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Cancer Core Length from Targeted Biopsy: An Index of Prostate Cancer Volume and Pathologic Stage

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Abstract

Objective: To study the relationship of maximum cancer core length, on targeted biopsy of MRI-visible index lesions, to volume of that tumor found at prostatectomy.

Patients and Methods: 205 men undergoing fusion biopsy and radical prostatectomy were divided into two groups: 136 in whom the maximum cancer core length came from an index MRI-visible lesion (targeted) and 69 in whom maximum cancer core length came from a non-targeted lesion. MRI was 3T multi-parametric and biopsy was via MRI-US fusion.

Results: In the targeted biopsy group, maximum cancer core length correlated with volume of clinically-significant index tumors (ρ=0.44–0.60, $p<0.01$). The correlation was similar for first and repeat biopsy and for transition and peripheral zone lesions (ρ=0.42–0.49, $p<0.01$). No correlations were found in the non-targeted group. Targeted maximum cancer core length (6–10 mm and >10 mm) and MRI lesion diameter (>20 mm) were independently associated with tumor volume. Targeted maximum cancer core lengths >10 mm and Gleason scores >7 were each associated with pathological T3 disease (OR, 5.73 and 5.04, respectively), but MRI lesion diameter lesion was not.

Conclusions: Maximum cancer core length on a targeted biopsy from an MRI-visible lesion is an independent predictor of both cancer volume and pathologic stage. This relationship does not exist for MCCL from a non-targeted biopsy core. Quantifying cancer core length on MRI-targeted biopsies may have a value, not previously described, to risk-stratify patients with prostate cancer before treatment.

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DISCLOSURES

Dr. Marks is co-founder of Avenda Health, Inc. In addition, Dr. Marks has a patent System for out of bore focal laser therapy, pending. Dr Priester reports employment with Avenda Health. All other authors have nothing to disclose.

Keywords

prostate cancer; MRI; targeted biopsy; tumor volume; pathologic stage

INTRODUCTION

Volume of tumor in the prostate (TV) is an important index of biological behavior, but a practical method for determination of TV prior to whole-organ dissection is lacking. TV has been correlated with Gleason score, pathological stage, and survival [1–6]. Gleason score may be obtained by biopsy, the reliability of which has substantially increased via targeting of MRI-visible lesions [7,8]. However, a method to predict TV has proven elusive. Regions of interest (ROI) on MRI are helpful in tumor localization, but quantitative tumor volumetrics derived from MRI images are poor indicators of actual TV [9].

The importance of TV was addressed by Stamey in 1993, when he reported in whole-organ studies that prostate cancers with a volume less than 0.5 cc lack metastatic potential [10]. The 0.5 cc cut-point was also found by Epstein and colleagues to define the lower limit of clinical significance [5], further emphasizing the relationship of TV to biological potential. Ahmed and colleagues, using template-based saturation biopsy of reconstructed radical prostatectomy specimens (i.e., a model), showed that a 6 mm length of tumor in any core predicted the presence of a 0.5 cc TV [11].

However, tumor metrics derived from random biopsies have only limited relationship to TV or pathologic stage in prostatectomy specimens [12–18]. In the present study, we sought to determine whether maximum cancer core length (MCCL) in biopsies taken directly from MRI lesions would foretell TV (cc) in the same prostates later removed surgically.

PATIENTS AND METHODS

Study Design

Men eligible for this retrospective study were all 1,647 who underwent MR/US fusion biopsy by a single urologist at UCLA (LSM) between 2010–2016 (Figure 1). MRI performance, interpretation, and fusion biopsy procedure using the Artemis system (Eigen, Grass Valley, CA) were as described previously [8]. All patients underwent 12-core systematic (template) sampling and, when an MRI region of interest (ROI) was present (Grade ≥3 by PI-RADSv2 or UCLA), sampling of the ROI at 3 mm intervals along the longest axis of the lesion. At least 3 cores were taken from all ROIs. All patients were enrolled in a prospective IRB-approved study protocol (#11–001580). Biopsy cores were obtained trans-rectally with 25 cm 18ga biopsy needles (Remington Medical, Inc., Alpharetta, GA) providing core samples of 1.3 mm diameter and 15 mm length.

209 of 1,647 men underwent radical prostatectomy (RP) at UCLA within 90 days of fusion biopsy. 4 patients were treated pre-operatively with LHRH therapy and were excluded. The remaining 205 were divided into two groups: 136 in whom the MCCL on biopsy was derived from the primary ROI on mpMRI [19]; these patients defined the targeted biopsy group (Group 1). The comparison group was the 69 patients in whom the MCCL was from a

non-targeted biopsy core (60 systematic biopsy, 5 tracking and 4 secondary targets); these patients defined the non-targeted biopsy group (Group 2). The primary ROI on mpMRI was defined as the target with the highest PI-RADSv2 or UCLA grade; if targets were of equal grade, then the target with the greatest ROI diameter (in mm) was defined as primary. The index lesion on RP was defined as the largest tumor by volume (cc) in the whole-mount RP specimen (Figure 2).

Tissue Processing

Each biopsy core was submitted in a separate bottle, assigned a unique identifier number and fixed in 10% formalin. Cores were evaluated for anatomic location, Gleason score and MCCL in mm. Discontinuous tumor foci that were ≥2 mm apart were given a composite measurement as the combined lengths of each focus.

Whole mount tissue processing was performed by slicing the organ from base to apex in 4 mm sections. Histologic sections were cut at a thickness of 3 to 4 microns. Cancer location, size and volume were assessed by three fellowship-trained urologic pathologists, as described by Eichelberger et al [20]. TVs were based on the greatest diameter of the tumor for each whole mount section, noting the percentage of tumor by quadrant. If tumor was largest from base to apex, the number of 4 mm slices involved was also used to determine the diameter. TV was calculated by multiplying the percent of organ-involvement by the volume of the tumor. In a test sample of 20 cases, the three genitourinary pathologists made independent TV determinations with an intra-class coefficient of 0.97. Tumors were staged by the TNM classification (AJCCth ed).

Statistical Methods

Descriptive statistics were used to summarize general patient characteristics. Spearman correlation coefficients were calculated to assess the relationship between MCCL and index TV at RP. TV had a right-skewed distribution, but a log transformation conferred a normal distribution. Thus, all analyses were conducted using the log transformed TV for each patient. Univariate linear regressions were used to determine significant correlates with log TV, and univariate logistic regressions were obtained to calculate odds ratios for T3 (versus T2) stage for characteristics including biopsy Gleason score, categorical MCCL, and ROI diameter, resulting in multivariate models. To graphically present the final multivariate linear regression model, we back transformed the parameter estimates to its original scale and plotted adjusted TV. Statistical significance was accepted at the two-sided $p<0.05$ level. Confidence intervals are 95%. All analyses were performed in SAS 9.4 (Cary, NC) by co-author LK.

RESULTS

Clinical Characteristics

Patient characteristics of both the targeted (Group 1) and non-targeted (Group 2) biopsy groups are summarized in Table 1. The majority of patients experienced no change in Gleason score from biopsy to RP, in line with prior findings [7]. Median MCCL was longer in the targeted group than in the non-targeted group (7.8 mm, IQR 6.0–9.3) vs 5.5 mm, IQR

4.0–7.0, p<0.01); however, median TV was not different between the groups (5.0 cc, IQR 3.3–10.0 vs 6.0 cc, IQR 3.5–8.8, respectively, p=0.86). T2 and T3/T4 pathologic staging was 56% and 44% for the targeted biopsy group and 75% and 25% for the non-targeted biopsy group (p<0.01).

Correlates of Tumor Volume

For the 136 men in Group 1, MCCL correlated with TV (ρ=0.44, p<0.01); however, no such correlation was found for the 69 men in Group 2 (Table 2). The primary ROI on mpMRI correlated with the index tumor on RP in 127/136 men (93%). For Group 1, significant correlations were noted for each Gleason score separately, except Gleason 6. The correlation coefficient increased with increasing Gleason scores from Gleason 3+4 (ρ=0.44) to Gleason 4+3 (ρ=0.55) to Gleason >7 (ρ=0.60). TV was weakly, but significantly correlated with the ROI diameter on MRI (ρ=0.32, p<0.01), in line with findings from previous publications [9]. Figure 3 demonstrates the relationships of TV and MCCL, by ISUP Grade Group (GG), for each patient in Group 1. The correlation of MCCL with TV was similar for first and repeat biopsy and for TZ and PZ lesions (ρ=0.42–0.49).

In univariate analysis, MCCL of 6–10 mm and >10 mm were each significantly associated with log TV when compared to the referent group of men with <6 mm (β=0.34; CI 0.06, 0.61 and β=0.97; CI 0.63, 1.31, respectively). In multivariate analysis, MCCL of 6–10 mm and >10 mm was an independent predictor of log TV (β=0.34; CI 0.08, 0.61 and β=0.80; CI 0.45, 1.15, respectively), regardless of MRI diameter (Table 3).

Correlates of Pathologic Stage

In univariate analysis of Group 1, Gleason score >7 and MCCL >10 mm were directly related to likelihood of T3 staging (OR=6.30; CI 1.86, 21.30; OR=9.69; CI 2.90, 32.36, respectively) (data not shown). ROI grade and diameter were not associated with pathologic stage. No correlation with pathologic stage was noted for any metric in Group 2.

In the multivariate model controlling for ROI diameter, biopsy Gleason and MCCL remained significantly associated with pathologic T3 staging (Table 4). For Gleason score >7, the odds ratio of T3 staging was 5.04 (p=0.02). MCCL >10 mm greatly increased the risk of T3 staging (OR=5.73; CI 1.48, 22.18). Neither the 6–10 mm MCCL sub-group nor the ROI diameter ≥10 mm were significantly associated with T3 staging.

DISCUSSION

The index lesion of prostate cancer, which usually determines natural history of the disease, is characterized by tumor volume and Gleason score [21]. The two parameters are often associated. Very small cancers, typically of low histologic grade, rarely metastasize. Large cancers, often of high grade, are much more concerning. Nearly all existing information about tumor volume has been obtained via study of excised prostates [2,4,5,22]. A reliable metric to foretell tumor volume prior to surgical excision would be highly desirable. The current work is a step toward that end.

In this study, we found that maximum cancer core length (MCCL)---when obtained by targeted biopsy from an MRI-visible region of interest (ROI)---was directly related to index tumor volume (TV) in whole mount sections, i.e., the longer the MCCL, the larger the TV. No such relationship pertained when the MCCL came from a non-targeted biopsy. The relationship of targeted MCCL to index TV held true, regardless of patient age, PSA, prostate volume, PSA density, PI-RADS score, or location of tumor within the prostate. With increasing Gleason score beyond 6, the relationship between the two variables strengthened, with patients with a Gleason score >7 having a correlation coefficient of 0.60. Targeted MCCL was also indicative of pathologic stage. For example, a long MCCL (>10 mm) was associated with increased frequency of T3 disease (OR = 5.73). If confirmed, these findings would provide a method for evaluating men with prostate cancer, which is not currently available.

The present work supports and expands the work of Baco and colleagues [23–25], who also investigated the MRI correlations of MCCL and index tumors. In the Baco work, no control group was present, since in that research only targeted biopsy was performed; in the present paper, we furnish data comparing the two methods (targeted and non-targeted) in the same cohort of patients, showing that only the targeted biopsies provide predictive information. Further, the present targeting method (one core every three mm of ROI) allows more thorough sampling of the lesion than the method reported by Baco et al. Despite differences in technology, both studies support the concept that MRI-targeted biopsies can provide information about volume of the index lesion. Additionally, the present work quantifies the relationship between cancer core length, index tumor volume and pathologic stage, potentially allowing a new metric to help guide treatment decisions.

The value of pre-biopsy MRI is strengthened by the present findings. Without MRI guidance, sampling would be only systematic, except for the occasionally-found hypoechoic lesion which could be targeted. Thus, the predictive information furnished by targeted biopsy, as shown in Table 2, would not be obtained. While challenged on the grounds of economics and resource limitations, pre-biopsy MRI for guidance has resulted in greatly increased accuracy of biopsy results [8,26]. For repeat biopsy situations, MRI guidance has been endorsed by the AUA and the SAR [27]. For first-biopsy situations, available data are not yet clear [28–30]. However, in the present study the predictive value of targeted MCCL held true equally for men undergoing either first or repeat biopsy; thus, an additional reason for pre-biopsy MRI---the potential for quantifying volume of the index tumor---is herein shown.

The present data indicate that a MCCL taken from an MRI-visible lesion, if in excess of 10 mm, portends the likelihood of a large, aggressive prostate cancer. How such information might fit with currently accepted predictors (e.g., Partin tables) and influence treatment decisions remains to be determined. When active surveillance or partial gland ablation are under consideration, additional information about tumor volume may be helpful for determining extent of treatment, or perhaps dissuading a conservative approach. As shown here, MCCL >10 mm from a targeted biopsy appears to be an independent predictor of cancer potential and pathologic staging.

The present findings may impact guidelines for patient selection for partial gland ablation. For example, patients with a TB MCCL of >10 mm may not be effectively treated focally if disease is extracapsular, which our model predicts. In addition, TB MCCL might be considered when planning ablation volumes and estimating treatment margins in a focal case. And further, a MCCL from a non-targeted biopsy may be of limited value when estimating index tumor volume and selecting patients for partial gland ablation.

Certain limitations apply. Overall, the Spearman rank correlation for targeted MMCL and RP TV is only 0.44. However, this correlation increases with increasing Gleason score and it is non-existent when an MCCL is from a non-targeted core. The confidence intervals are somewhat wide, perhaps related to sample size. This may also explain individual patient exceptions at the extreme of our range, at least with regard to predictions of pathologic stage as noted in Figures 2a and 2b. Figure 2a demonstrates that a patient with a small TB MCCL may still harbor T3 disease, although the statistical model overall predicts otherwise. These exceptions require further study. Our findings set a framework to consider such questions.

The role of TV in pathogenesis is not clarified by this work, only the ability to quantify it. Radical prostatectomy, rather than saturation template biopsy, was used to provide a ground truth. Determination of tumor volume was only a close estimate. Index TV was used rather than total TV. And the results were obtained by a single group of experienced investigators, working with MRI/ biopsy/pathologic methods developed over nearly 10 years of collaboration, which might limit generalizability of the study. These considerations aside, the utility of targeted MCCL for prediction of index tumor volume, clearly supported by the present data, creates a hypothesis to be tested in a prospective trial.

CONCLUSIONS

Targeted biopsy of MRI-visible lesions yields maximum cancer core lengths that correlate with tumor volume in radical prostatectomy specimens and pathologic stage of disease. Non-targeted biopsies do not yield comparable information. The present data add a reason for MRI-guided biopsy and suggest a metric---targeted cancer core length (MCCL)---that may help stratify prostate cancer risk and aid in determining treatment.

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ABBREVIATIONS

MCCL	maximum cancer core length
RP	radical prostatectomy
TV	tumor volume
ROI	region of interest

MRI	magnetic resonance imaging
PI-RADSv2	Prostate Imaging Reporting and Data System Version 2
UCLA	University of California at Lost Angeles
TRUS	trans-rectal ultrasound
LHRH	luteinizing hormone-releasing hormone
SD	standard deviation
CI	confidence interval
IQR	inter-quartile range
OR	odds ratio
CaP	cancer of the prostate
TZ	transition zone
PZ	peripheral zone
GS	Gleason score
AUA	American Urological Association
SAR	Society of Abdominal Radiology
ISUP	International Society of Urological Pathology
GG	grade group

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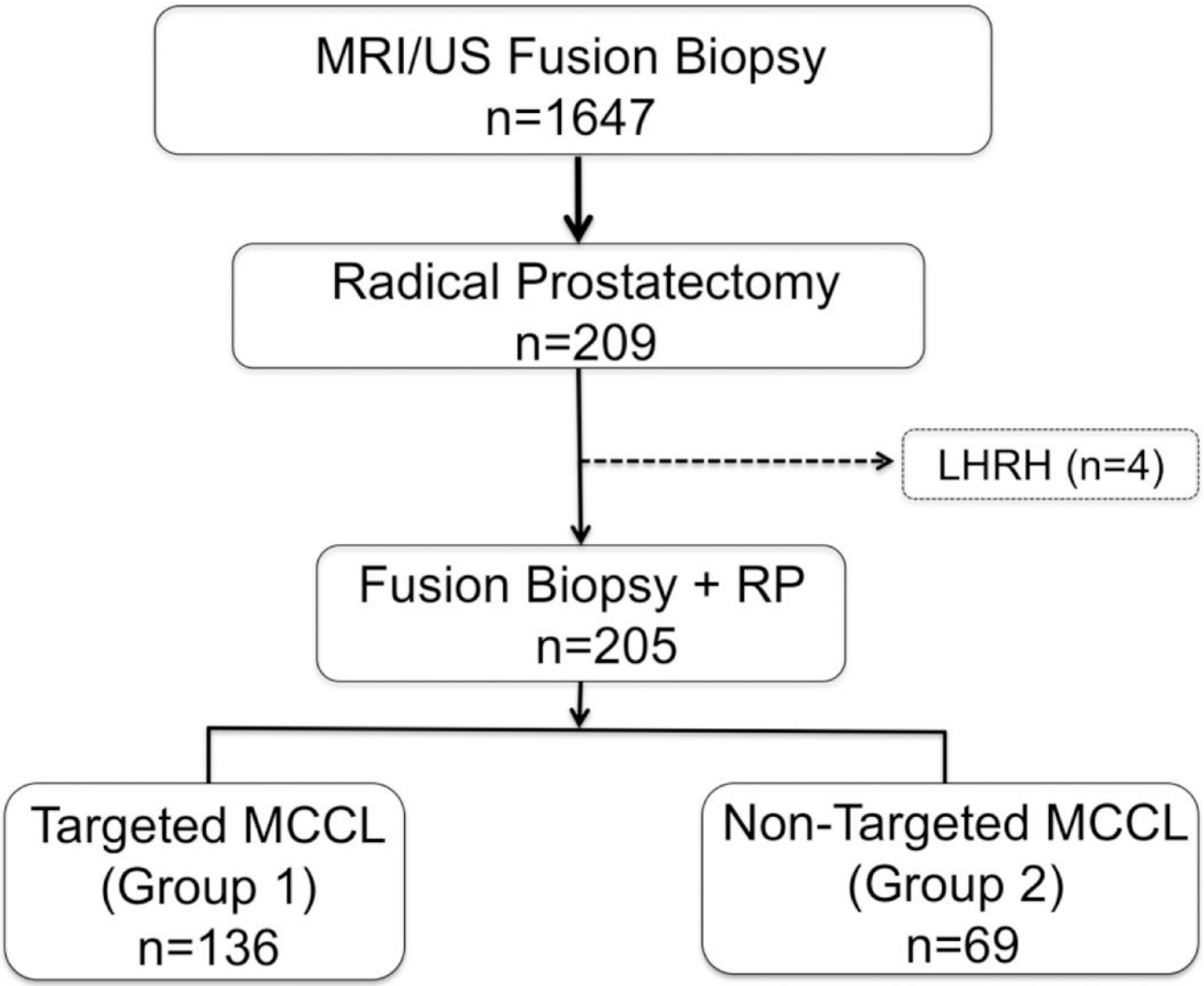

Figure 1:
Patient Flow Chart. In the targeted men (Group 1), the MCCL on MR/US fusion biopsy was from the primary ROI on mpMRI. In the non-targeted men (Group 2), the MCCL was from either a systematic or tracking biopsy or secondary target.

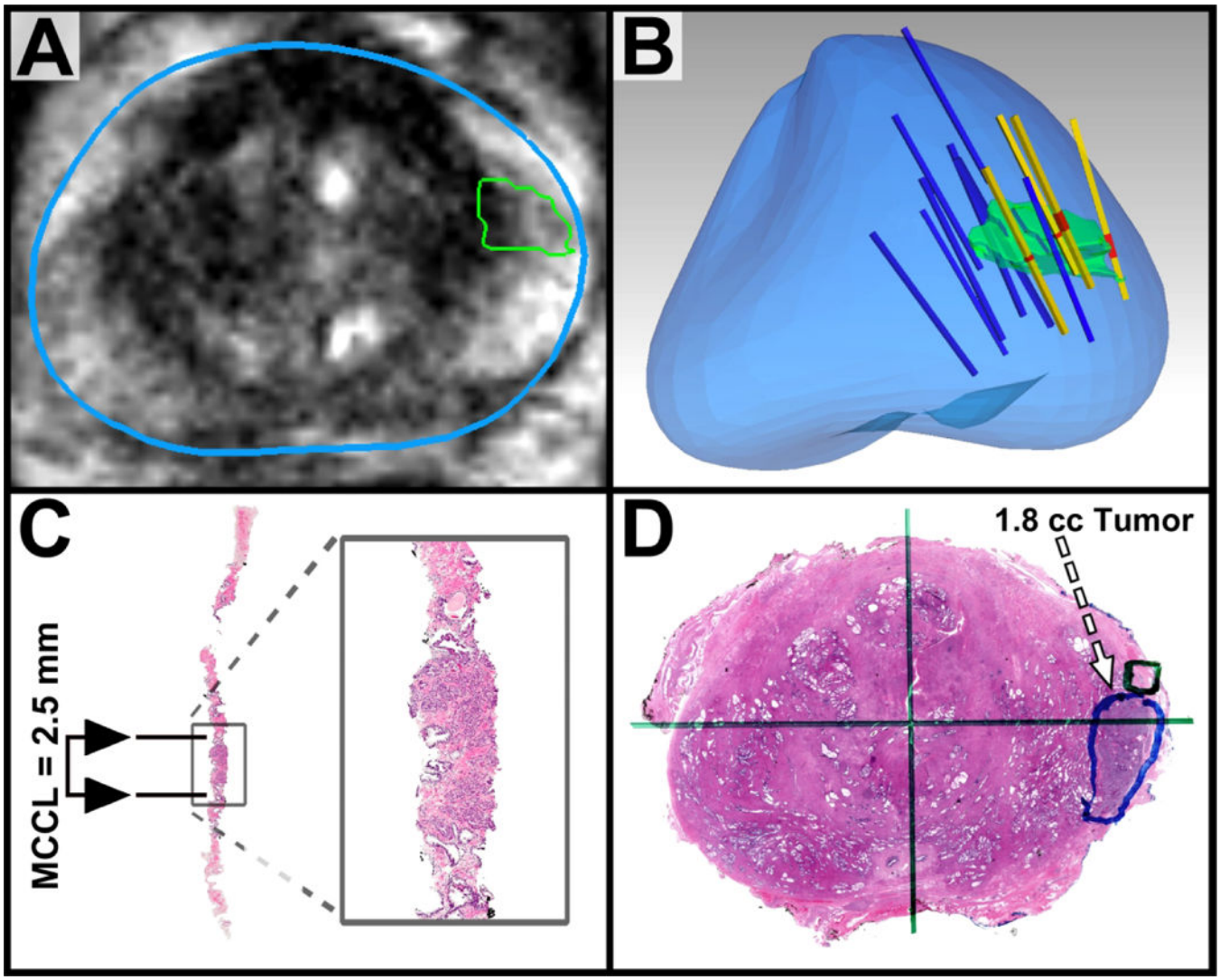

Figure 2a:

Example of short CCL indicating small tumor. Pt is 67 year old with a PSA of 7.4 ng/m, prostate volume = 37 cc. A. MRI demonstrates a grade 4 region of interest (ROI, green outline) of 10 mm in left peripheral mid-gland . B. Targeted biopsy cores (yellow) are placed in ROI; CCL shown in red. Blue cores are systematic. C. Maximum cancer core length (MCCL) from ROI measures 2.5 mm (Gleason 7). D. RP whole mount section demonstrates an index tumor volume of 1.8 cc. Pathologic stage is pT3a, N0, Mx with negative surgical margins. 218×174mm

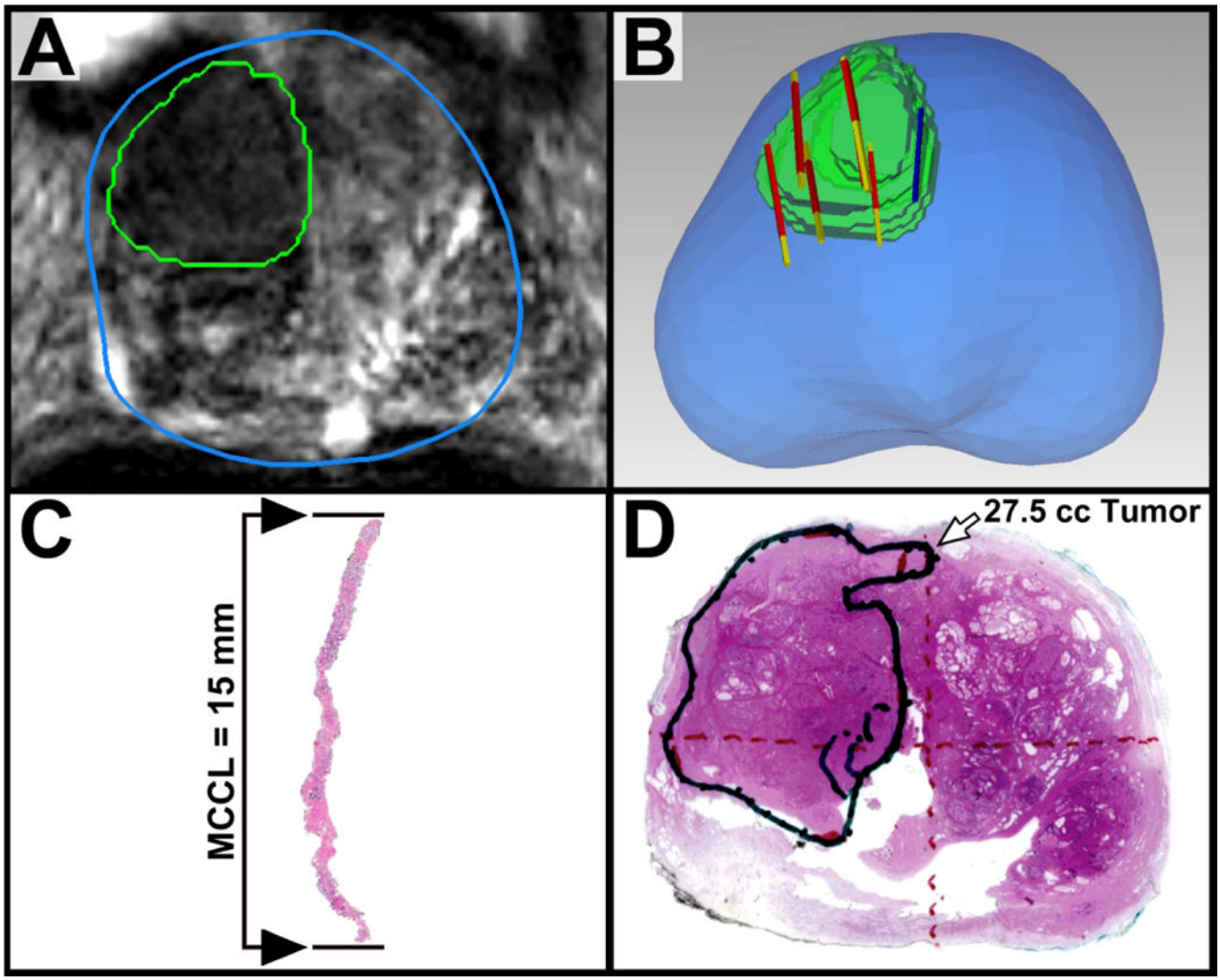

Figure 2b:

Example of long CCL indicating large tumor volume. Pt is 62 year old with a PSA of 14.4 ng/ml and prostate volume of 110 cc. A. MRI demonstrates a grade 5 ROI (green outline) of 24 mm at the right anterior central gland. B. Targeted biopsy cores (yellow) are placed in ROI. CCL shown in red. C. Entire core length is replaced by cancer (Gleason 7); MCCL = 15 mm. D. RP whole mount section demonstrating Gleason 3+4=7 CaP and an index tumor volume of 27.5 cc. Pathologic stage is pT2c, N0, Mx with negative surgical margins. Note that MRI underestimates actual tumor size (REF #9).

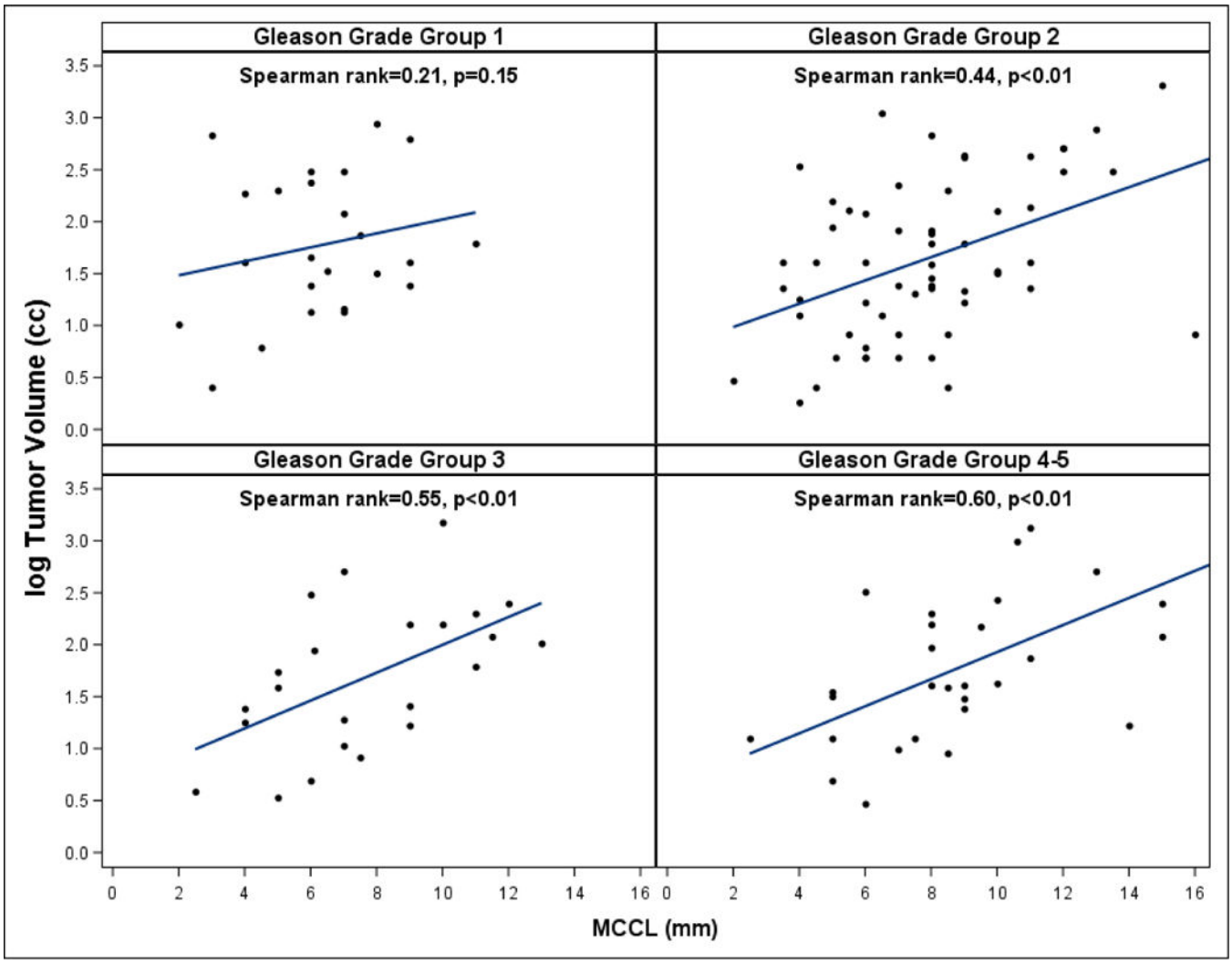

Figure 3:

Scatter plot showing the Spearman rank correlation, by Gleason Grade Group (GG), for MCCL on targeted biopsy taken from the primary MRI-visible lesions (horizontal axis) and log volume of that tumor in radical prostatectomy specimens (vertical axis). The best fit regression line is noted for each GG. For GG 1, there is no correlation. For all grade groups beyond 1, the correlation is significant and increases.

Table 1

The patients' characteristics (N = 205).

	Targeted n=136	Non-targeted n=69	p value
Age, mean (SD)	62.8 (6.6)	62.3 (5.7)	0.62
Ethnicity, % (n)			
White	81% (110)	87% (60)	0.27
Non-White	19% (26)	13% (9)	
Family history of prostate cancer, % (n)	16% (20)	32% (13)	0.03
Previous Biopsy			
No	38% (52)	30% (21)	0.27
Yes	62% (84)	70% (48)	
PSA (ng/ml), median (IQR)	7.3 (5.3–11.8)	6.3 (4.4–8.2)	0.06[b]
RP Prostate volume (cc)[a], median (IQR)	37.1 (29.0, 46.0)	36.0 (25.3–53.2)	0.62[b]
PSA density (ng/ml/cc), median (IQR)	0.19 (0.14–0.31)	0.15 (0.10–0.21)	0.03[b]
Zone			
Peripheral	73% (98)	-----	
Transition	27% (37)	-----	
Gleason pattern, % (n)			
3+3	18% (24)	32% (22)	<0.01
3+4	44% (60)	52% (36)	
4+3	17% (23)	9% (6)	
>7	21% (29)	7% (5)	
MCCL			
median (IQR)	7.8 (6.0–9.3)	5.5 (4.0–7.0)	<0.01[b]
<6 mm	24% (32)	54% (37)	<0.01
6–10 mm	58% (78)	42% (29)	
>10 mm	19% (26)	4% (3)	
ROI grade			
0–2	-----	19% (13)	<0.01
3	23% (31)	49% (34)	
4	46% (62)	20% (14)	
5	32% (43)	12% (8)	
Maximum ROI diameter			
<10 mm	22% (30)	35% (22)	0.02
10–20 mm	64% (87)	62% (39)	
>20 mm	14% (19)	3% (2)	

[a] Volume from TRUS, planimetric

[b] Wilcoxon rank-sum test

Table 2

Spearman rank correlations of MCCL with index TV.

	Targeted (n=136)			Non-Targeted (n=69)		
	n	**ρ**	**p value**	**n**	**ρ**	**p value**
All	136	0.44	<0.01	69	−0.01	0.96
Gleason 6 (GG 1)	24	0.21	NS	22	0.02	0.96
Gleason 7	83	0.47	<0.01	42	0.01	0.94
3+4 (GG 2)	60	0.44	<0.01	36	−0.09	0.61
4+3 (GG 3)	23	0.55	<0.01	6	0.76	0.08
Gleason >7 (GG≥4)	29	0.60	<0.01	5	−0.56	0.32

Table 3

Univariate and multivariate linear regression analysis of log index TV.

	Univariate		Multivariate	
	β (95 % CI)	**p**	**β (95 % CI)**	**p**
Age	0.004 (−0.01, 0.02)	0.65		
Race	−0.01 (−0.32, 0.31)	0.95		
Family history of prostate cancer	−0.22 (−0.57, 0.14)	0.23		
PSA (ng/ml)				
≤10 (referent)	----	----		
>10	**0.62 (0.37, 0.87)**	**<0.01**		
Prostate volume, TRUS (cc)	**0.01 (0.004, 0.02)**	**<0.01**		
PSA density (ng/ml/cc)				
<0.15 (referent)	----	----		
≥0.15	**0.27 (−0.001, 0.54)**	**0.05**		
Biopsy Gleason sum	0.08 (−0.07, 0.23)	0.29		
ROI Grade[a]				
3–4 (referent)	----	----		
5	**0.34 (0.08, 0.60)**	**0.01**		
Clinical T Stage				
T2 (referent)	----	----		
T3	**0.46 (0.22, 0.69)**	**<0.01**		
Biopsy MCCL				
<6 mm (referent)	----	----	----	----
6–10 mm	**0.34 (0.06, 0.61)**	**0.02**	**0.34 (0.08, 0.61)**	**0.01**
>10 mm	**0.97 (0.63, 1.31)**	**<0.01**	**0.80 (0.45, 1.15)**	**<0.01**
ROI maximum diameter				
<10 mm (referent)	----	----	----	----
10–20 mm	0.20 (−0.09, 0.48)	0.17	0.11 (−0.16, 0.38)	0.43
>20 mm	**0.88 (0.49, 1.28)**	**<0.01**	**0.61 (0.21, 1.01)**	**<0.01**

[a]UCLA Score, range 3–5

Table 4

TB characteristics predicting the likelihood (OR) of pathological T3 disease.

	OR (95% CI)	p value
Biopsy Gleason score		
3+3 (referent)	-----	-----
3+4	1.25 (0.39, 4.01)	0.71
4+3	2.11 (0.47, 9.57)	0.33
>7	**5.04 (1.31, 19.33)**	**0.02**
MCCL		
<6 mm (referent)	----	----
6–10 mm	2.31 (0.77, 6.96)	0.14
>10 mm	**5.73 (1.48, 22.18)**	**0.01**
ROI diameter		
<10 mm (referent)	----	----
≥10 mm	2.75 (0.92, 8.25)	0.07