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Spatial distribution of biopsy cores and the detection of intra-lesion pathologic heterogeneity

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Abstract

Objectives: The objective of this study was to determine if spatial distribution of multiparametric magnetic resonance imaging–transrectal ultrasound (mpMRI-TRUS) fusion biopsy cores to the index lesion reveals trends in the detection of intra-lesion Gleason heterogeneity and a more optimal prostate biopsy strategy.

Methods: Index lesion was the lesion with longest diameter on T2-weighted (T2W)-MRI. In cohort 1, fusion biopsy cores biopsies were taken in areas in the center of the target as well as 1 cm laterally on each side. For cohort 2, targeted biopsies were taken from the center of the lesion only. Heterogeneity was defined as difference in maximum Gleason score obtained from fusion cores in the center of the index lesion *versus* cores obtained from the periphery (cohort 1), or any difference in maximum Gleason score obtained from fusion cores targeted to the index lesion (cohort 2) compared with systematic 12 cores TRUS biopsy.

Results: Ninety-nine consecutive patients (35 and 64 in cohorts 1 and 2, respectively) with median age (SD) and prostate-specific antigen (PSA) of 66.9 (±5.9) and 9.7 (±8.2) respectively, were included. Age, PSA, Prostate Imaging Reporting and Data System (PI-RADS) score, and preoperative MRI lesion size were not significantly different between cohorts. Gleason heterogeneity was observed at a significantly higher rate in cohort 1 *versus* cohort 2 (58% *versus* 24%; $p = 0.041$). In cohort 1, cores obtained from the center of the lesion had higher Gleason score than cores obtained from the periphery of the targeted lesion in 57% of cases.

Conclusions: We demonstrate that there is observable tumor heterogeneity in biopsy specimens, and that increased number of cores, as well as cores focused on the center and periphery of the largest lesion in the prostate, provide more comprehensive diagnostic information about the patient's clinical risk category than taking nonspecific cores targeted within the tumor.

Keywords: biopsy core distribution, cancer detection rate, fusion biopsy, Gleason heterogeneity

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Introduction

The current gold-standard approach for the detection of prostate cancer (PCa) involves taking 12 transrectal ultrasound (TRUS) guided cores (systematic biopsy). When compared with prostatectomy pathology, this approach is estimated to under-grade or misdiagnose up to nearly half (46%) of all tumors.[1,2] Prior to the advent of magnetic resonance imaging (MRI) as an aid for the diagnosis of PCa, this unguided sampling was the most optimal strategy available to clinicians. However, multiparametric (mp) MRI-TRUS fusion guided biopsy strategies have given urologists a targeted approach that enables prioritized sampling to areas suspicious for harboring cancer.[3,4] Using this approach, the addition of two biopsy cores to lesions visible with MRI resulted in 30% higher rate of detection of high-risk and

17% less detection of low-risk tumors.[5] Despite these promising results, there is evidence in the literature that the addition of two targeted cores may still not be optimal, and may leave the index lesion undersampled.

Although not fully understood, a growing body of evidence suggests that PCa exhibits intratumor histological heterogeneity.[6–8] Aihara *et al*. mapped spatial Gleason distributions for 101 radical prostatectomy specimens, and found that the largest lesion in each specimen only was comprised of a single Gleason grade in 10% of cases, with over 50% of prostates containing more than two Gleason grades.[9] Among multiple grade specimens, 53% had the highest-grade PCa found in the center of the tumor, with lower-grade cancer found in the periphery. Mesko *et al*. demonstrated that Gleason heterogeneity is detectable on biopsy in a study of 53 patients and reported a 55% rate of Gleason heterogeneity, defined as a difference in Gleason scores between two cores within a single target in patients with at least two positive cores.[10] Porpiglia *et al*. reported that by using six targeted cores in lesions >8 mm in diameter, Gleason heterogeneity was detected at twice the rate as was found in tumors ⩽8 mm targeted with four cores (26.4% *versus* 12.6%).[11] Although it is difficult to discern from this study whether the increased detection of heterogeneity was attributable to additional cores or to increased tumor diameter, this study sheds light on the fact that the optimal strategy for placement and number of cores within the prostate has not yet been optimized for maximal cancer detection. In this study, we present a prostate biopsy strategy that builds from the foundation of previous studies in pursuit of improved detection of PCa.

Methods

Patient selection

Demographic and clinical data were prospectively collected and retrospectively reviewed on 99 patients who underwent mpMRI-TRUS biopsy at our institution in 2017. Patients who underwent prostate MRI and a combination of fusion and systematic biopsy were included in the study. All patients included were either experiencing a primary diagnosis or were enrolled in an active surveillance protocol, that is, no patients received prior hormone or radiation treatment for PCa. Exclusion criteria were patients with a maximum diameter of <1 cm for their index tumor as this was deemed insufficient to appropriately distinguish biopsies taken from the center *versus* periphery. Also excluded were patients with tumors designated a Prostate Imaging Reporting and Data System (PI-RADS) score <3.

MRI

Patients underwent MRI at our institution on a 1.5 Tesla scanner with diaper coil, or at outside facilities with second opinion interpretation and targeting by our radiology team (SD, CR, or DM). Modalities used included T2-weighted (T2W), diffusion weighted imaging (apparent diffusion coefficient and high-B value), and dynamic contrast-enhanced sequences. Each lesion was assessed and given a PI-RADS score that was used as a factor for inclusion criteria. The index lesion was defined as the lesion with the largest diameter on T2-weighted imaging with the highest PI-RADS score. Patients were then retrospectively separated into two cohorts according to the number and spatial distribution of cores targeted to the index lesion.

Biopsy

Patients in the traditional fusion biopsy (tFbx) cohort underwent transrectal mpMRI-TRUS fusion biopsy under previously described protocols.[5] In this cohort, patients received a total of two biopsy cores to the index lesion designated on MRI. Patients in the novel fusion biopsy (nFbx) cohort received a total of four biopsy cores to the index lesion. In this cohort, patients received two targeted cores directly to the center of the index lesion, in addition to two targeted cores taken peripherally from opposite ends of the longest-diameter appreciated on T2W imaging in the left–right plane (Figure 1). In addition to targeted biopsy, patients in both cohorts received a systematic 12-core biopsy.

Heterogeneity. In the nFbx cohort, cores taken from the center of the tumor were compared and the highest value Gleason score was used to represent the 'maximum' Gleason score obtained from the center of the tumor. The same method was performed to determine the maximum Gleason score from the periphery. Gleason heterogeneity was then assessed by comparing maximum Gleason scores between the center and periphery. In the tFbx cohort, two cores were taken from

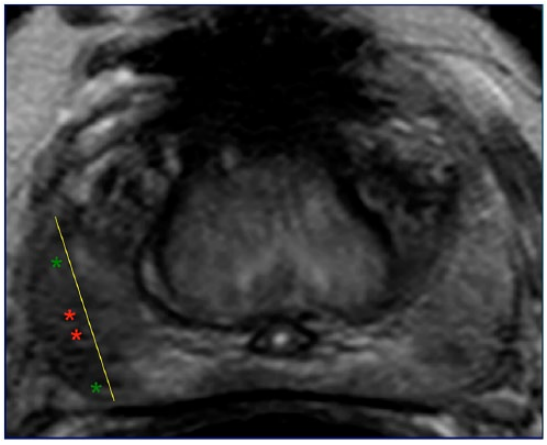

Figure 1. Biopsy template used for patients in cohort 1. Patients received two biopsy cores targeted to the center of the lesion (marked in red), and two cores to the periphery (marked in green) along the axis of maximal lesion diameter (yellow line).

random locations in the center of the tumor and were compared to assess the rate of heterogeneity.

Pathology

Pathologic data from biopsy was collected and analyzed for the highest Gleason score. The results of this collection were then assorted based on the biopsy modality used to obtain the sample. In the tFbx cohort, the maximum Gleason scores were obtained from each patient's systematic biopsy results as well as from targeted biopsy results, so that the source of the highest overall Gleason score from the prostate could be determined. Intra-tumor Gleason heterogeneity was defined in this cohort as any difference in Gleason scores obtained between the targeted biopsy cores taken from the index tumor.

In the nFbx cohort, the maximum Gleason scores were obtained from the patient's systematic biopsy cores; however, the maximum Gleason score from targeted biopsy was further subclassified into the maximum Gleason score from cores taken from the center of the tumor and cores taken from the periphery of the tumor. Gleason heterogeneity in this cohort was defined as a difference in the maximum Gleason score between the center and periphery.

Statistics. Statistical analysis was performed using SPSS version 21 (Chicago, IL). Chi-squared test was used to compare the maximum Gleason scores between the center and periphery in nFbx cohort and between cores in tFbx cohort. Continuous parameters between cohorts were compared using Mann–Whitney test.

Results

A total of 99 patients were included in the study with mean age (standard deviation, SD) and prostate-specific antigen (PSA) (SD) of 66.9 (±5.9) years and 9.7 (±8.2) ng/ml, respectively. A total of 35 and 64 patients were included in nFbx and tFbx cohorts, respectively.

Demographic and clinicopathologic data are listed in Table 1. Age, PSA, PI-RADS score, and maximum Gleason score from systematic biopsy were similar between cohorts.

Heterogeneity

The median number of biopsy cores taken from cohort 1 was four (2 center, 2 periphery) and from cohort 2 was two.

Gleason heterogeneity was observed at a significantly higher rate in cohort 1 *versus* cohort 2 (58% *versus* 24%; $p = 0.041$). Further, in cohort 1, Gleason scores from cores obtained from the center of the lesion were higher than Gleason scores obtained from the periphery in 57% of cases.

Discussion

Our results showed that spatial placement of biopsy cores in tumors has the potential to reveal trends in the distribution of intra-tumor Gleason scores, which could potentially provide a foundation for future strategies in which additional cores are targeted only to the areas in the tumor thought to harbor the highest Gleason grades.

Prior biopsy strategies have 'saturated' the prostate with biopsy cores in an attempt to maximize the potential to detect cancer, yet often this strategy increases the risk of quality-of-life side effects[12,13] and tends to overdiagnose clinically insignificant disease compared with standard sextant biopsy.[13] In contrast to increased 'blind' sampling, mpMRI-TRUS fusion biopsy has shown the potential to detect more high-risk disease and less low risk by targeting MRI-suspicious areas with two additional biopsy cores.[5] However, the addition of two biopsy cores to these areas may not be enough. Lesion size on MRI is often underrepresented compared with tumor extent

Table 1. Baseline characteristics.

	Saturation biopsy		Total	*p* Value
	Yes	No		
Patients	35	64	99	
Age, mean (IQR)	66.8 (6.0)	66.9 (5.8)	66.9 (5.9)	0.915
PSA (ng/ml), median (IQR)	9.8 (8.9)	9.7 (7.7)	9.7 (8.2)	0.671
PI-RADS score, *n* (%)				0.663
3	8 (23.5)	23 (37.1)	31 (32.3)	
4	18 (52.9)	23 (37.1)	41 (42.7)	
5	7 (20.6)	15 (24.2)	22 (22.9)	
Lesion size (mm), median (IQR)				
	22.3 (3.0)	18.0 (2.8)	19.6 (2.9)	0.342
Prostate volume on MRI (cc), median (IQR)	91.0 (53.8)	79.2 (40.7)	83.1 (45.5)	0.59
Gleason scores: systematic biopsy				0.881
Benign	21 (61.8)	35 (54.7)	54 (56.2)	
3 + 3	6 (17.6)	19 (29.7)	25 (26.0)	
3 + 4	3 (8.8)	5 (7.8)	8 (8.3)	
4 + 3	1 (2.9)	2 (3.1)	3 (3.1)	
4 + 4	3 (8.8)	3 (4.7)	6 (6.2)	
Intra-tumor Gleason score heterogeneity, *n* (%)	7 (58.3)	6 (24.0)	13 (35.1)	0.041

IQR, interquartile range; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen.

on prostatectomy, which may make optimal biopsy placement difficult to discern.[14] Further, accuracy of MRI–ultrasound coregistration is not perfect and is highly dependent on user experience, and therefore carries the risk of misrepresenting the target for biopsy.[15,16]

One strategy that theoretically could improve the chances of detecting the full extent of cancer in a heterogeneous tumor is increasing the number of cores targeted to the tumor.[17] In 2016 the NCI group explored the relationship between the number of cores targeted to the index tumor and the ability to detect maximal cancer in the prostate.[18] By assigning biopsy cores in 6 mm intervals throughout the index lesion and then comparing biopsy pathology to prostatectomy pathology, they observed a significantly lower rate of clinical risk category upgrade compared with a cohort of patients who received the traditional two targeted cores to the index lesion (7% *versus* 18%, $p = 0.021$).

Our strategy of targeting two cores to the center of the lesion and two cores to the periphery could potentially offset several of these concerns. By broadening the area biopsied, concerns about MRI coregistration error are alleviated. By increasing the number of cores, a comprehensive representation of all pathology present within the tumor is more likely. These results contribute to the pursuit of the optimal number and spatial placement of biopsy cores within the prostate.

Our study has some limitations. The expansion of the number of targeted cores to the index lesion from the traditional targeted biopsy method used previously at our institution may introduce bias, as many previous studies have demonstrated increased PCa detection with increased biopsy cores taken, whether targeted or systematic; therefore, there is inherent risk of results being affected by the difference in the number of biopsy cores used between cohorts. However, a comparison of this nature is relevant owing to the large volume of institutions currently employing a two-core approach targeted to the index lesion. Second, because both the number and spatial distribution of cores changes with the new biopsy method, it is difficult to ascertain the contribution of each to our results. Future studies should experiment with controlling either the spatial location or number of cores between cohorts, in order to evaluate which has a greater impact on the detection of Gleason heterogeneity, as well as comparison of different biopsy targeting strategies with radical prostatectomy tumor maps as the gold standard. The inclusion of men on an active surveillance protocol may influence Gleason score distribution and thus reporting for the entire cohort. Lastly, this study was a single-institution study that hopefully will be expanded to a multi-institutional study in the future.

Conclusion

Despite evidence of its existence in the literature, intra-tumor histopathologic heterogeneity remains a poorly understood phenomenon. Our study builds on previous studies that have reported a trend in detecting higher-grade pathology in the center of prostate tumors compared with the periphery. By targeting the center and the periphery of lesions, urologists can collect more comprehensive pathologic data regarding the patient's disease than with nonspecific targeted biopsy.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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