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Original article

Optimal sampling scheme in men with abnormal multiparametric MRI undergoing MRI-TRUS fusion prostate biopsy

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Abstract

Objectives: To determine the implications of different prostate sampling schemes on the diagnosis of clinically significant prostate cancer (csPCA, ISUP group 2–5) and clinically insignificant prostate cancer (ciPCA, ISUP group 1) in men with abnormal multiparametric magnetic resonance imaging (mpMRI) undergoing MRI-transrectal ulrasound fusion targeted biopsies.

Materials and Methods: This is a retrospective analysis of a cohort including all men who had a single lesion on mpMRI of the prostate performed between January 2016 and June 2017. All men underwent an MRI-transrectal ulrasound fusion biopsy and systematic (SBx) sampling of the prostate, which combined and were considered the standard of reference. The hypothetical 3 biopsy sampling schemes were defined as follows: Targeted biopsy only (TBx), TBx + ipsilateral SBx (ipsi-SBx) and TBx + contralateral SBx (contra-SBx) and were evaluated for the detection of csPCA and ciPCA. Sensitivity and 95% intervals were calculated, McNemar test was used to compare sensitivities between the various sampling schemes.

Results: TBx + SBx detected csPCa in 47% (55 of 116) of the 116 men who met eligibility criteria. Sensitivity and 95% confidence intervals for csPCa detection was 85.5% (73.3%–93.5%), 96.4% (87.5%–99.6%), and 92.7 (82.4%–98%) for TBx alone, TBx + ipsi-SBx and TBx + contra-SBx, respectively. csPCa detection rates were higher for both TBx + ipsi-SBx and TBx + contra-SBx compared to TBx alone. Clinically insignificant cancers alone were detected in 7.7% (9 of 116), 10.3% (12 of 116), and 14.6% (17 of 116) of the cohort by TBx only and TBx + ipsi-SBx, and TBx + contra-SBx, respectively.

Conclusions: TBx + ipsi-SBx may increase the detection of csPCa while limiting overdiagnosis of indolent cancers.

Keywords: Prostate; Prostate cancer; Biopsy; Targeted biopsy; MRI; Systematic biopsy

1. Introduction

Prostate cancer is the most common cancer in men with an estimated incidence of over 164,000 new cases in 2018 in the United States [1]. As multiparametric magnetic resonance imaging (mpMRI) is becoming more available, the use of MRI-transrectal ultrasound (TRUS) fusion targeted prostate biopsy (TBx) is rising and has the potential of becoming the new standard of care [2].

TBx increases the detection of clinically significant prostate cancer (csPCa) while minimizing the detection of clinically insignificant prostate cancer (ciPCa) [3,4]. In many cases, systematic biopsies (SBx) are performed in

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conjunction with TBx. While additional SBx may yield higher cancer detection rates of up to 20%, most of the additionally detected tumors have been shown to represent ciPCa [5].

Despite the increased use of active surveillance for patients with ciPCa [6], overdiagnosis of ciPCa may still lead to overtreatment and have profound impact on the patients' quality of life [7]. Furthermore, increased number of biopsy cores seen when both systematic and targeted approaches are combined may be associated with more pronounced patient inconvenience, pain and possibly with higher complication rate [8].

Various prostate sampling schemes have been suggested with some groups advocating only TBx [9], while others suggesting that TBx and SBx should still be combined [10]. A previous report has suggested TBx + limited SBx scheme only including SBx performed on the ipsilateral side of the target lesion [11], thus possibly compensating for inherent MRI-TRUS fusion inaccuracies [12,13].

The goal of our study was to determine the implications of different sampling schemes on the diagnosis of csPCa and ciPCa in men with abnormal mpMRI undergoing MRI-TRUS fusion targeted biopsies.

2. Materials and methods

2.1. Study design and population

This institutional review board-approved, HIPAA-compliant single center, observational, single-arm study is a retrospective review of prospectively generated data following the START consortium recommendations [14]. The cohort included all men who had a single Prostate Imaging Reporting and Data System v2 [15] (PI-RADS v2) $\geq$ 3 lesion on 3 Tesla mpMRI of the prostate performed between January 2016 and June 2017, which was followed by both MRI-TRUS fusion biopsy including TBx and SBx sampling of the prostate (Fig. 1). Men who had no SBx—at the discretion of the physician performing the biopsy—were excluded from the analysis.

2.2. Multiparametric MRI

Imaging studies were performed on a 3 Tesla MRI scanner (Philips, Best, Netherlands) with an endorectal and a phased-array surface coil, including T2-weighted, diffusion-weighted, and dynamic contrast-enhanced images. Images were prospectively interpreted by 1 of 9 board-certified radiologists using PI-RADS v2 score (mpMRIs performed after December 2016) or a Likert scale score (before January 2017)—a 1–5 scale of the likelihood of clinically significant cancer that follows the same principles as PI-RADS, and that has been previously validated as predictive of targeted biopsy outcome [16]. The latter—mpMRIs scored using a Likert scale—were reviewed by single, experienced radiologists (D.N.C., with 15 years of experience interpreting prostate MRI) who provided a PI-RADS score for each of the lesions. All radiologists were board certified, with a minimum of 5 years of experience in the interpretation of mpMRI, reading an average of 100+ cases annually.

2.3. MRI-TRUS fusion biopsies and hypothetical sampling schemes

Targeted biopsies were performed using 1 of 2 image fusion systems (UroStation, Koelis; UroNav InVivo) and consisted of 2–3 cores from the suspicious areas. In addition, the usual 12-core template systematic biopsies (12-SBx) were obtained on the same session. Each biopsy was performed by 1 of 4 urologists with 3+ years of experience with targeted biopsies. All specimens were prospectively analyzed by 1 of 3 experienced uropathologists and reported according to the recommendations by the International Society of Urological Pathology [17]. Three hypothetical biopsy sampling schemes were defined: (1) TBx only; (2) TBx + ipsilateral SBx (ipsi-SBx); and (3) TBx + contralateral SBx (contra-SBx)

2.4. Standard of reference and endpoint

The standard of reference was defined as TBx + 12-SBx. Endpoints were defined as the rate of csPCa and ciPCa detection for each of the sampling schemes previously described. International Society of Urological Pathology grade group (GG) 2 or greater cancers were considered csPCa. Upgrading was defined as any increase in GG.

2.5. Statistical analysis

Rates of csPCa and ciPCa detection, and upgrading were calculated for each of the described sampling schemes. Sensitivities and 95% confidence intervals (CI) were calculated. Based on the fact that test results are paired, McNemar test (with Bonferroni correction) was

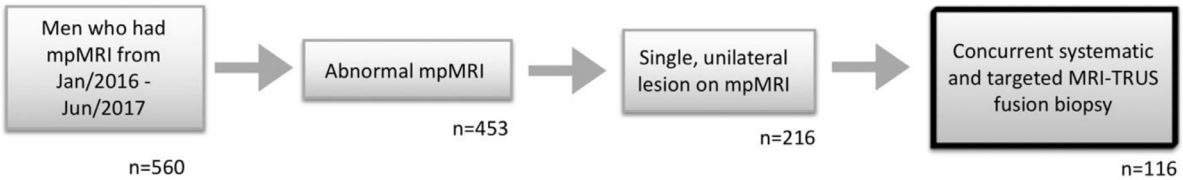

Fig. 1. Patient eligibility criteria. mpMRI = multiparametric magnetic resonance imaging; TRUS = transrectal ultrasound.

used for pairwise comparisons of the different schemes. Statistical significance was defined as 2-sided $P < 0.05$. Statistical analysis was performed using SPSS v25 (IBM corp. Armonk, NJ) and SAS v9.4 (SAS Institute Inc., Cary, NC).

3. Results

A total of 116 men were included in the final cohort. Cohort characteristics are summarized in Table 1.

3.1. Clinically significant cancer detection rate and upgrading rate

TBx + 12-SBx detected csPCa in 47% (55 of 116) of men. Of these, 58% (32 of 55) were GG 2, 25% (14 of 55) GG 3, 6% (3 of 6) GG 4, and 11% (6 of 55) GG 5. TBx alone, TBx + ipsi-SBx and TBx + contra-SBx would have missed csPCa (Fig. 2) in 14.5% (8 of 55), 3.6% (2 of 55), and 7.2% (4 of 55) of cases, respectively (Fig. 3). Individual pathologic outcomes for TBx, vs. TBx + ipsi-SBx/contra-SBx are reported in Supplemental Table 1 A-C, sensitivities with 95% CI are reported in Table 2. There was a trend toward higher sensitivity of TBx + ipsi-SBx vs. TBx only (96.4% vs. 85.5% $P = 0.03/0.09$ after Bonferroni correction).

Overall, 18% (10 of 55), 3.6% (2 of 55), and 12.7% (7 of 55) of patients would have been missed or misclassified (upgrading by at least 1 GG by the standard of reference, Fig. 4) by TBx alone, TBx + ipsi-SBx and TBx + contra-SBx, respectively, compared to TB + 12-SBx. Modified sensitivities and 95% CI are reported in Table 2. Using this definition sensitivity was significantly higher for TBx + ipsi-SBx vs. TBx only (96% vs. 82%, $P = 0.01/0.04$ after Bonferroni correction).

Subgroup analysis including only patients on active surveillance revealed upgrading in 16.7% (3 of 18) for TBx only and 5.6% (1 of 18) for both TBx + ipsi-SBx and TBx + contra-SBx.

Table 1
Cohort and MRI characteristics

Age (y) Mean, SD		63.7 ± 8.33
PSA (ng/ml) Mean, SD		10.36 ± 14.59
PSAD (ng/ml/cc) Mean, SD		0.22 ± 0.29
Prostate volume (cc) Mean, SD		54.12 ± 30.39
Indication	Primary detection	55 (47%)
	Previous negative biopsy	43 (37%)
	Active surveillance	18 (16%)
PI-RADS v2 score	3	31 (27%)
	4	47 (40%)
	5	38 (33%)
Lesion size (mm) Mean, SD		14.32 ± 9.50
Location	Peripheral zone	84 (72%)
	Transitional zone	32 (28%)

PSA = Prostate Specific Antigen; PSAD = PSA density; SD = Standard deviation.

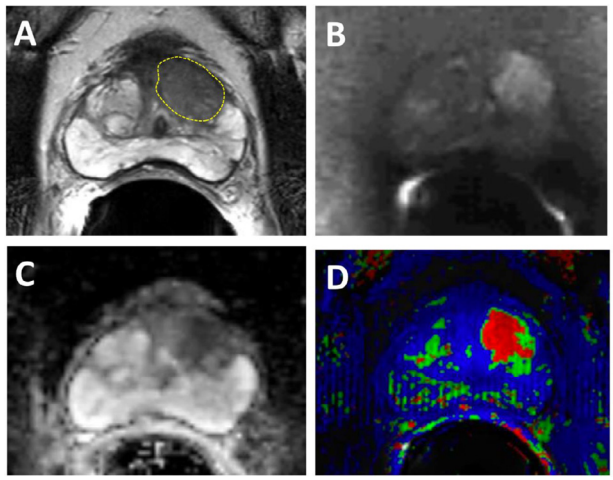

Fig. 2. Example of clinically significant prostate cancer missed by targeted biopsies and detected by ipsilateral systematic sampling. 77-year-old biopsy-naïve man with rising PSA, most recent 11.0 ng/ml, underwent multiparametric MRI that demonstrated a 2.0 cm lesion in the left mid anterior transition zone (*dashed area*) which was hypointense on T2-weighted images (**A**), hyperintense on diffusion-weighted images (**B**), with markedly low ADC values (**C**) and abnormal contrast kinetics (*red area* in **D**), a PI-RADS 5 lesion. Targeted biopsies revealed high-grade prostatic intraepithelial neoplasia in 2 of 2 cores, and systematic cores identified grade group 2 cancer in 2 of 4 cores from the left mid and apex, up to 25% of the core containing tumor. ADC = apparent diffusion coefficient; PI-RADS = prostate imaging reporting and data system.

Contra-SBx detected csPCa in 15% (18 of 116) of men in the cohort. In only 1.8% (2 of 116) of these men, csPCa would have been diagnosed exclusively by contra-SBx. Of those 2 men, one was biopsy-naïve and the other on active surveillance due to small volume grade group 1 disease.

Sensitivity analysis was performed based on lesion size stratified as small (< 10 mm) medium (10–15 mm) and large (>15 mm) (Supplemental Table 2), detection rates were not statistically significant based on lesion size, although analysis may have been influenced by the small groups.

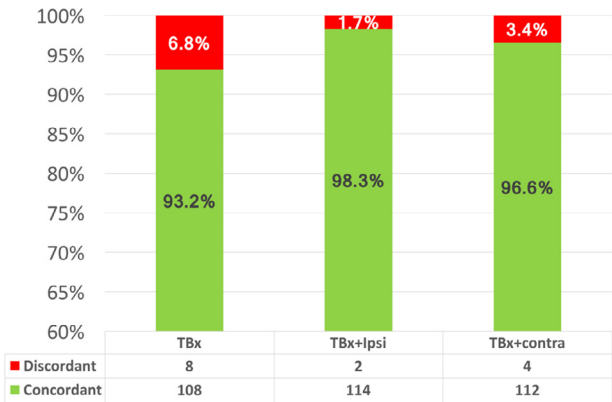

Fig. 3. Concordance of the different biopsy schemes in detection of clinically significant prostate cancer. Contra = contralateral systematic biopsy; Ipsi = ipsilateral systematic biopsy; TBx = targeted biopsy.

Table 2
Clinically significant prostate cancer detection and upgrading rate per biopsy sampling scheme compared with targeted plus 12-core systematic sampling

	TBx + 12 core SBx (standard of reference)		Sensitivity (95% confidence interval)	Comparison[a]		
A. csPCa detection						
		Positive		TBx only	TBx + ipsi	TBx + contra
TBx Only	Negative	8	85.5%		0.03	0.12
	Positive	47	(73.3%–93.5%)		(0.09)	(0.36)
TBx + ipsi	Negative	2	96.4%	0.03		0.68
	Positive	53	(87.5%–99.6%)	(0.09)		(2.04)
TBx + contra	Negative	4	92.7%	0.12	0.68	
	Positive	51	(82.4%–98%)	(0.36)	(2.04)	
Total (TBx + 12 core SBx)		55				
B. csPCa detection and upgrading[b]						
		Positive		TBx only	TBx + ipsi	TBx + contra
TBx Only	Negative	10	82%		0.01	0.24
	Positive	45	(72%–92%)		(0.04)	(0.74)
TBx+ipsi	Negative	2	96%	0.01		0.18
	Positive	53	(91%–100%)	(0.04)		(0.54)
TBx+contra	Negative	7	87%	0.24	0.18	
	Positive	48	(78%–96%)	(0.74)	(0.54)	
Total (TBx + 12 core SBx)		55				

[a] McNemar test, *P* value (*P* value after Bonferroni correction). TBx = targeted biopsies; SBx = systematic biopsies; ipsi = SBx ipsilateral to the MRI-visible lesion; contra = SBs contralateral to the MRI-visible lesion; csPCa = clinically significant prostate cancer (grade groups 2–5).
[b] Tumors that were upgraded by at least 1 grade group by the standard of reference were considered to be false negatives.

31% (36 of 116) of men underwent radical prostatectomy and whole-mount histopathology did not reveal csPCa exclusively in the hemiprostate contralateral to the MRI-visible lesion in any of these men.

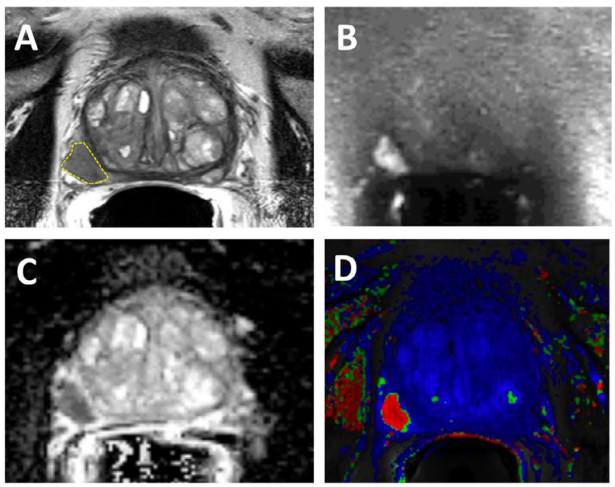

Fig. 4. Example of grade group upgrade by ipsilateral systematic sampling. 70-year-old man with 2 previous negative 12-core biopsies and rising PSA, most recent 8.9 ng/ml, underwent multiparametric MRI that demonstrated a 1.0 cm lesion in the right base posterolateral peripheral zone (*dashed area*) which was hypointense on T2-weighted images (**A**), hyperintense on diffusion-weighted images (**B**), with markedly low ADC values (**C**) and abnormal contrast kinetics (*red area* in **D**), a PI-RADS 4 lesion. Targeted biopsies revealed grade group 2 cancer in 2 of 2 cores, up to 40% of the core length involved by tumor, and systematic cores from the right base identified grade group 3 cancer in 1 of 2 cores from the right base, 50% of the core containing tumor. PSA = prostate-specific antigen; PI-RADS = prostate imaging reporting and data system.

3.2. Clinically insignificant cancer detection rate

Clinically insignificant cancers alone were detected in 7.7% (9 of 116), 10.3% (12 of 116), and 14.6% (17 of 116) for TBx only and TBx + ipsi-SBx, and TBx + contra-SBx, respectively. TBx + 12-SBx detected ciPCa in 13.7% (16 of 116) (Fig. 5).

4. Discussion

Substantial evidence shows that TBx increases the detection of csPCa compared to SBx [3,18,19], however, due to concerns of missing csPCa both are often performed at the same time. While this strategy may increase the rate of overall cancer detection [19], it also introduces the risk of detecting an excessive number of indolent tumors, possibly leading to overtreatment [19]. A trend toward completely

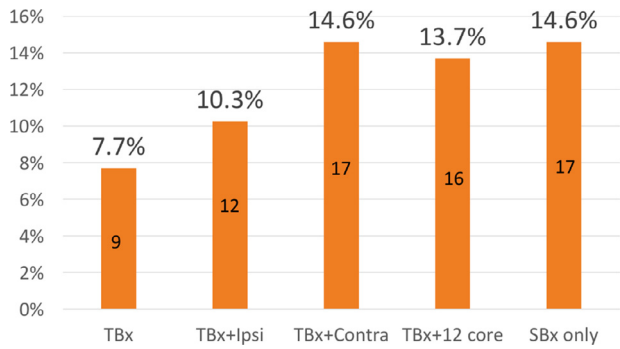

Fig. 5. Clinically insignificant cancer detection rate. Contra = contralateral systematic biopsy; Ipsi = ipsilateral systematic biopsy; SBx = systematic biopsy; TBx, targeted biopsy.

omitting systematic biopsies may be evident from the PRECISION trial [4], completely omitting biopsies in men with negative MRI, and still demonstrating higher clinically significant cancer detection compared to a pathway of systematic biopsies only. However, this approach may still be premature, especially in the absence of long term follow-up and patient outcome data. In this study, we sought to define the optimal biopsy scheme achieving the highest csPCa detection rate and accurate grading while minimizing the detection of ciPCa in men with a single lesion on mpMRI undergoing prostate biopsies.

Overall, csPCa was detected using TBx + 12-SBx in 47% of men. The calculated sensitivities for TBx, TBx + ipsi-SBx, and TBx + contra-SBx were 85.5%, 96.4%, and 92.7%, respectively, showing a trend toward statistically significant difference between TBx and TBx + ipsi-SBx. Since prostate biopsies ought to provide the most accurate diagnosis, and upgrading may affect patient management and treatment decisions, we also sought to identify those cases in which the GG of a csPCa would have been underestimated —modified sensitivities calculated were 82%, 96.4%, and 87.3% for TBx, TBx + ipsi-SBx, and TBx + contra-SBx, respectively, with statistically significant advantage of TBx + ipsi-SBx compared to TBx only.

Bryk et al. evaluated similar sampling schemes in a cohort of 211 men reporting an overall csPCa detection rate of 23% and sensitivities of 73.5%, 96%, and 81.6% for TBx, TBx + ipsi-SBx, and TBx + contra-SBx, respectively, concluding that optimal results would be achieved by eliminating contra-SBx [11]. Our sensitivity for TBx + ipsi-SBx was similar. However, sensitivities for both TBx only and TBx + contra-SBx were higher in our cohort. There are several differences between the studies which may explain those results. First, overall csPCa detection rate in our cohort was significantly higher at 47% compared to 23% by Bryk, with our rate being in the range of other reports evaluating TBx [3,19,20]. Second, Bryk et al. did not use PI-RADS scoring and included patients with low suspicion of cancer on mpMRI, the latter likely decreasing the prebiopsy probability of cancer. Lastly, there was a relatively high percentage of PIRADS 5 lesions in our cohort (33%) which may also account for the higher detection rate of TBx alone.

In an attempt to reduce overdiagnosis, the second parameter essential for optimal sampling is ciPCa detection. In our cohort, overall ciPCa detection rate was 7.7% for TBx only, compared to 13.7% for TBx + 12-SBx. TBx + ipsi-SBx resulted in an absolute increase of <3% in ciPCa detection compared to TBx only, and TBx + contra-SBx resulted in a 7% absolute increase of ciPCa detection. While the absolute rate is low, the near doubling of ciPCa would have significant implications on a population basis as MRI-TRUS fusion biopsies become more common.

While completely omitting SBx may be premature [10], our findings suggest that an optimal biopsy scheme may include TBx + ipsi-SBx only, thus completely missing or misclassifying csPCa in less than 4% of the men while maintaining a minimal ciPCa detection rate and avoiding 50% of sampling, supporting the conclusions of Bryk et al. [11]. The definition of optimal strategy, however, may vary from patient to patient as some individuals and providers would prefer to decrease the degree of uncertainty by increasing the number of biopsies even if at the cost of increased detection of ciPCa. Similarly, the biopsy scheme may vary among different medical centers. While MRI-TRUS fusion biopsies are rapidly becoming the preferred technique at many institutions, other strategies such as direct MRI-guided in-bore biopsies are also available [21]. Access to this type of capability may influence the biopsy scheme utilized during targeted biopsies. Finally, our analyses were performed at a patient level, which is reasonable for men considered for whole gland treatment options such as radical prostatectomy and radiation therapy. As options for focal therapy emerge, however, assessment of these different biopsy schemes will need to take into consideration the implications of missing csPCa on a per-lesion basis.

Our study has several limitations, first, although data was prospectively collected this was a retrospective analysis and our cohort size is relatively small. Second, our cohort was limited to men with single mpMRI lesion to enable assessment of the relationship between lesion location and systematic sampling laterality. Third, the ideal standard of reference would have been correlated with radical prostatectomy specimens in men with cancer and long-term clinical follow-up in those without cancer. While the use of TBx + 12-SBx as the standard of reference reflects the pragmatic approach of our investigation, additional tumors may have been missed. Fourth, this was a mixed cohort including patients with different indications for MRI —e.g., elevated prostate-specific antigen (PSA) without previous biopsy, elevated PSA with previous negative biopsy, rising PSA while on active surveillance. Our cohort size precluded a subgroup analysis. Fifth, each MRI was reviewed by 1 of 9 radiologists; while we acknowledge the known interobserver variability in assigning PI-RADS scores, such issue is present in clinical practice and therefore, keeping in mind that, multiple readers should render our results more valid in the real world. Finally, all biopsies were performed by experienced providers in a tertiary center, thus results may not be applicable to all institutions.

5. Conclusions

In conclusion, our results suggest that a biopsy scheme including TBx + ipsi-SBx increases the detection of csPCa while limiting overdiagnosis of indolent cancers. Future studies using radical prostatectomy specimen, larger cohorts and long-term clinical follow-up as standards of reference in various patient scenarios will facilitate adoption of this proposed biopsy scheme.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urolonc.2018.10.009.

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