Pathologists Perspective on Focal Therapy: The Role of Mapping Biopsies and Markers

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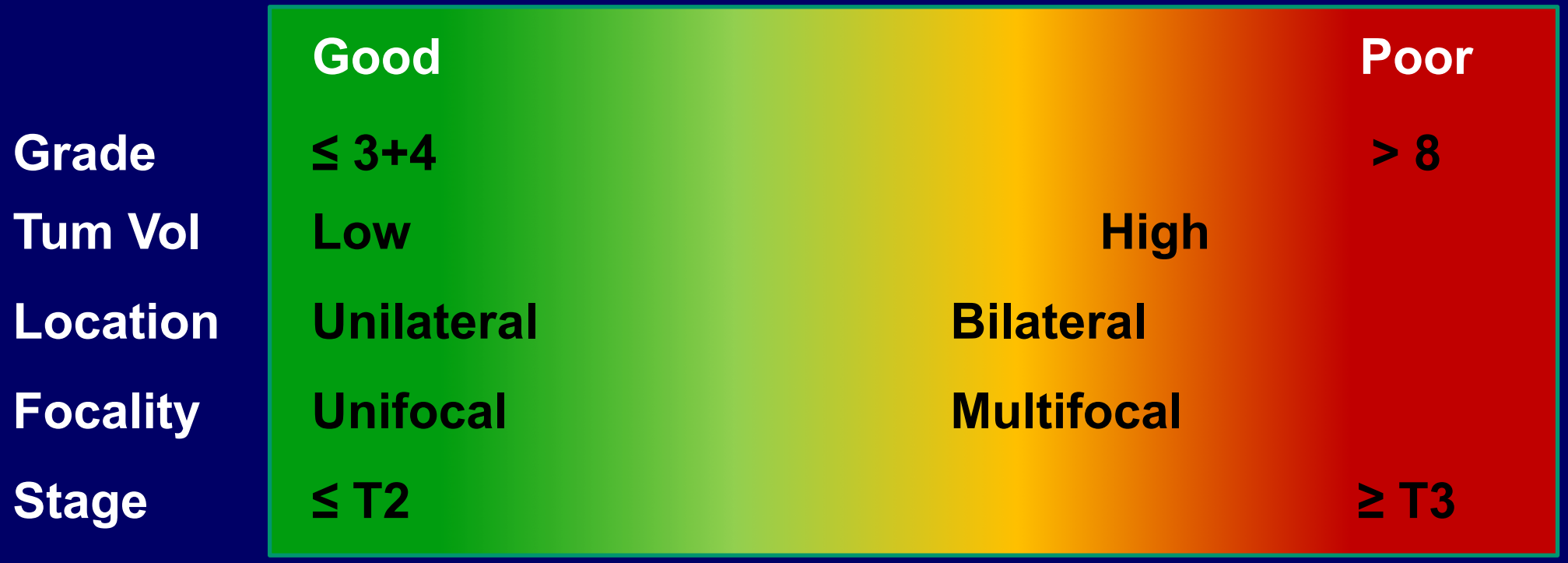
Disclosures

- MDxHealth– consultant
- 3DBiopsy - shareholder

Identifying the Best Candidates for Targeted Focal Therapy



Other factors:

- Therapeutic modality
- Physician philosophy
  - Cancer cure vs. cancer control
  - Alternative to AS vs. alternative to radical Tx

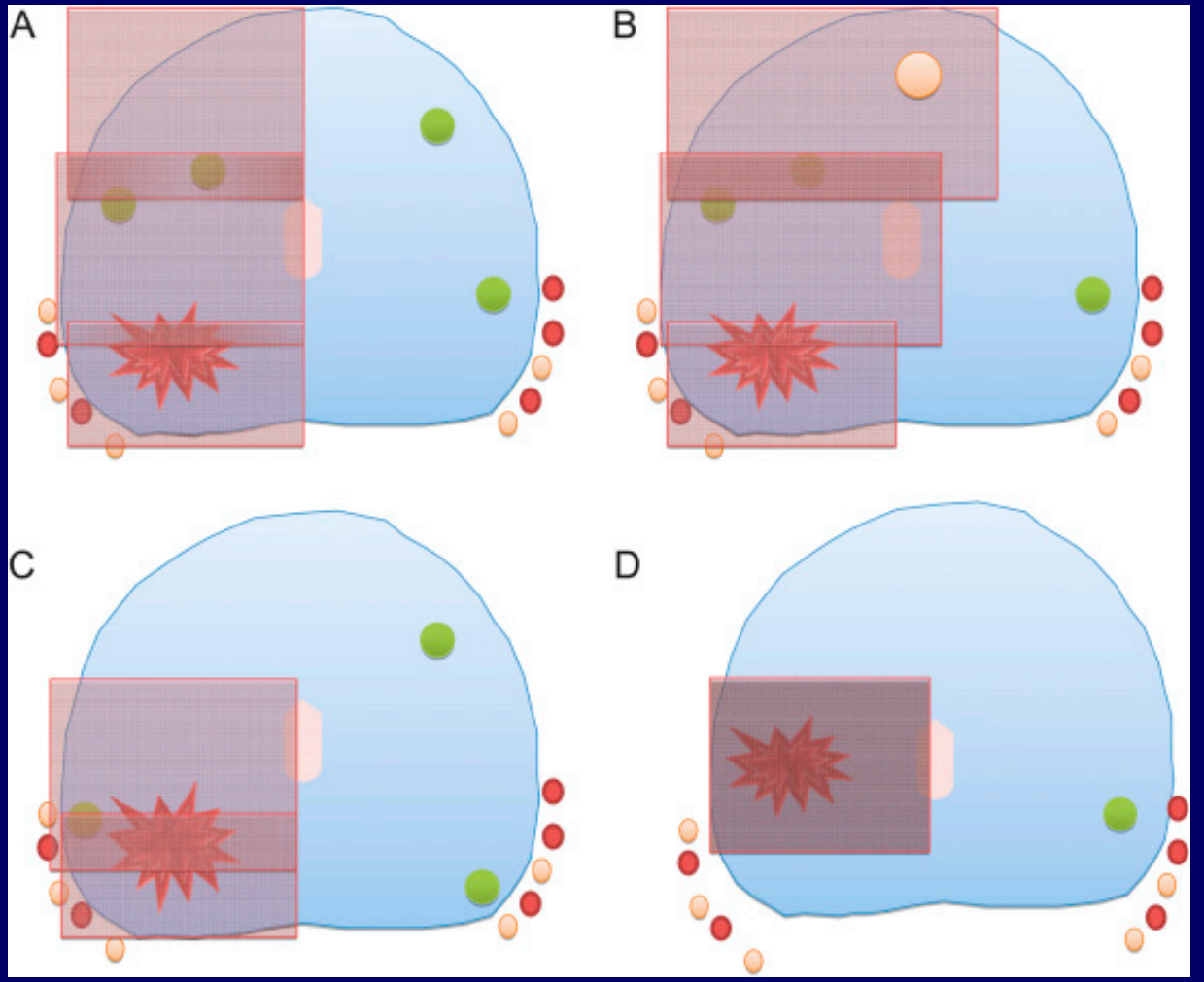
Focal Ablation Strategies

A. Hemiablation

B. Extended ablation

C. Quadrant ablation

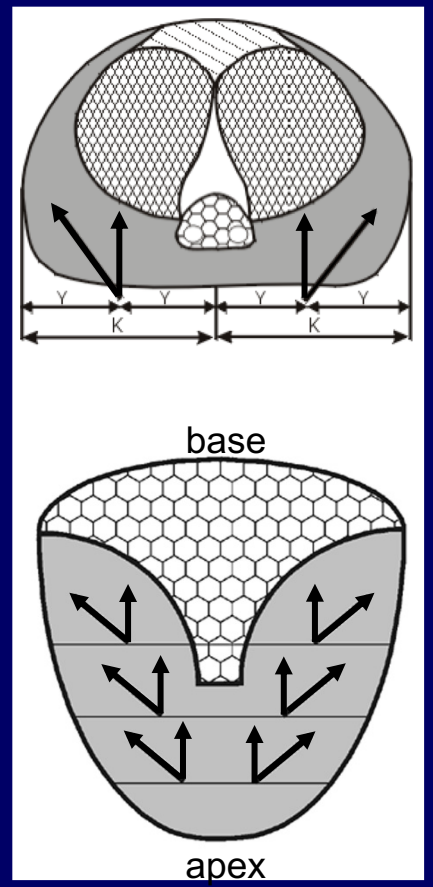
D. Site specific ablation



Ahmed HU, et al. Eyr Urol 2015;68:927-36.

Prostate Cancer Detection by TRUS-Guided Transrectal Needle Biopsy

- Cancer sampling is a function of tumor volume: prostate volume
  - Similarly, sampling of high-grade tumor is a function of high-grade component: prostate volume
  - Anterior prostate relatively undersampled
- Biopsy may not sample the highest grade or index lesion
- Biopsy poor staging tool
- Inadequate for precise tumor localization



*Risk of Pathologic Upgrading or Locally Advanced Disease in Early Prostate Cancer Patients Based on Biopsy Gleason Score and PSA: A Population-Based Study of Modern Patients**[1]

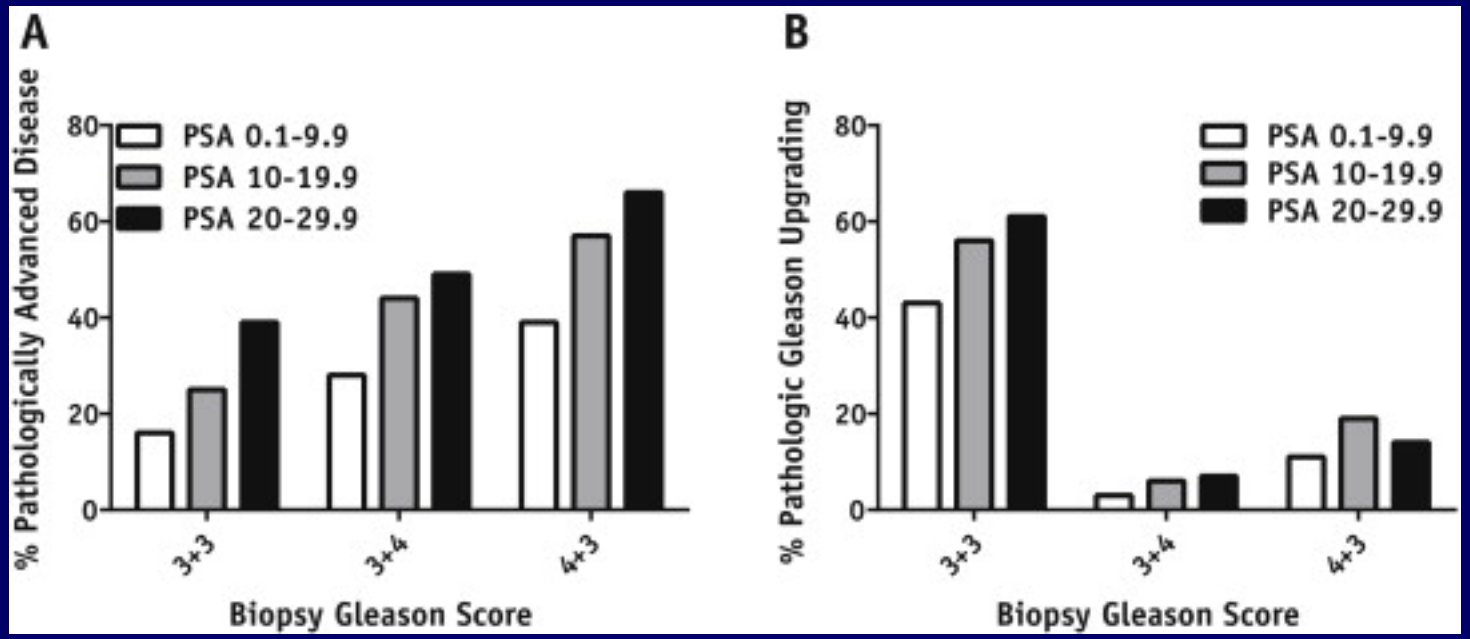


Fig. 1. Percentage of patients who had pathologically advanced disease (A) and Gleason score upgrading (B), stratified by prostate-specific antigen (PSA) concentration and biopsy Gleason score.

*Based on 25,858 patients from the SEER database.

http://dx.doi.org/10.1016/j.ijrobp.2015.01.051

1. Caster JM et al. *Int J Radiation Oncol Phys* 2015;92:244-51.

Identifying Prostate Cancers Appropriate for Focal Therapy

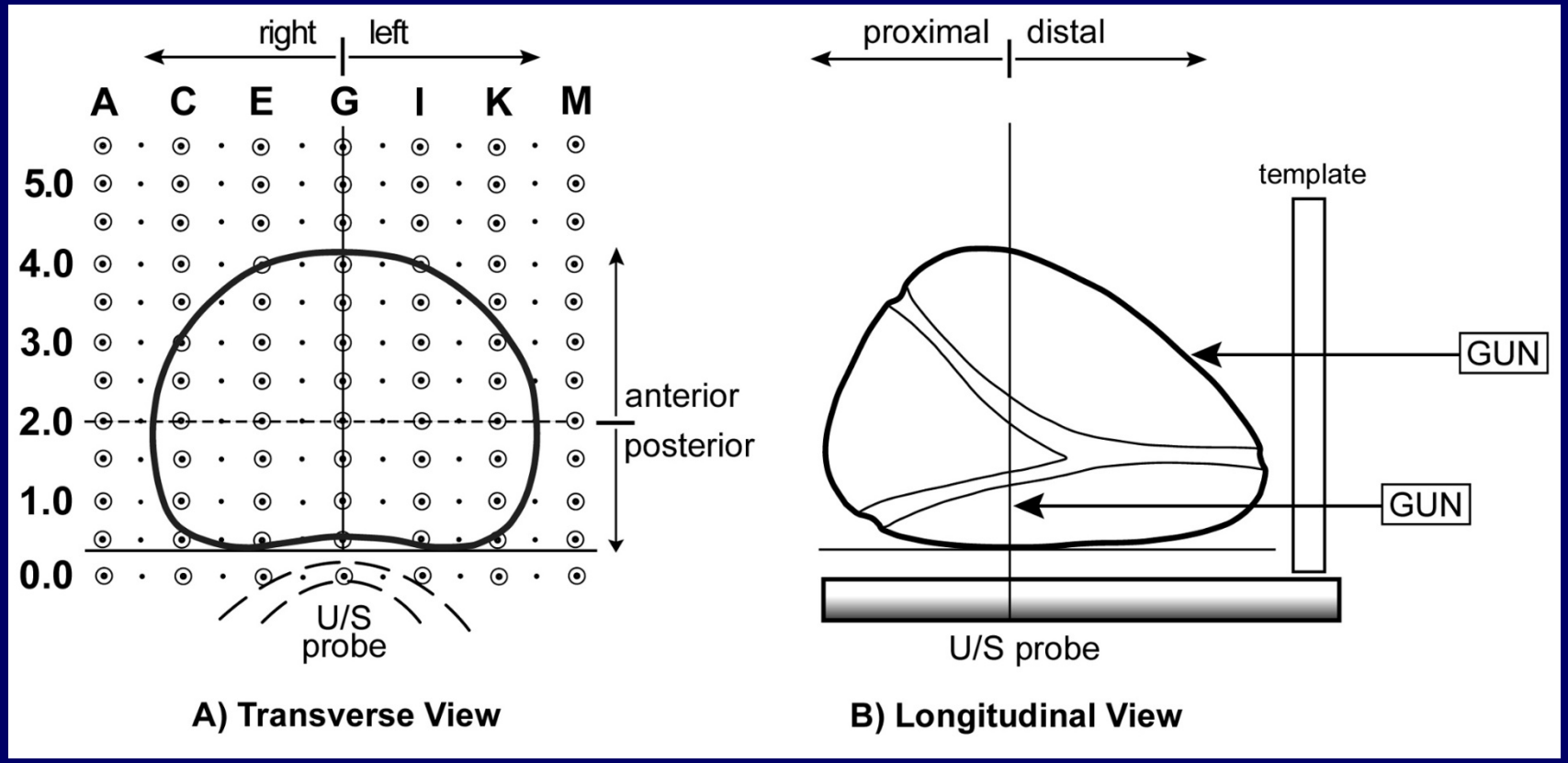
Concerns

- How can we accurately assess:
  - tumor grade and aggressiveness?
  - tumor extent (multifocality, volume, location)?
- Once cancer location is known, can we precisely deliver therapy to the target?

Potential Solutions

➢ Increase precise sampling: transperineal template-guided mapping biopsies (TTMB)

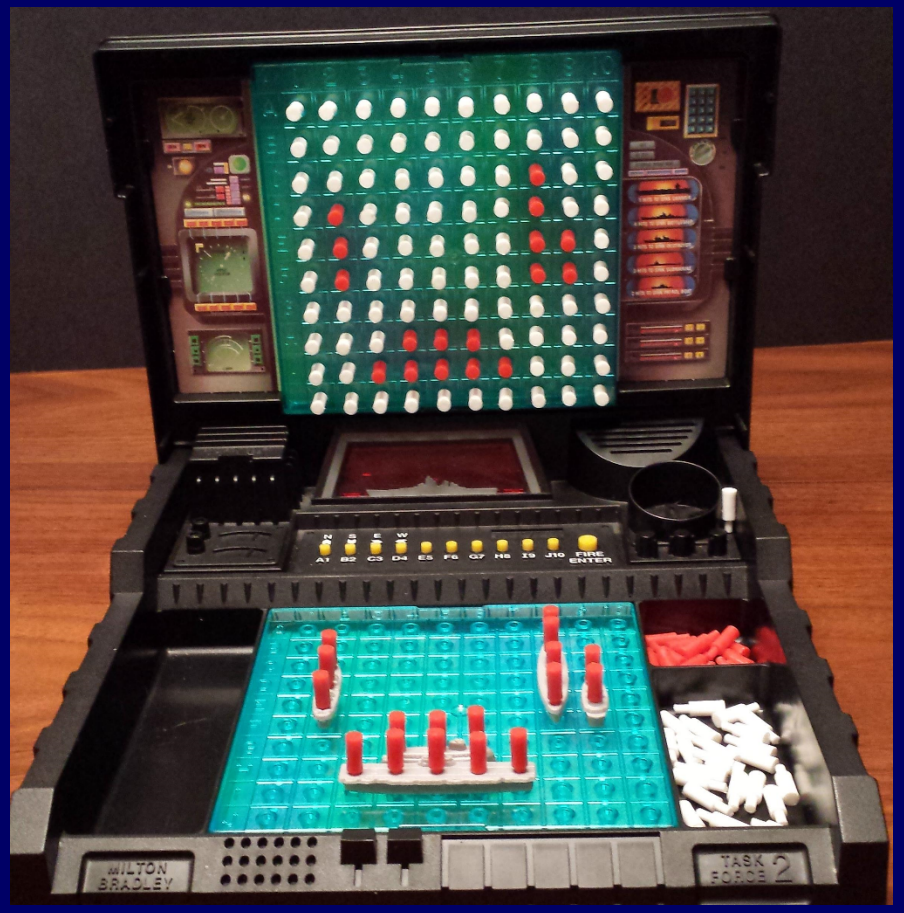
Template-Guided 3D Mapping Biopsies



Crawford, ED, et al., *BJU Internat* 2005; 96:999-1004

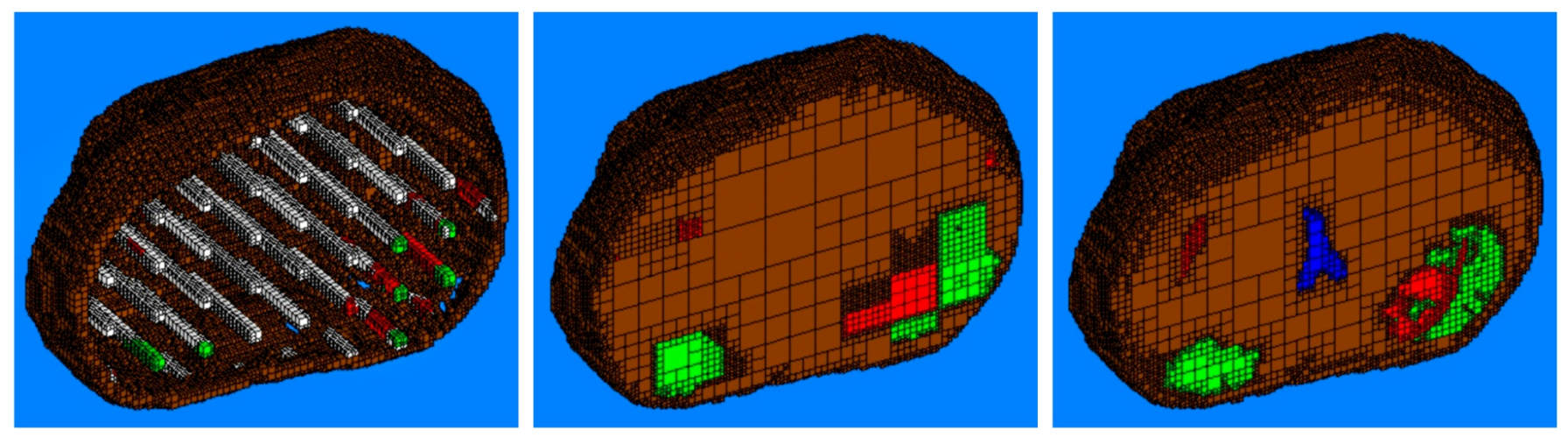
Playing Battleship

TRUS Biopsy

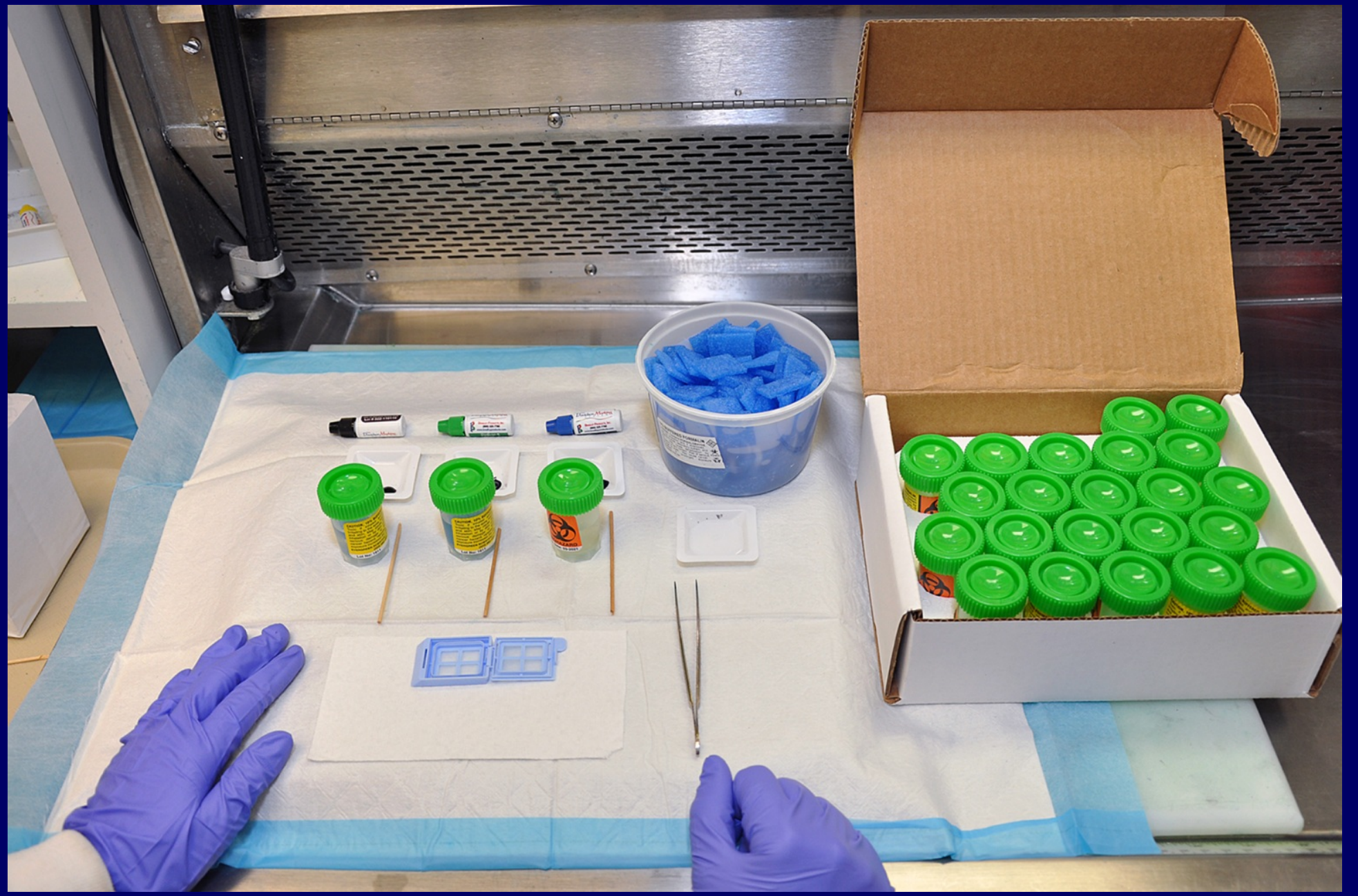


Transperineal Mapping Biopsy

3D Mapping Biopsy: Reverse-Reconstruction Model



- Saturation grid-biopsy data (left)
- Reverse-reconstruction model (center)
- Actual RRP specimen (right)
- Model error: -15% for Gleason 3+4 tumor (right, 5.1 cc)
  +15% for Gleason 3+3 tumor (left, 0.09 cc)
- Theoretical volume threshold = 0.042 cc



Specimen	Length (cm)	Slide #	Ink	Diagnoses
2JB	1.4	1	Yellow	Benign prostatic tissue
2JA	1.0	1	Green	Benign prostatic tissue
2IB	1.5	1	Blue	Benign prostatic tissue
2IA	0.5	2	Yellow	Benign prostatic tissue
2HB	0.8	2	Green	Benign prostatic tissue
1DA	0.8	2	Blue	Benign prostatic tissue
1CB	1.6	3	Yellow	Benign prostatic tissue
1CA	1.0	3	Green	Benign prostatic tissue
1B	0.1	3	Blue	Benign fibromuscular tissue
2K	0.3	4	Yellow	Benign prostatic tissue
1FB	1.4	4	Green	Benign prostatic tissue
1FA	0.6	4	Blue	Benign prostatic tissue
1EB	1.5	5	Yellow	Benign prostatic tissue
1EA	1.5	5	Green	**Prostatic adenocarcinoma, Gleason grade 3(95%) + 4(5%), (score=7); involving 3.7mm (35%) of core length; 4mm from inked tip**
1DB	1.8	5	Blue	Benign prostatic tissue
1IB	1.7	6	Yellow	Benign prostatic tissue
1IA	1.3	6	Green	Benign prostatic tissue
1HB	1.4	6	Blue	Benign prostatic tissue
1HA	1.0	7	Yellow	Benign prostatic tissue
1G	1.7	7	Green	Benign prostatic tissue
0E	1.2	7	Blue	Benign prostatic tissue
0D	1.6	8	Yellow	**Prostatic adenocarcinoma, Gleason grade 4+ 4 (score=8); involving 0.7mm (6%) of core length; 9mm from inked tip**
0C	1.0	8	Green	Benign prostatic tissue
1K	1.5	8	Blue	**Prostatic adenocarcinoma, Gleason grade 3+ 3 (score=6); involving 0.6mm (5%) of core length; 7.8mm from inked tip**
1J	0.9	9	Yellow	Benign prostatic tissue
6I	1.8	9	Green	Benign prostatic tissue
6H	1.3	9	Blue	Benign prostatic tissue
6F	1.6	10	Yellow	Benign prostatic tissue
6EB	2.0	10	Green	Benign fibromuscular tissue
6EA	1.2	10	Blue	Benign prostatic tissue

3DBiopsy 3D Mapping Software version 0.6ALPHA1

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Nelson Stone (admin)
Remaining Study Licenses: Unlimited
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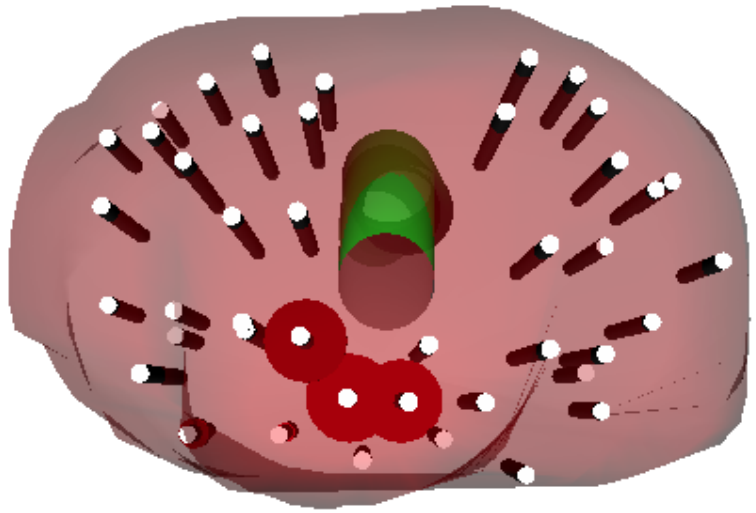
Patient's Name: Crawford, David
MRN: SPCU2018



base left
posterior

Orientation

Axial | Sagittal

US Contours

Prostate	31 cc	
Urethra		
Rectum		
Seminal Vesicle 1		
Seminal Vesicle 2		

Sites

ID:

Grid Location:

Core Length (mm): 0

Gun Setting (mm): 0

Number of sites: 43
Volume Removed (cc): 0.55
Largest Opening (mm): 11

Planned | Biopsied | Positive

Lesions

Type here to search

11:56 AM
3/18/2018

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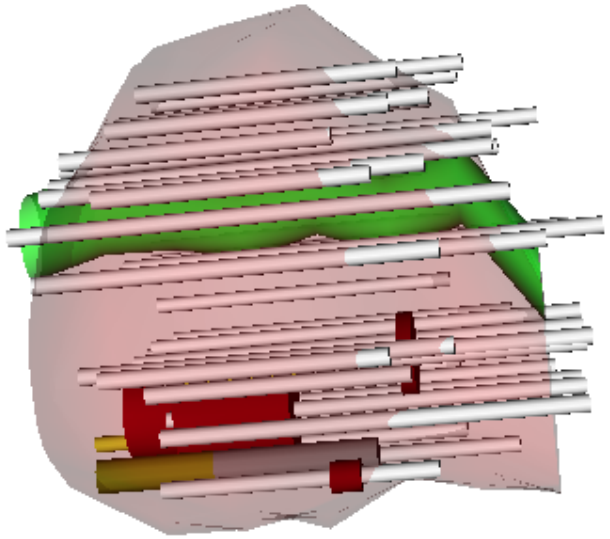

base left posterior

Orientation

Axial | Sagittal

US Contours

Prostate	31 cc	
Urethra		
Rectum		
Seminal Vesicle 1		
Seminal Vesicle 2		

Sites

ID: 39

Grid Location: (C,1.5)

Core Length (mm): 17

Gun Setting (mm): 20

Number of sites: 43

Volume Removed (cc): 0.55

Largest Opening (mm): 11

Planned | Biopsied | Positive

Lesions

Type here to search

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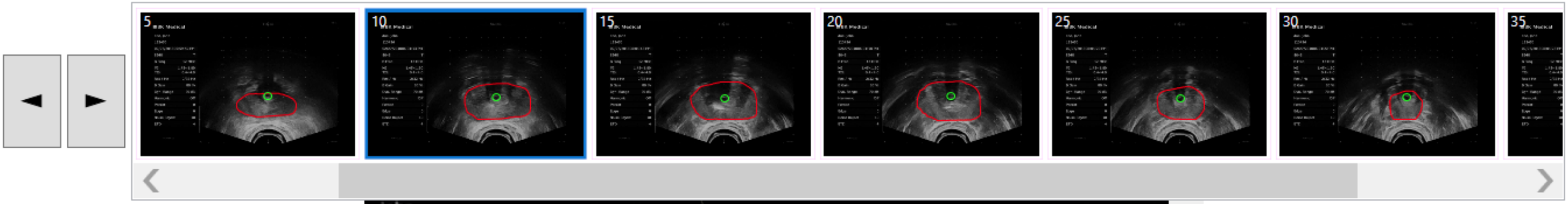


Image Magnification

121% | Fill | 100%

Template

Type 1

Sites

ID: 39

Grid Location: (C,1.5)

Core Length (mm): 17

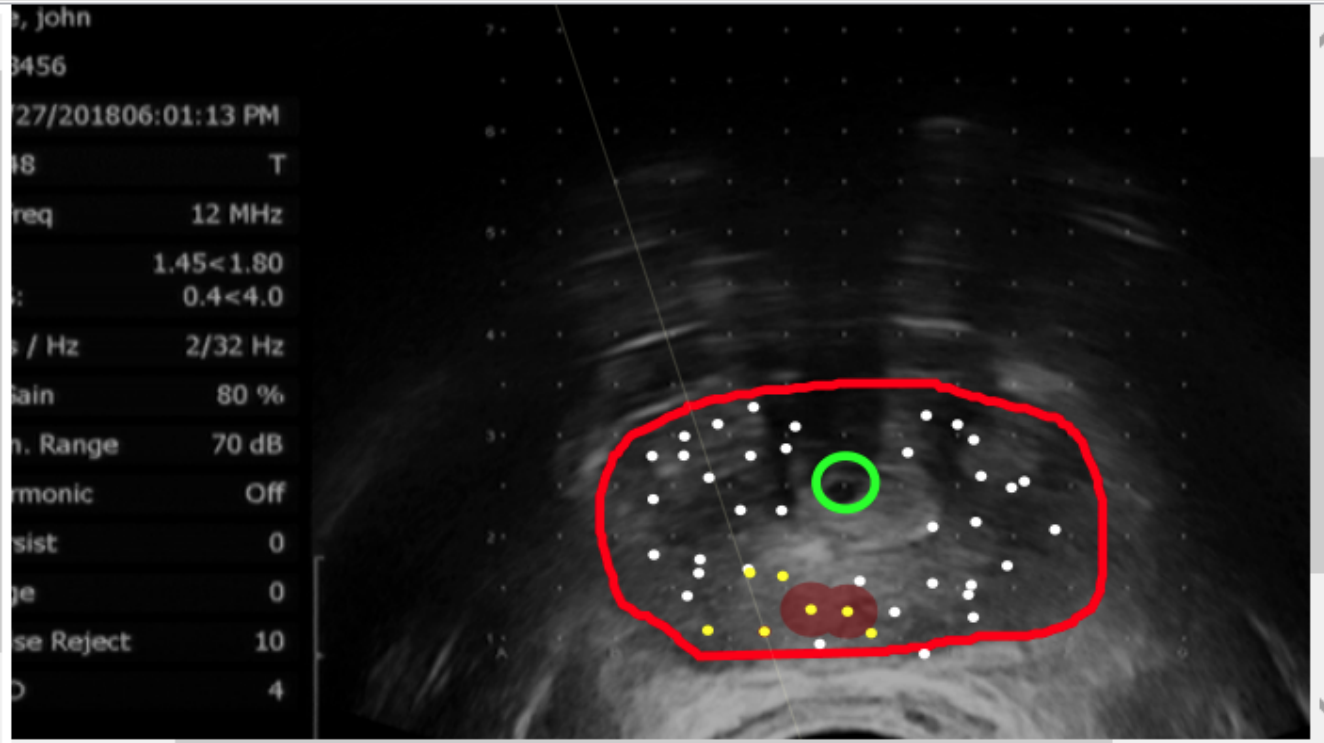
Gun Setting (mm): 20

Go to Largest Opening

Number of sites: 43

Volume Removed (cc): 0.55

Largest Opening (mm): 11



Prostate	31 cc	
Urethra		
Rectum		
Seminal Vesicle 1		
Seminal Vesicle 2		

Contour Thickness

Lesions

Gleason Score	Site ID	Volume (cc)
3+3	26	0.024
3+4	33	0.009
3+4	34	0.244
3+4	35	0.149
3+4	38	0.007
3+4	41	0.005
4+3	39	0.012

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3/18/2018

Comparison of TRUS guided transrectal biopsy and 3D mapping biopsy (n=215)

	TRUS Guided Bx	3DMBx
Median No. biopsy cores (range)	12 (6-23)	56 (8-124)
Median No. positive cores (range)	1 (1-8)	2 (0-19)
No. Gleason score:		
5	1	0
6	155	98
7	24	61
8	0	8
9	0	1
Neg	35	47

46% of tumors upstaged on 3DMBx

Barqawi et al. *J Urol* 2011;186:80-5

Clinical risk stratification of patients diagnosed with prostate cancer by TRUS Bx vs. subsequent transperineal template prostate mapping (TTMP)

Risk stratification	TRUS Bx n, (%)	TTMP n, (%)
Biopsy naïve	47 (12)	0 (0%)
No cancer	75 (19)	67 (17)
Low risk	132 (34)	78 (20)
Intermediate risk	128 (33)	80 (21)
High risk	3 (1)	166 (42)

Low risk = GS ≤3+3, ≤3 mm max core positive
Intermediate risk = GS 3+4 and/or 4-5 mm max core positive
High risk = GS ≥ 4+3 and/or ≥6 mm max core positive

Adapted from: Valerio M, et al. *BJU Internat* 2015; doi: 10.1111/bju.13306.

Location and grade of prostate cancer diagnosed by transperineal template-guided mapping biopsy after negative transrectal ultrasound-guided biopsy[1]

	No. Prior Biopsies (Count [%])			
Cancer Sites	**0**	**1**	**2**	**Total**
(A) Association between number of prior biopsies and location of cancer sites (Pearson x^2: P=0.007)				
Anterior only	43 (20.7)	97 (29.9)	52 (35.6)	192 (28.3)
Posterior only	21 (10.1)	42 (12.9)	20 (13.7)	83 (12.2)
Anterior & posterior	144 (69.2)	186 (57.2)	74 (50.7)	404 (59.5)
Total	208 (100)	325 (100)	146 (100)	679 (100)
(A) Association between number of prior biopsies and location of Gleason score ≥ 7 cancer (Pearson x^2: P=0.009)				
Anterior only	10 (7.6)	36 (20.3)	22 (24.4)	68 (17.0)
Posterior only	9 (6.9)	13 (7.3)	7 (7.8)	29 (7.3)
Anterior & posterior	112 (85.5)	128 (72.3)	61 (67.8)	301 (75.6)
Total	131 (100)	177 (100)	90 (100)	398 (100)

1. Bittner N, et al. *Am J Clin Oncol* 2016; doi: 10.1097/COC.0000000000000352.

Correlation of Transrectal vs. Transperineal Template Biopsy Grade with Whole-Mount Prostatectomy Grade (N=25)

Biopsy Type	Prostatectomy	
	Upgraded	Downgraded
Transrectal	52%	8%
Transperineal	12%	16%

Crawford ED et al Prostate 2013;73:778-87.

Is transperineal prostate biopsy more accurate than transrectal biopsy in determining final Gleason score and clinical risk category? A comparative analysis[1]

- 431 prostatectomy specimens in which PCa was diagnosed by TRUS Bx (mean # cores 14.83, n=283) or TTB (mean # cores 22.14, n=148):
  - 22.3% of tumors diagnosed by TRUS Bx upgraded from GS≤6 to GS≥7 on final pathology vs. 14.2% of tumors diagnosed by TTB (p=0.04)

TRUS Bx = transrectal ultrasound guided biopsy
TTB = transperineal template biopsy

1. Scott S, et al *BJU Internat* 2015;116 Suppl 3:26-30.

Identifying Prostate Cancers Appropriate for Focal Therapy

Concerns

- How can we accurately assess:
  - tumor grade and aggressiveness?
  - tumor extent (multifocality, volume, location)?
- Once cancer location is known, can we precisely deliver therapy to the target?

Potential Solutions

- Increase precise sampling: transperineal template-guided mapping biopsies (TTMB)
- Add imaging

Detection of Prostate Cancer by mpMRI Compared with Prostatectomy Specimen

	Thompson et al 2014[1]	Russo et al 2015[2]	Radtke et al 2016[3]
N	48	115	120
Field Strength	1.5/3 T	1.5T	3T
Endorectal coil	--	+	--
Def. significant lesion MRI	PI-RADS ≥ 3	--	PI-RADS≥2
Def. csPCa	GS≥7 or GS6≥5 mm	Largest lesion (mean=1.3mL)	1)EPE, 2) highest GS, 3) largest tumor
Sens/Spec	98/43	90.4/-	85/-
NPV/PPV	75/91	NR	78/49

1. Thompson J et al. Multiparametric magnetic resonance imaging guided diagnostic biopsy detects significant prostate cancer and could reduce unnecessary biopsies and over detection: a prospective study. *J Urol* 2014;192:67-74.
2. Russo F et al. Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mpMRI) using whole-mount histological sections as the reference standard. *BJU Int* 2016;118:84-94.
3. Radtke JP et al. Multiparametric magnetic resonance imaging (MRI) amd MRI-transrectal ultrasound fusion biopsy for index tumor detection: correlation with radical prostatectomy specimen. *Eur Urol* 2016;70:846-53.

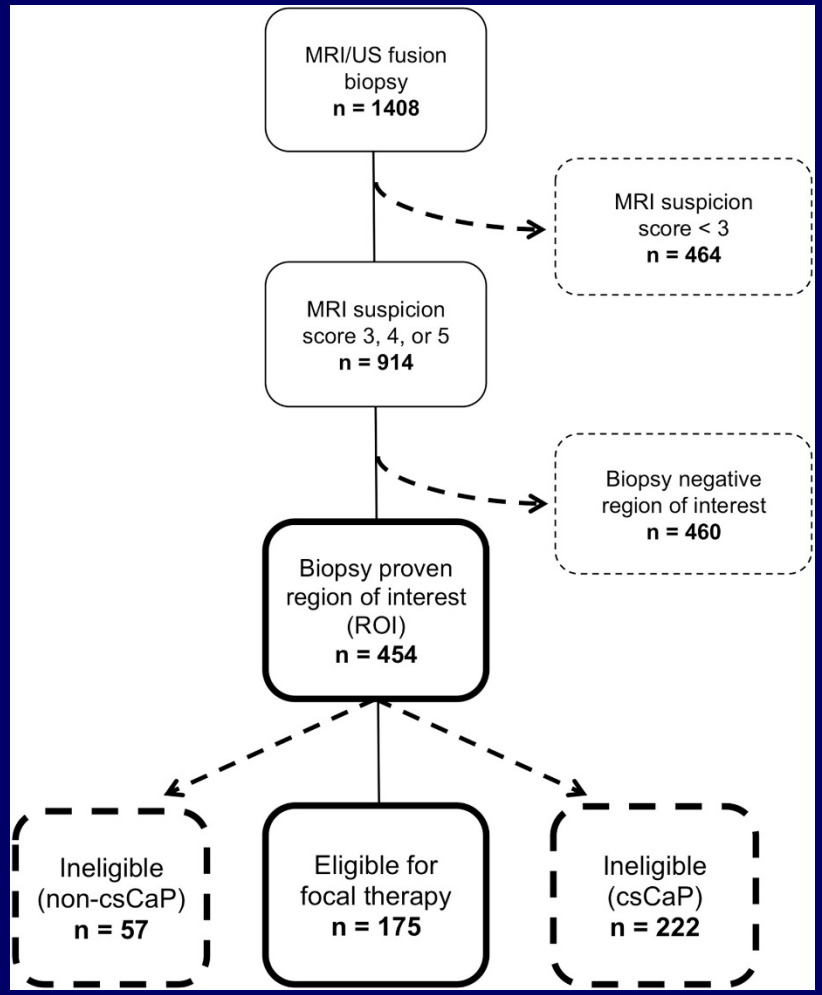
Detection of Prostate Cancer by mpMRI Compared with Template-Guided Mapping Biopsy

- Mortezavi A., et al 2018:[1]
  - 415 pts with mpMRI (3T, -ERC) followed by TTMB
  - Detection of csPCa (GS ≥ 3+4)
  - 124 with neg mpMRI → 32 (25.8%) csPCA detected on TTMB
  - 291 with Likert ≥ 3:
    - 129 (44.3%) csPCa detected on fusion-directed biopsy
    - 176 (60.5%) csPCa detected on TTMB
    - 187 (64.3%) csPCa detected when combined
- Sivaraman A, et al. 2015:[2]
  - TTMB (Barzells) identified tumor in 27/74 (36%), men with prior negative MRI-TRUS Bx
    - 19/27 (70.4%) significant (GS≥7 and/or max pos core length ≥4mm)
    - 8/27 (29.6%) GS≥7
    - 18/27 (66.7%) anterior tumors

1. Mortezavi A, et al. Diagnostic accuracy of mpMRI and fusion-guided targeted biopsy evaluated by transperitoneal saturation prostate biopsy for the detection and characterization of prostate cancer. J Urol 2018 doi: 10.1016/j.jurol.2018.02.067.
2. Sivaraman A, et al. Clinical utility of transperineal template-guided mapping biopsy of the prostate after negative magnetic resonance imaging-guided transrectal biopsy. *Urol Oncol* 2015;33:329.e7-329.e11.

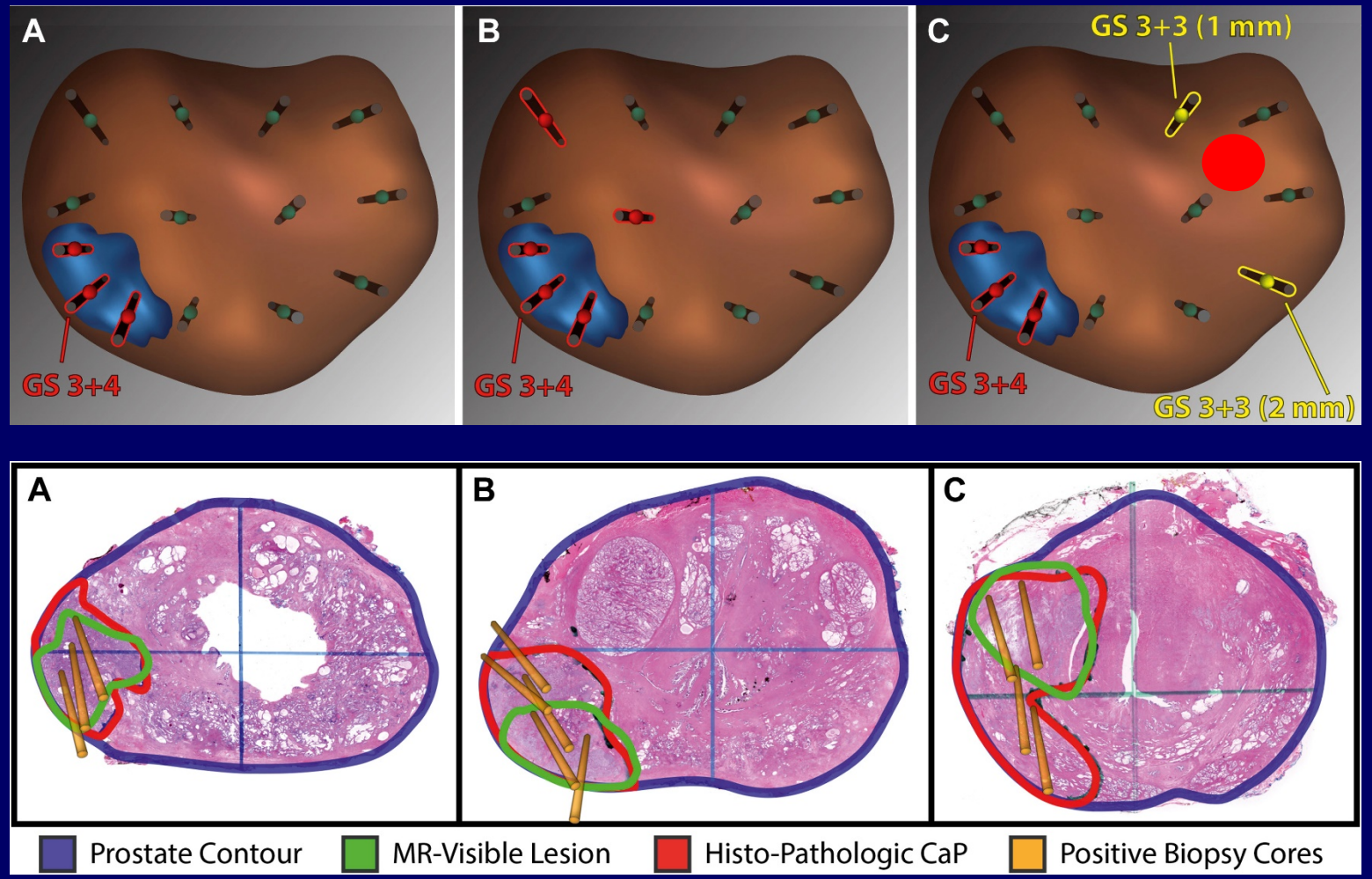
Focal therapy eligibility determined by magnetic resonance imaging/ ultrasound fusion biopsy[1]

- 454 men with PI-RADS ≥3 lesions on mpMRI (3T,ERC) & positive MRI/TRUS fusion Bx + 12-core systematic Bx
- FT eligibility assessed for 3 ablative strategies based on location of positive Bxs
  - Site specific
  - Quadrant
  - Hemigland



1. Nassiri N, et al *J Urol* 2018;199:453-458

Focal therapy eligibility determined by magnetic resonance imaging/ ultrasound fusion biopsy[1]



1. Nassiri N, et al *J Urol* 2018;199:453-458

Multifocal Prostate Cancer: Gleason Grade of Secondary (Non-Index) Tumor Foci <0.5 cc

- UC database of whole-mount prostatectomy cases that underwent 3D-reconstruction (N=200, 2009-2016)
  - 75% 3+3 (Grade group I)
  - 15% 3+4 (Grade group II)
  - 10% ≥ 4+3 (≥ Grade group III)

Prostate Cancer Database, Univ. of Colorado AMC

A single-center evaluation of the diagnostic accuracy of multiparametric MRI against transperineal prostate mapping biopsy: an analysis of men with benign histology and insignificant cancer following TRUS biopsy[1]

- 426 pts with negative or low risk prostate cancer on TRUS biopsy followed by mpMRI (1.5T)
- Subsequent TTMB as reference
- mpMRI with PI-RADS ≥3 had AUC 0.754 for GS ≥ 4+3 tumor on TTMB
  - Sens = 87
  - Spec = 55.3

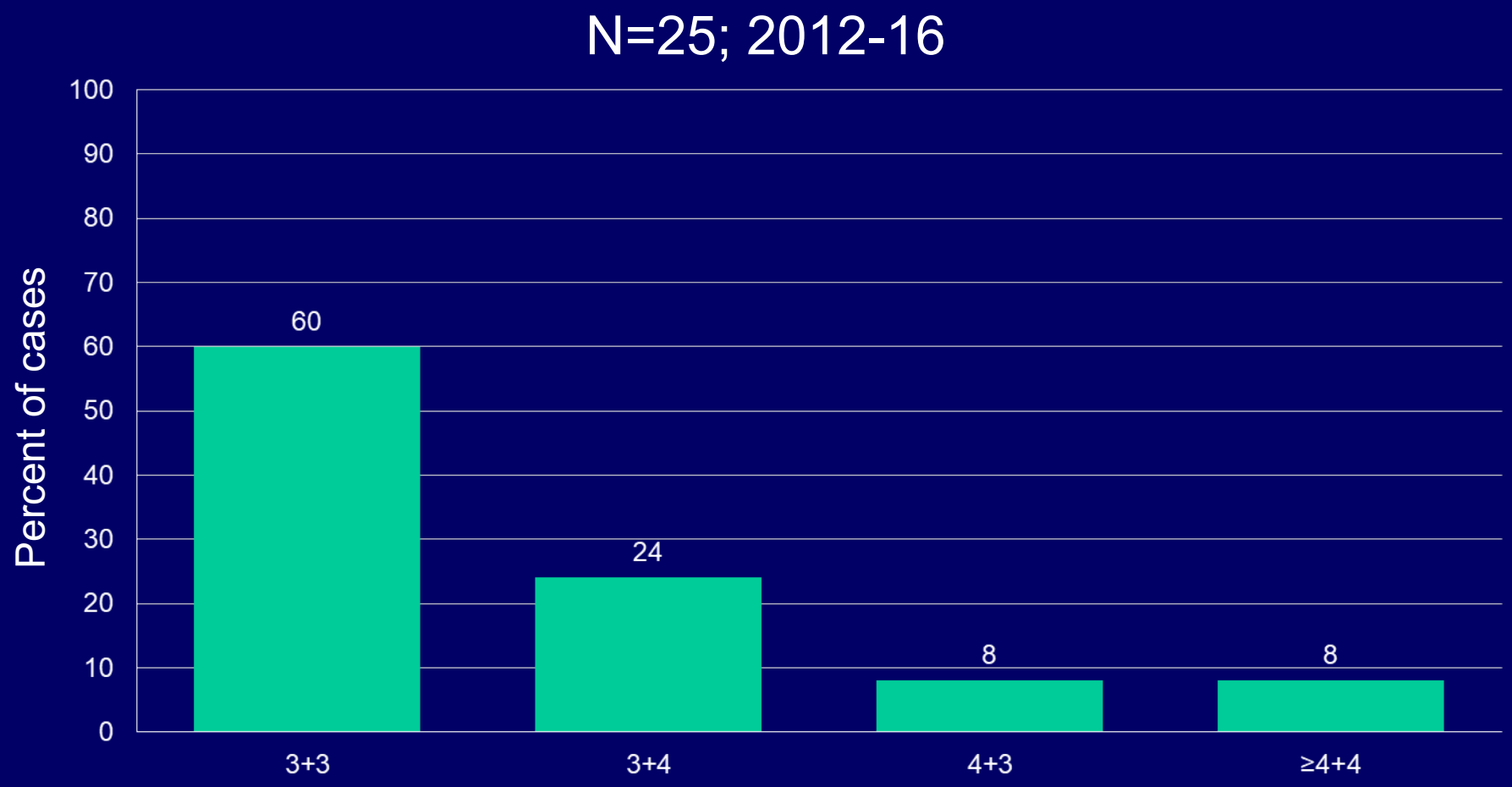
1. Pal RP, et al *J Urol* 2018; doi: 10.1016/j.juro.2018.02.072.

Monitoring the Efficacy of TFT

- Monitor as active surveillance
  - PSA
  - Follow-up biopsy (12 core)
- mpMRI, MRI/TRUS fusion biopsy[1,2]

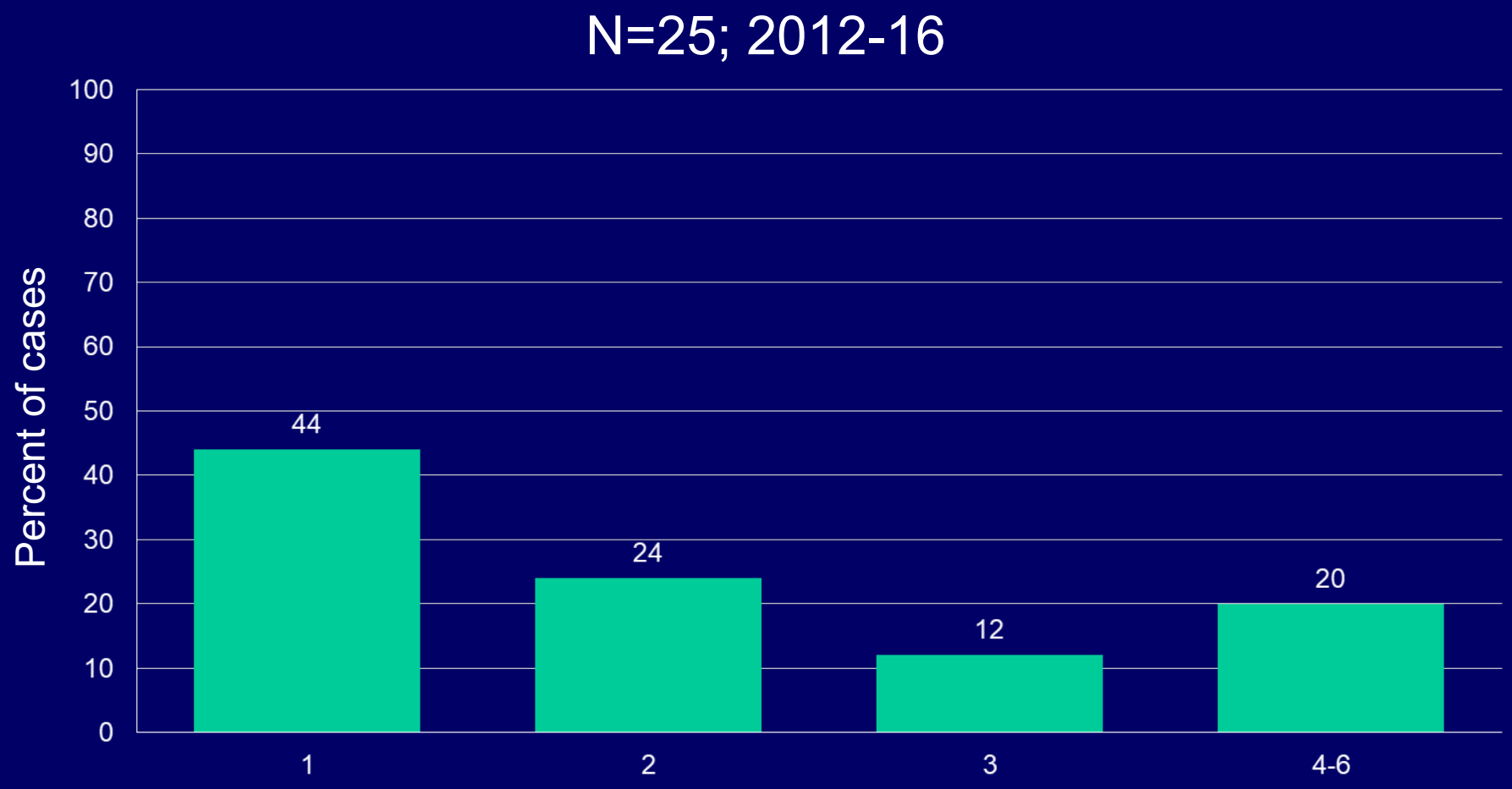
1. Scheltema MJ, et al. Preliminary diagnostic accuracy of multiparametric magnetice resonance imaging to detect residual cancer following focal therapy with irreversible electroporation. *Eur Urol Focus* 2017 doi: 10.1016/j.euf.2017.10.007.
2. Gaur S and Turkbey, B. Prostate MR imaging for posttreatment evaluation and recurrence. *Radiol Clin N Am* 2018;56:263-75.

Grade of residual prostate cancer detected on follow-up monitoring biopsy after TFT



Prostate Cancer Database, Univ. of Colorado AMC

No. of positive cores of residual prostate cancer detected on follow-up monitoring biopsy after TFT



Prostate Cancer Database, Univ. of Colorado AMC

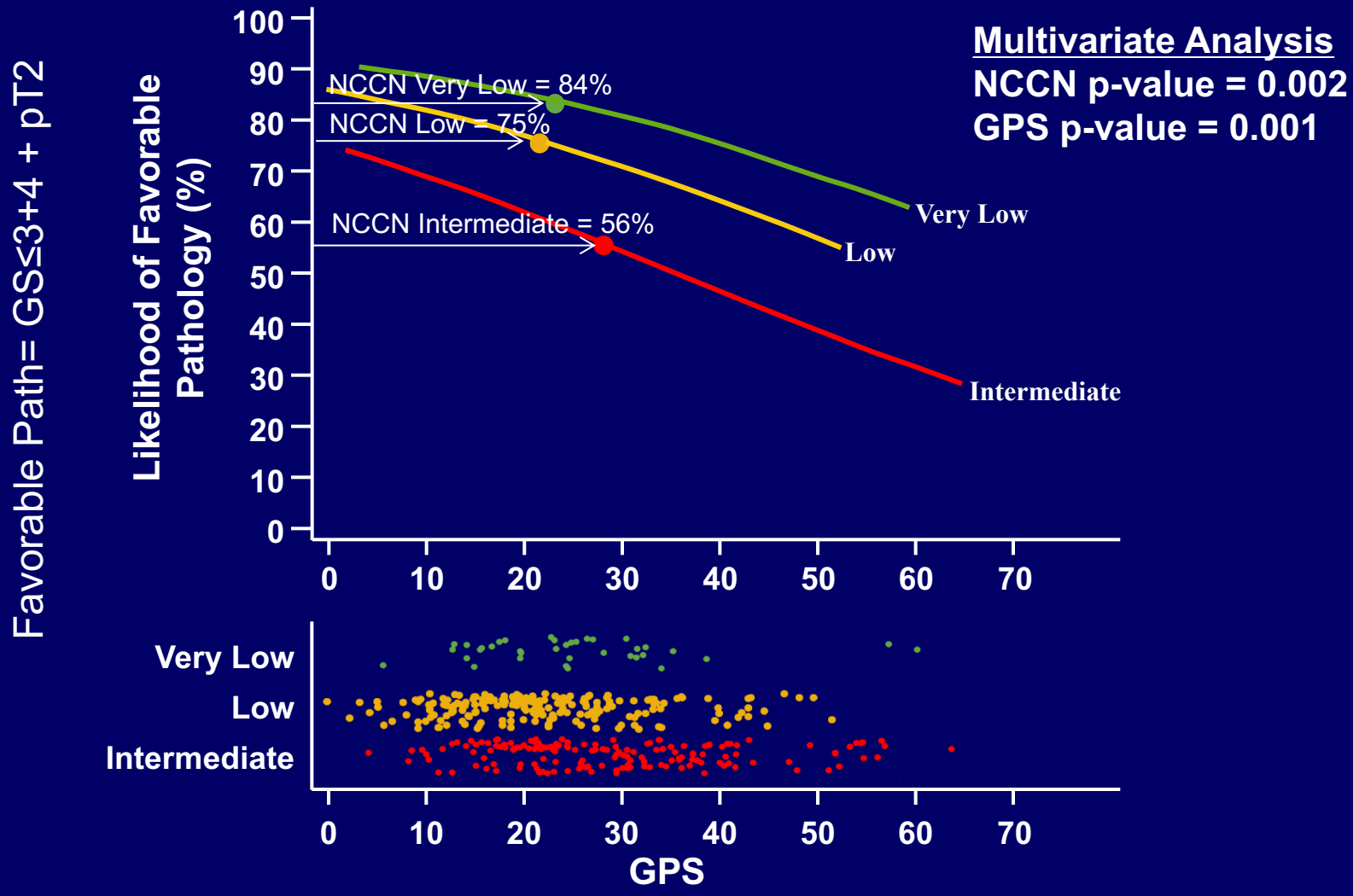
Monitoring the Efficacy of TFT

- Monitor as active surveillance
  - PSA
  - Follow-up biopsy (12 core)
- mpMRI, MRI/TRUS fusion biopsy[1,2]
- Role of Biomarkers?
  - Indication for rebiopsy?
    - SelectMDx, 4K, Phi?
  - If PCa detected on follow-up biopsy?
    - Cell cycle progression [CCP] score (Prolaris®, Myriad Genetics)
    - Prostate Genomic Score RT-PCR expression assay (Onco*type*DX®, Genomic Health)

1. Scheltema MJ, et al. Preliminary diagnostic accuracy of multiparametric magnetice resonance imaging to detect residual cancer following focal therapy with irreversible electroporation. *Eur Urol Focus* 2017 doi: 10.1016/j.euf.2017.10.007.
2. Gaur S and Turkbey, B. Prostate MR imaging for posttreatment evaluation and recurrence. *Radiol Clin N Am* 2018;56:263-75.

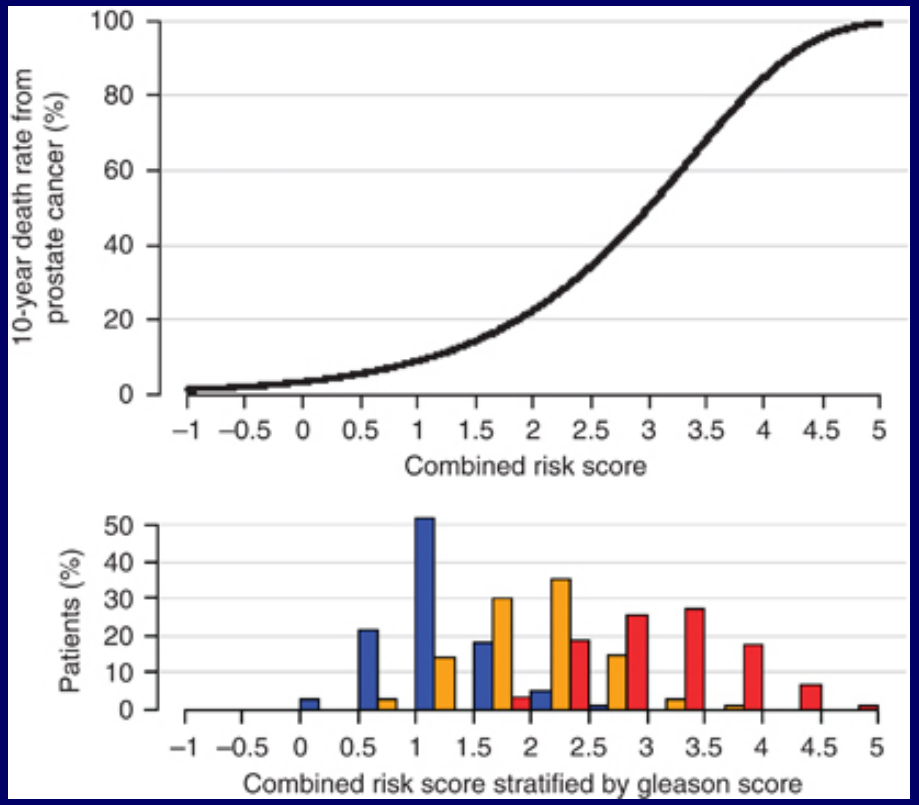
UCSF Validation Study of GPS

Improved Risk Discrimination with Addition of GPS to NCCN in 395 Men with Very Low-Intermediate Risk Prostate Cancer on Biopsy



Klein EA et al, *Eur Urol* 2014;66:550-60. http://eorder.sheridan.com/30/app/orders/3732/article.php

Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort[1]*



Combined risk score: derived from CCP+GS+PSA
Blue bars=GS<7, yellow bars=GS7, red bars=GS>7

Prolaris®, Myriad Genetics, Inc.

1. Cuzick J et al. *Br J Cancer* 2012:106:1095-9.

Monitoring the Efficacy of TFT

- Monitor as active surveillance
  - PSA
  - Follow-up biopsy (12 core)
- mpMRI, MRI/TRUS fusion biopsy[1,2]
- Role of Biomarkers?
  - Indication for rebiopsy?
    - SelectMDx, 4K, P
  - If PCa detected on
    - Cell cycle progr ®, Myriad Genetics)
    - Prostate Genomi on assay (Onco*type*DX®, Genomic Health)

1. Scheltema MJ, et al. Preliminary diagnostic accuracy of multiparametric magnetice resonance imaging to detect residual cancer following focal therapy with irreversible electroporation. *Eur Urol Focus* 2017 doi: 10.1016/j.euf.2017.10.007.
2. Gaur S and Turkbey, B. Prostate MR imaging for posttreatment evaluation and recurrence. *Radiol Clin N Am* 2018;56:263-75.

Conclusions

- Pathological features are important for appropriate patient selection for focal therapy
  - Grade
  - Volume
  - Location
- Traditional transrectal biopsy schemes are inaccurate
- Transperineal mapping biopsies offer improved pathological accuracy
- mpMRI + MRI/TRUS fusion biopsy may be useful for determining eligibility for focal therapy in some patients
  - May underestimate tumor burden
- Role of biomarkers in patient selection and monitoring yet to be determined