 95 men (38%) in the MRI-targeted group, 64 of 248 (26%) in the standard-biopsy group (*P*=0.005)
- MRI: not only non-inferior, but superior to standard TRUS-biopsy for the detection of clinically significant cancer
- Fewer men undergoing MRI-targeted biopsy were found to have indolent (Gleason 3+3) cancers

MRI-FIRST

- Prospective, multicenter, paired diagnostic study, conducted at 16 centers in France to address whether MRI before biopsy would improve detection of clinically significant prostate cancer in biopsy-naive patients

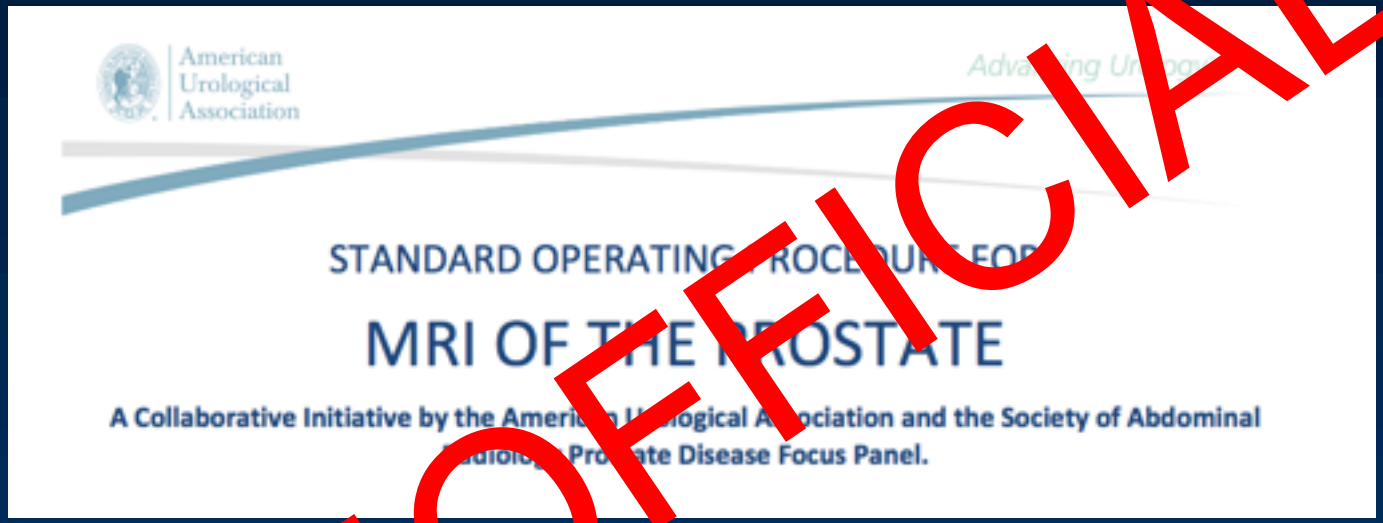
	ISUP grade group ≥2 (csPCa-A)	ISUP grade group ≥2 or ISUP grade group 1 with MCCL ≥6 mm (csPCa-B)	ISUP grade group ≥3 (csPCa-C)
Systematic biopsy	29·9% (24·3–36·0)	32·7% (26·9–38·9)	15·1% (10·9–20·2)
Targeted biopsy	32·3% (26·5–38·4)	35·9% (29·9–42·1)	19·9% (15·2–25·4)
Systematic biopsy and targeted biopsy	37·5% (31·4–43·8)	41·8% (35·7–48·2)	21·1% (16·2–26·7)
Added value of systematic biopsy*	5·2% (2·8–8·7)	6·0% (3·4–9·7)	1·2% (0·2–3·5)
Added value of targeted biopsy†	7·6% (4·6–11·6)	9·2% (5·9–13·4)	6·0% (3·4–9·7)
p value‡	0·38	0·26	0·0095

Results are % (95% CI) of 251 patients, or p value. ISUP=International Society of Urological Pathology. csPCa=clinically significant prostate cancer. MCCL=maximal cancer core length. *Difference between the detection rate obtained by combined systematic biopsy and targeted biopsy, and by targeted biopsy alone. †Difference between the detection rate obtained by combined systematic biopsy and targeted biopsy, and by systematic biopsy alone. ‡From the comparison of detection rates obtained by systematic biopsy and targeted biopsy.

Table 3: **Detection of clinically significant prostate cancer, according to biopsy strategy**

- All - TRUS systematic and hypoechoic directed biopsies, +2 cores of MRI targets if ROI 3,4,5.
- N= 275 patients were enrolled, 53 (21%) had ROI≤ 2 = excluded
- Detection of clinically significant disease by systematic biopsy (30%) and targeted biopsy (32%) did not differ significantly (*P*=0.38),
- 87.5% of non-significant cancer was found on systematic biopsy and only 25% on targeted sampling =75% of indolent cancers were identified by systematic biopsy alone

2019 – Updated SOP MRI Prostate



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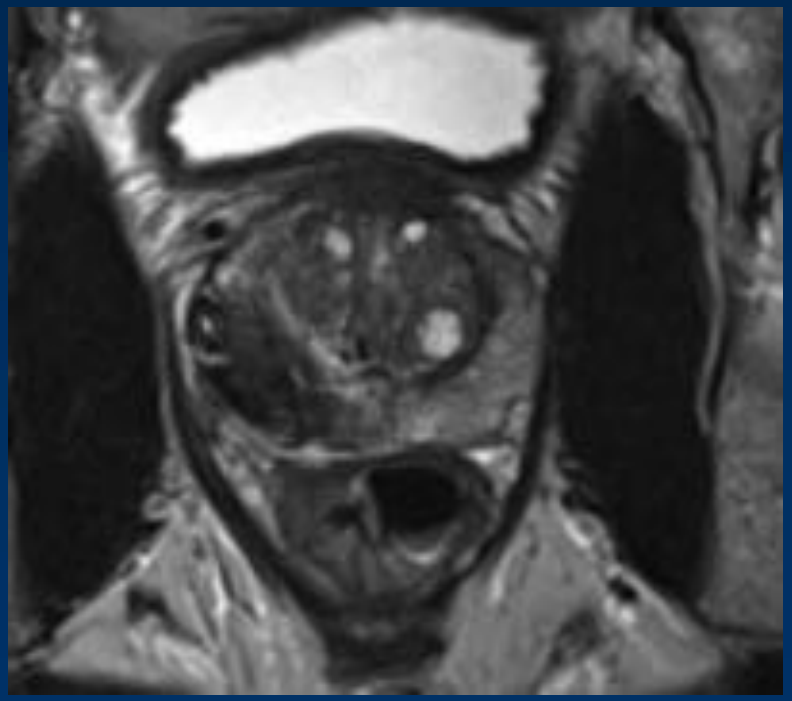
- **Keypoint:** *Two randomized clinical trials have provided level 1 data to support the recommendation of mpMRI prior to biopsy for all men*

Prostate Cancer Localization

Focal Therapy

Risk Assessment



Challenges of the Focal Therapy Paradigm

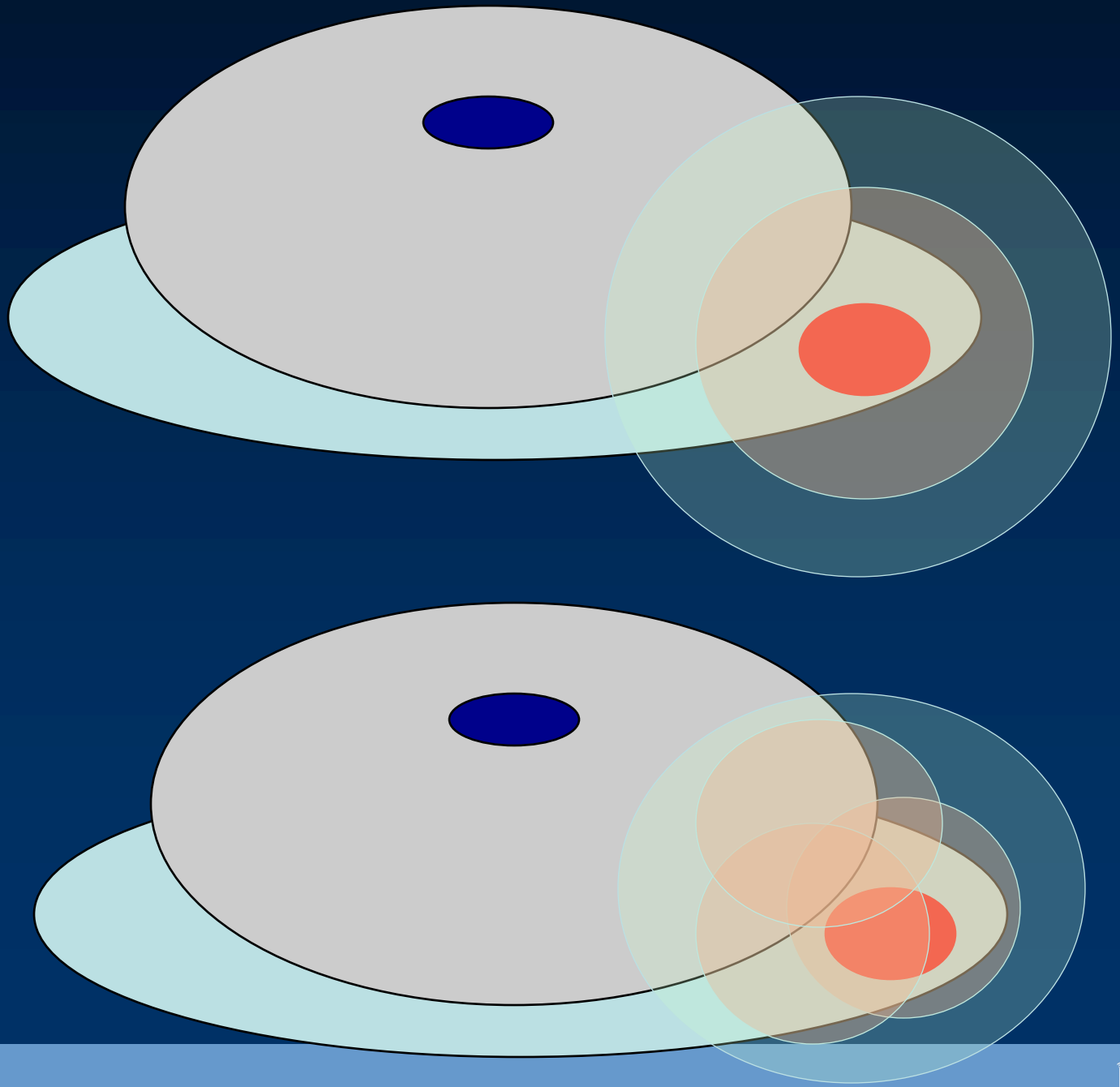
- Candidate Selection
- Method of Delivery
  - Image guided
  - Biopsy guided
- Treatment Planning
  - Extent
  - Adequacy of Margin
- Outcome Measures
- How do we prove benefit
  - Cost
  - QOL
  - Survival

Key Concepts

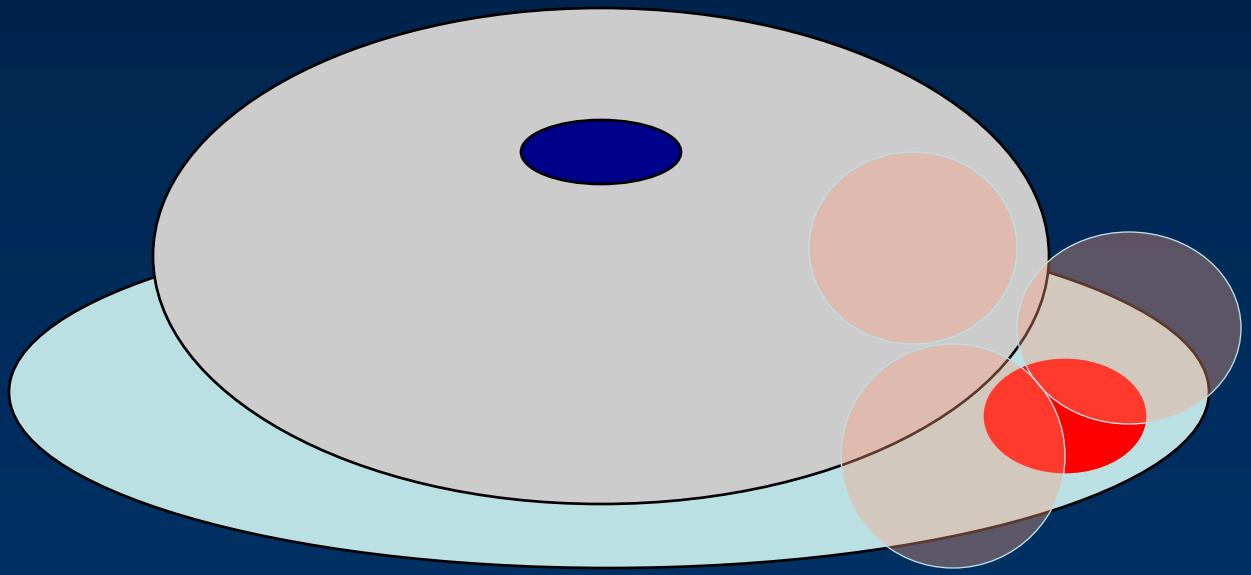
- Balance of focal treatment vs. adequacy of treatment
- Confluence of tissue destruction
- Inaccuracy of localization
  - Can be overcome by increasing tissue treated
- Dispersion of thermal energy
  - Contributes to toxicity

Potential Reasons for Focal Therapy Failure

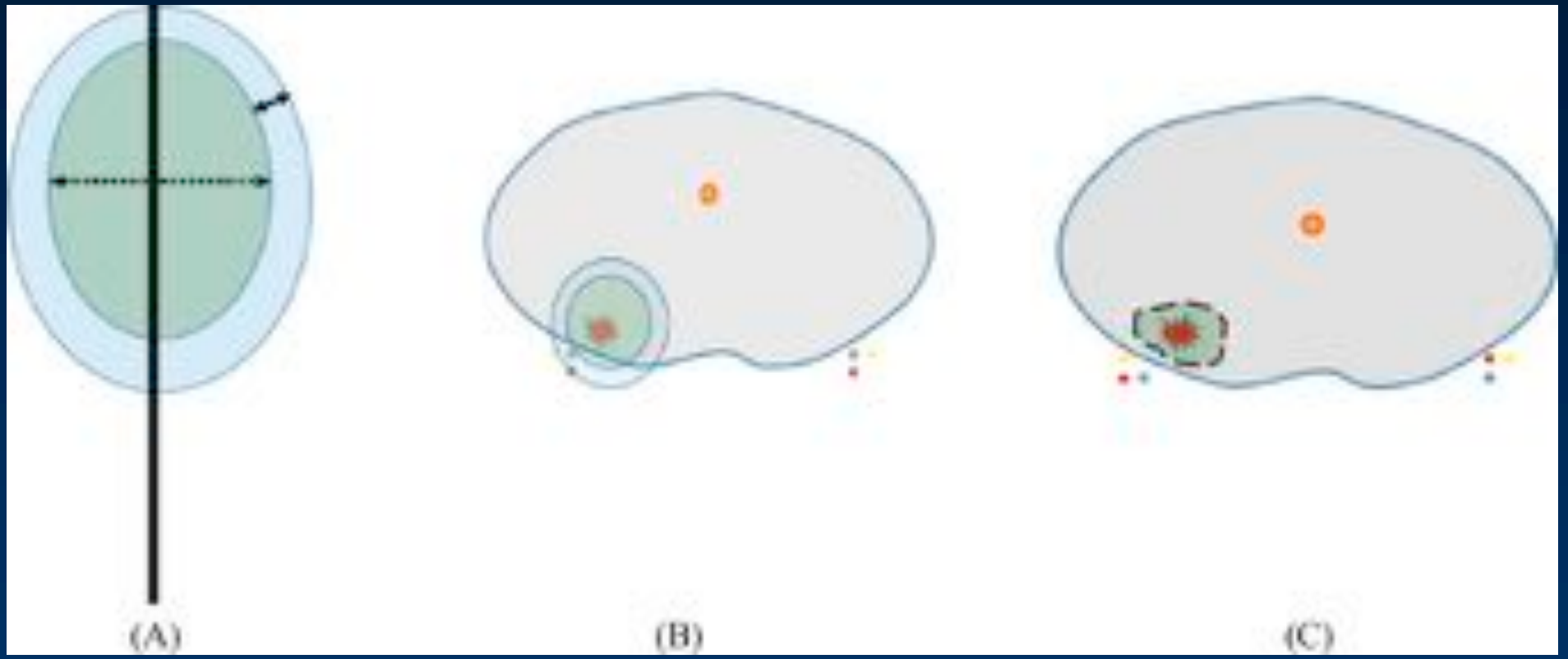
- Poor localization by imaging
  - Inadequate detection
  - Incomplete demonstration of tumor
- Poor staging biopsy
  - Implies disease missed by MRI and biopsy
  - Under-sampling at baseline
- Inadequate treatment
  - Under-treatment of target zone
  - Inadequate margin



Non-confluent Undertreatment

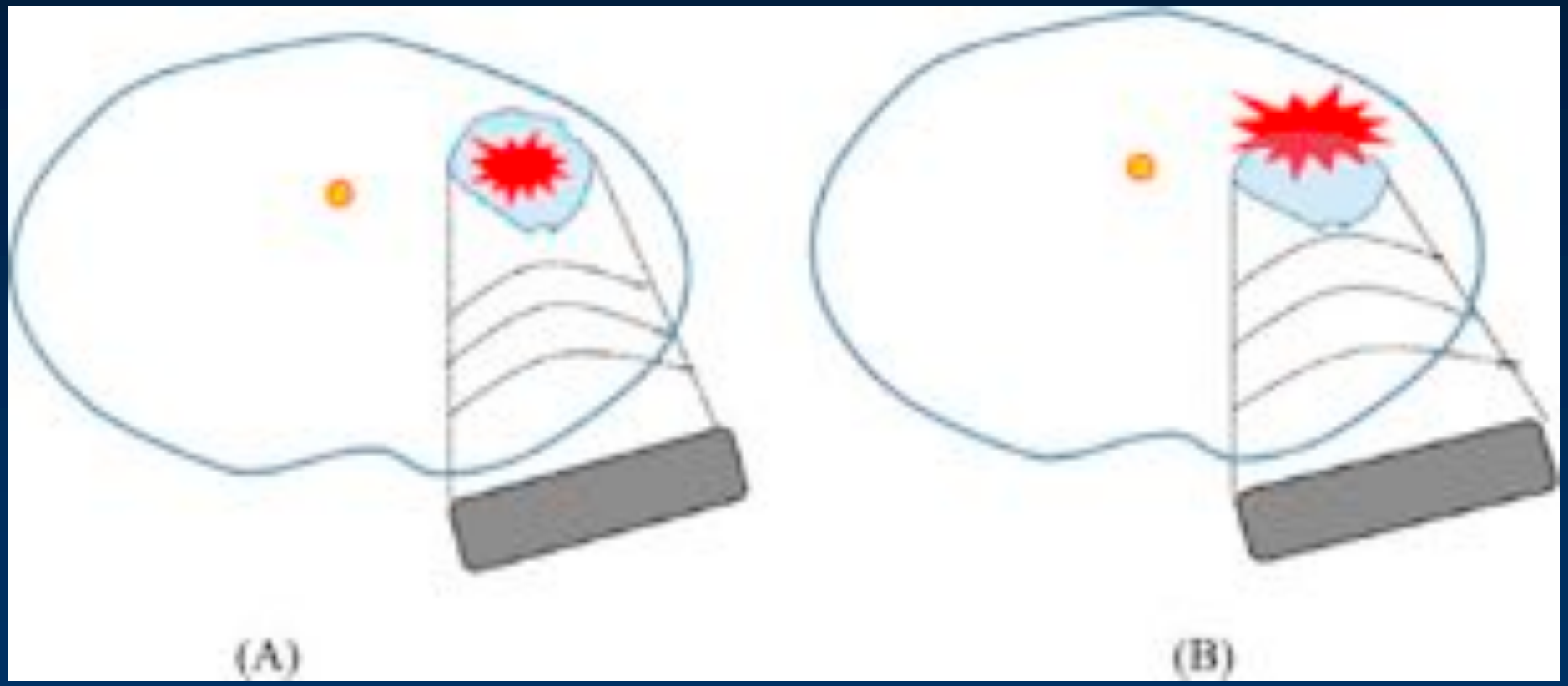


Cryotherapy vs HIFU



Graphical representation of the ablation volume with for cryotherapy and high-intensity focused ultrasound. (A) A cryo probe with an ice ball. The dotted arrows show the kill zone and the solid arrow shows the safety margin. (B) Cryoablation of a posterior lesion for which the safety zone for the ice ball extends beyond the prostatic capsule. (C) More precise control of the ablation zone with high-intensity focused ultrasound.

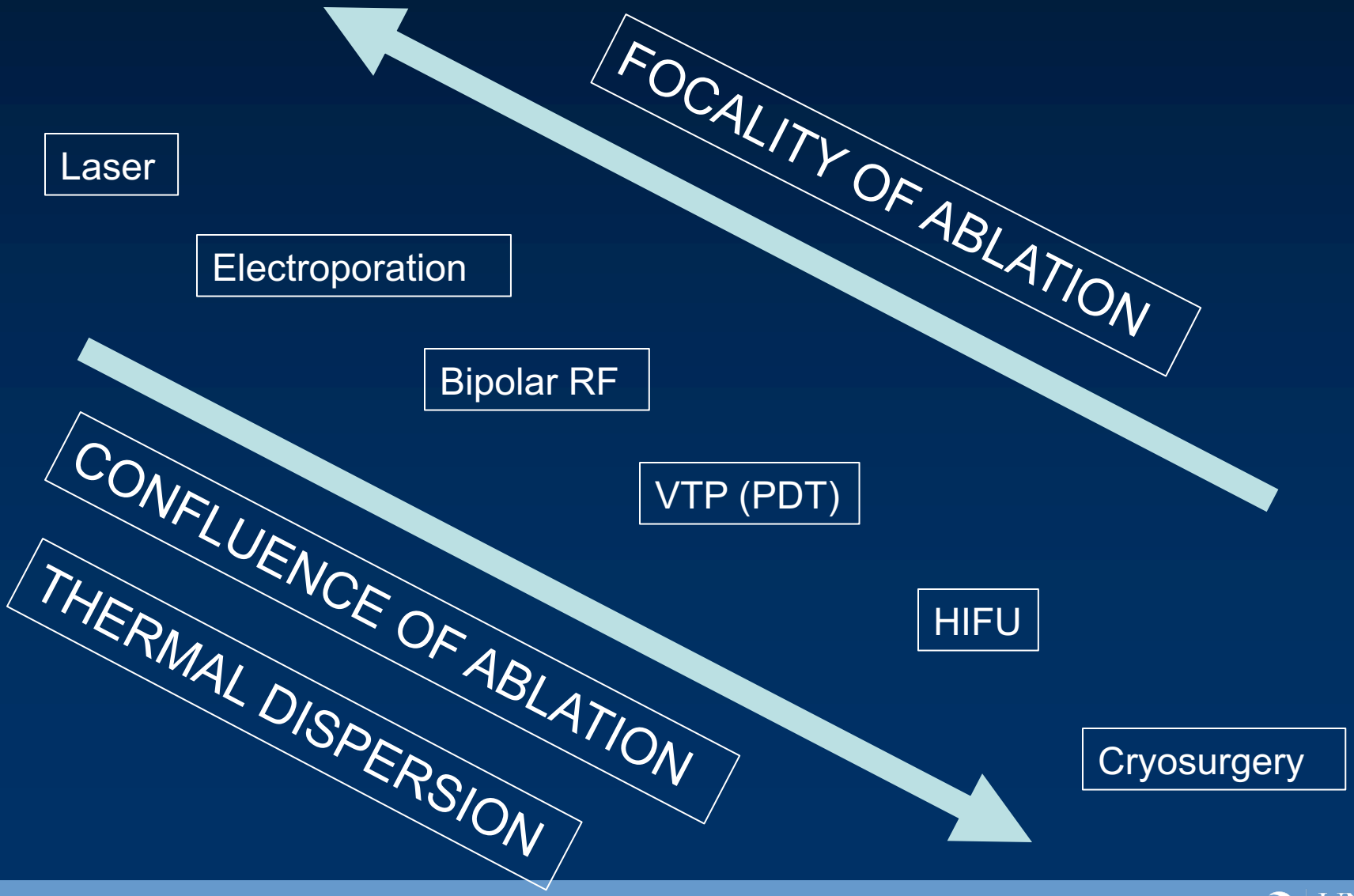
Cryotherapy vs HIFU



Graphical representation of anterior displacement of lesion during high-intensity focused ultrasound (HIFU). (A) Cancer within the HIFU target at the beginning of the treatment. (B) Prostatic edema along the HIFU pathway pushes the lesion anteriorly away from the target region.

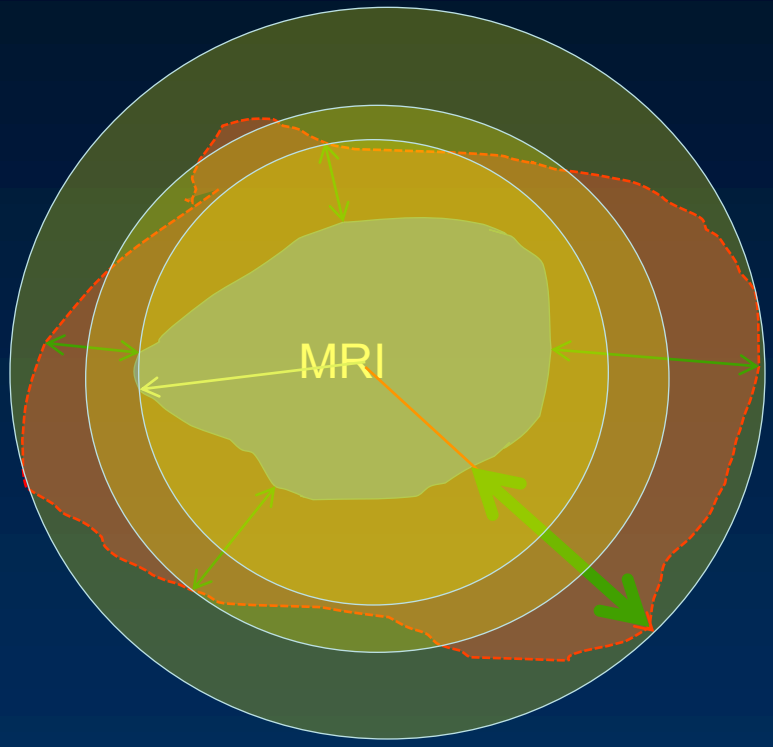
Focal Therapy for Prostate Cancer: An “À la Carte” Approach European Urology, 2016, Available online 6 January 2016

Spectrum of Energy Sources



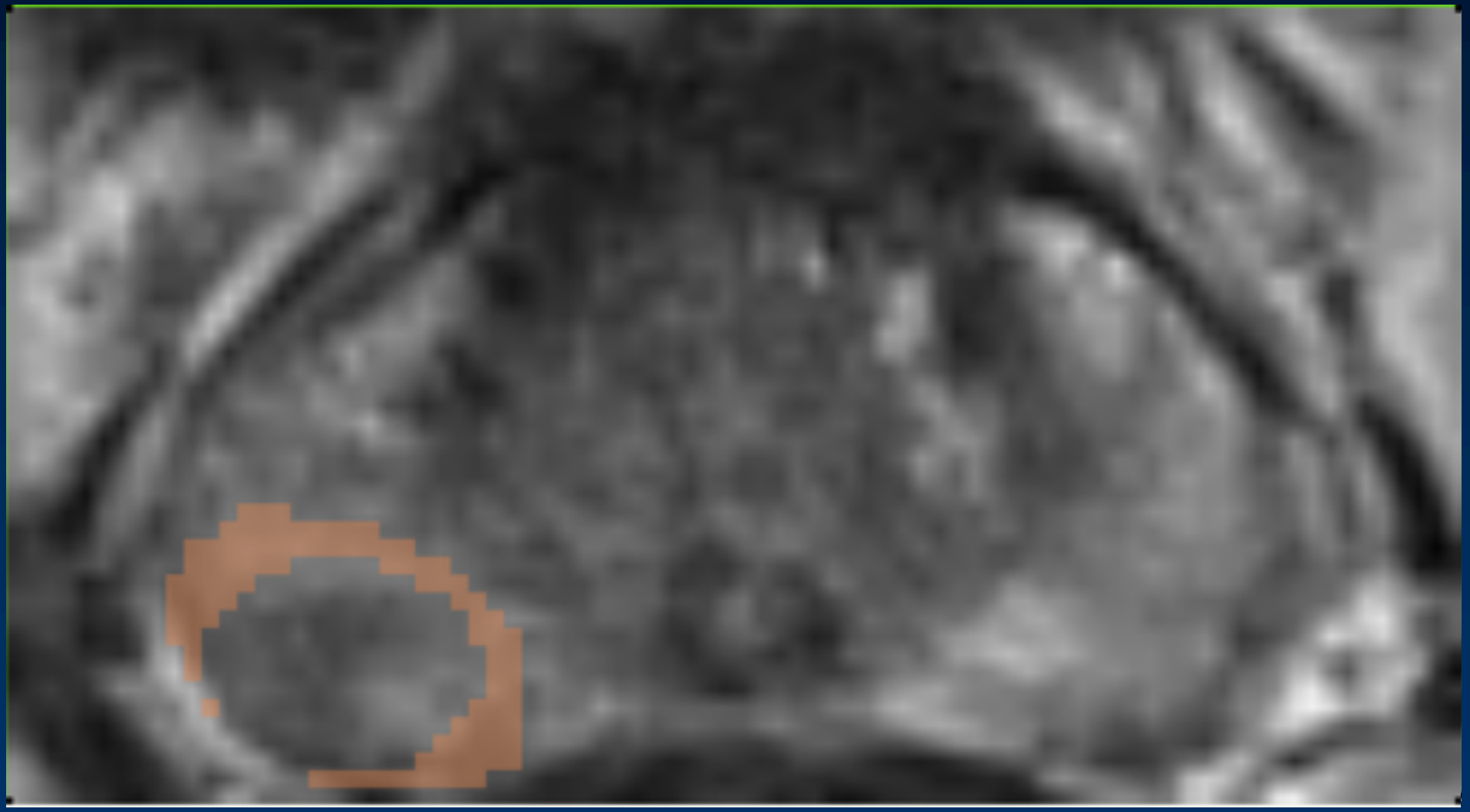
Factors Affecting Choice of Energy Selection

- Extent of ablation
- Size of tumor/Extent
- Method of tumor detection
  - Image detected → more focal
  - Biopsy detected → wider ablation
- Ability to achieve confluent destruction
- Location of tumor within the prostate
  - Proximity to nerves
  - Distance from rectum
  - Apex



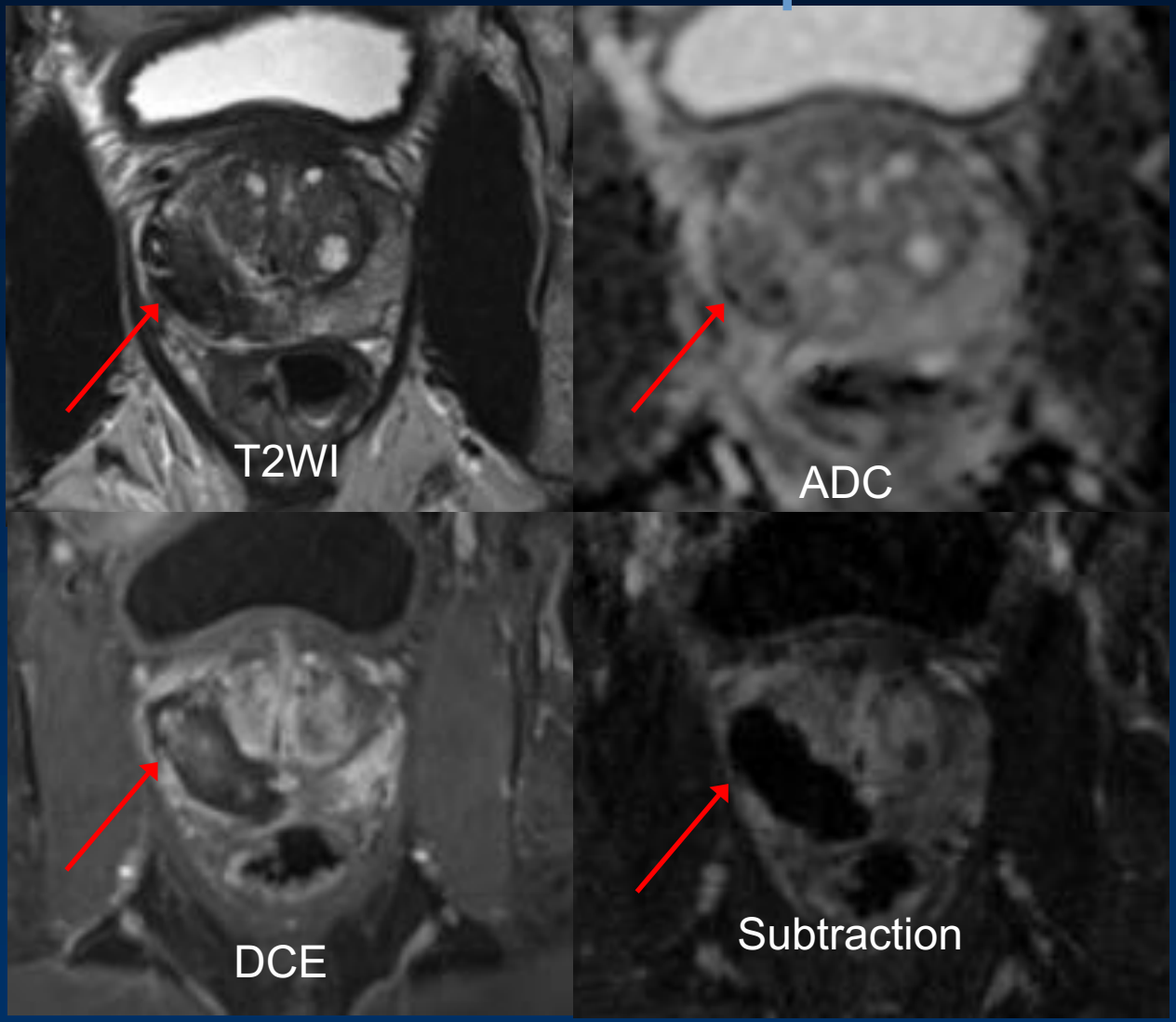
: Histo Boundaries
: Radius MRI
: Radius Histo
: Hausdorff Distances
: Hausdorff Max

Lenobin et al, J Urology, 2015



Lenobin et al, J Urology, 2015

Case Example



- No residual evidence of tumor
  - Ablation cavity appears to encompass previously noted tumor
  - No significant extraprostatic necrosis

Conclusions

- MR targeted biopsy offers unique benefits in all biopsy indications:
  - Reduction of Gleason 6 cancer detection without reduction of high grade detection in men with no previous biopsy
- Focal therapy is evolving from fiction to fact and driven by appropriate disease detection, localization and risk assessment
  - Implementation is feasible, but the benefits remain to be validated
- Long-term outcomes for validation will remain a challenge for the future