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ORIGINAL ARTICLE

Power Doppler Sonography (PDS) and Modified TRUS Systematic Biopsies – Can this Combination Adequately Replace Multiparametric Prostate Magnetic Resonance Imaging (mp-MRI) in Candidates for Re Biopsies Who cannot Undergo mp-MRI

Sergey Kravchick[1] · Eugenia Cherniavsky[2] · Ronit Peled[3] · Shmuel Cytron[4] · Guy Verhovsky[5]

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Abstract

The MRI targeted biopsy (MRI-TBx) may increase the detection rate of clinically significant cancer (csPCa) in candidates for re-biopsy. However, there will be several patients in whom MRI is contraindicated. In this retrospective study we assessed the ability of combination of PDS guided biopsies (PDS-TBx) and modified SBx to substitute MRI-TBx. 154 men with persistently elevated PSA were referred for re-biopsy. Our protocol included a combination of MRI-TBx, DPS-TBx and modified SBx with additional biopsies from anterior lateral horns and anterior aspects of apex. MRI findings were defined as suspicious lesions (MRI-SL) and highly suspicious lesions (MRI-HL), based on PIRADS scale. In 40 patients csPCa was detected. While, MRI diagnosed csPCa in 36 patients (23%, n-36/154): 25% and 92% of biopsies targeted to the MRI- SL and MRI-HSL confirmed csPCa. Thirty-eight PDS hypervascular areas were found, while csPCa was diagnosed in 84% of these lesions, or in 28 patients (18%, n-28/154). SBx detected csPCa in 34 cores or in 21 patients (13%, n – 21/154). SBx missed cancers in the in the anterior aspect of middle gland. Combination of PDS-TBx + SBx detected csPCa in 35 (88% of csPCa) patients. Strongest predictors for the csPCa presence were MRI-HSL, PDS' lesions and biopsies from anterior aspect that included apex, mid gland and anterior lateral horns ($p < 0.001$ and p-0.008, respectively). The combination of PDS-TBx + SBx may miss 15% of csPCa detected by MRI. However, it can detect additional 10% of csPCa that were missed by MRI. To improve the accuracy of this combination, the anterior aspect of middle gland should be also included in the modified SBx. These changes in combination can make it helpful in candidates for re-biopsy who cannot undergo MRI.

Keywords Prostate cancer · Targeted biopsy · Diagnostic · Imaging

Introduction

Previous study had shown that nearly 38% of Medicare patients undergo a repeat biopsy within 5 years of an initial negative biopsy [1]. In order to reduce the false-negative rate of primary TRUS-Biopsy, the MRI-targeted biopsy is generally used, as it can identify highly suspicious lesions that would otherwise be missed by repeat systematic sampling and detect the same number of men with csPCa using fewer cores [2, 3]. It is still unclear if MRI-US fusion has advantage over cognitive MRI-TBx, as the former can be more histologically informative but did not increase cancer detection [4]. While the superiority of one technique over another is still controversial, and even though MRI-TBx can still miss from 4 to 17% of csPCa, MRI-TBx in combination with systematic (SBx) was generally accepted as "gold standard" practice for re-biopsy: both cost effective and beneficial technique [5–9].

Dr Ronit Peled has passed away.

✉ Guy Verhovsky
guy.verchovsky@gmail.com

[1] Department of Urology, Upstate Medical University, Syracuse, NY, USA

[2] Department of Radiology, Barzilai Medical Center, Askelon, Israel

[3] Epidemiology and Statistics, Ben Gurion University, Beersheba, Israel

[4] Department of Urology, Barzilai Medical Center, Askelon, Israel

[5] Department of Urology, Yitzhak Shamir Medical Center, Tel Aviv, Israel

However, there always be patients who cannot undergo MRI since they have a pacemaker, defibrillator, metallic foreign bodies or suffer from claustrophobia [10, 11]. What is the alternative for these cases? We hypothesized that combination of power Doppler guided biopsies (PDS-TBx) with modified SBx will be as accurate as MRI-TBx in detecting and thereby diagnosing csPCa. Thus, the plot of our retrospective study based on our routine practice for re-biopsy at the period from 03.2010 to 9/2014, which included cognitive MRI targeted biopsy (MRI-TBx) in addition to the combination of modified systematic (SBx) and power Doppler guided (PDS-TBx) biopsies (Fig. 1a, b). Accordingly, we tried to compare the accuracy of PDS-TBx and SBx combination with the results of MRI-TBx. We suggested that in this way we can assess a possible benefit of former combination in patient who cannot undergo MRI.

Patients and Methods

After obtaining approval from the ethics committees of our hospital (0077–13 BRZ) and outpatient clinic (Leumit 02.05.001–09.08.2015) and according to the informed consent of all patients: Before biopsies all patients were informed about the fact that MRI and color doppler quidded biopsies require additional 3 biopsies to every lesion. Patient were informed about possible higher risk for hematuria, hematospermia and infection associated with the increased number of biopsies.

We have reviewed the records of patients who underwent re-biopsies from 03/2010 to 9/2015. The inclusion criteria were at least one set of negative biopsies and persistently elevated PSA obtained ≥6 months after TRUS-biopsies, as well as patients' agreement to undergo mp-MRI and re-biopsies. All biopsies were done by the same urologist (K.S.). The BK-Medical model 1846 ultrasound unit with a biplanar 5–10-MHz side-firing transducer (model 8531; BK-Medical, Herlev, Denmark) was used. Because until 2010 we had a little experience with mp-MRI of prostate, we added cognitive MRI-TBx to our re-biopsy protocol, which included PDS-TBx (3 biopsies taken from each PDS hypervascular area) and modified 16-SBx (12 systematic biopsies +4 biopsies from anterior horns of mid gland and anterior aspects of apex). We took 3 biopsies from each MRI suspicious lesion. Each biopsy was sent separately, and the site of the biopsy was assigned. This helped us to draw a scheme of csPCa locations.

Positive MRI findings were defined as suspicious lesion (MRI -SL: 3 on a 5-point PIRADS scale) and highly suspicious lesion (MRI-HSL: PIRADS >3), while all other lesions were qualified as benign. For PDS a low pulse repetition frequency (PRF) with maximal filtration and persistence were preferred. Hypervascular pattern was considered as a positive PDS findings. In order to identify the suspicious area rather than the hypervascularity, PDS signal was sought in the transverse and sagittal planes. MRI-TBx and PDS-TBx were sent separately. It was presumed that in some cases MRI and PDS areas of interest might lie very close to each other, or the trajectory of previous biopsy came along these areas. The latter can be detected by "a white path" that is left after previous biopsy (Fig. 2). We called this a possible biopsy overlap and made the appropriate sign in records. We tried the avoid the areas with "white path" and not to re-biopsy MRI and PDS lesions when systematic biopsies were performed. However, sometimes we could not exclude the "biopsying" of these lesions.

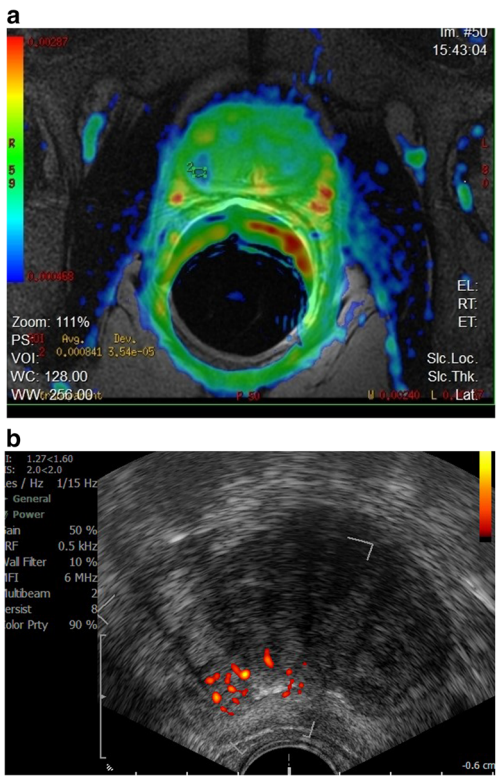

Fig. 1 **a** Highly susp. MRI **b** Highly susp. MRI and PDS

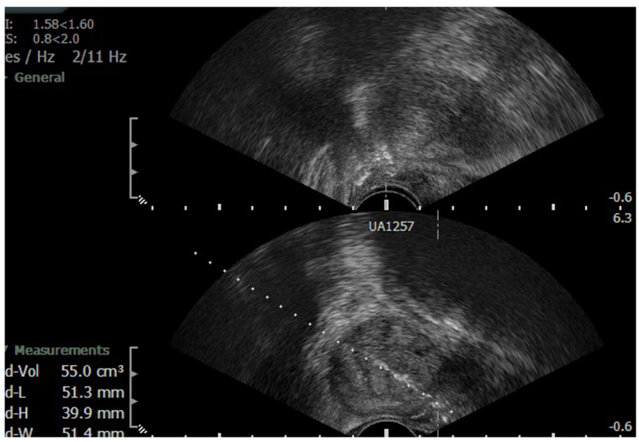

Fig. 2 White path indicating previous biopsy trajectory

As it had been shown by anatomic studies, the pain associated with apical/anterior zone biopsy originates from anal pain fibers below the dentate line of the rectum [12]. The main problem is that this area is very close to the prostatic apex and as a result every biopsy directed to the anterior apex causes anal rather than prostatic pain. In our previous study we found that the injection of 1–1.5 ml of 1% lidocaine directly into the rectal wall might decrease the pain [13]. In addition, the injection of lidocaine into the space between rectum and apex helps to expand the space between the rectal wall and the apex. As a result, the apex is pushed upwards and the optimal trajectory to its anterior aspect is created.

Clinically significant cancer (csPCa) was defined as cancer of Gleason score ≥ 7, Gleason score 6 involving ≥50% of core or seeing in ≥3 cores. We assessed and compared the outcomes relative to the: csPCa diagnostic rate of MRI-TBx, PDS-TBx, SBx and combination of the latter two. The logistic regression model was used to assess the strongest predictor for csPCa, and the Pearson's chi-square test of association was employed to evaluate the relationship between different methods of biopsies. The confirmation of csPCa on the pathological reports was a dependent variable. Because of the small samples sizes of our study we use Fisher's exact test. For these purposes we used SPSS-15 software.

Results

154 men met the inclusion criteria. Patients mean age, body mass index and PSA were 68.54 ± 4.6, 28.53 ± 3.86 and 7.54 ± 3.26, respectively. PCa was diagnosed in 59 patients, while csPCa was found in 40 patients (detection rate − 38% and 26%, respectively). Patients with MRI-HSL and PDS lesions were significantly younger ($p < 0.05$). Biopsies targeted to the MRI-HSL and PDS lesions had the highest detection rates for csPCa ($p < 0.05$) (Table 1). Logistic regression analysis showed 3 strongest predictors for csPCa detection, namely MRI-HSL, PDS lesions and biopsies taken from anterior aspect of prostate (Table 2). The Pearson's chi-square test showed strong association between csPCa and MRI-HSL, PDS and SBx from anterior aspect of prostate. It also showed significant association between MRI -HSL and PDS hypervascular lesions (Table 3). Our mapping of positive for csPCa showed that that 48% of these lesions were in the anterior aspect of prostate. This zone included apex, mid gland and anterior lateral horns. There were no positive biopsies in base. Possible biopsies overlap was found in 31 patients.

MRI-SL's were identified in 34% (n-52), while MRI-HSL's in 23% (n-36). The detection rate for csPCa by MRI-SL and MRI-HSL targeted biopsies was 25% (39 out of 156 cores) and 91% (99 out of 108 cores), respectively [Table 1]. Consequently, MRI diagnosed csPCa in 36 patients (23%, n-36/154) and missed 4 patients csPCa (10% of 40 patients with csPCa).

Thirty-eight PDS hypervascular areas were found. The detection rate for csPCa by PDS-Tx was 28% (32 out of 114 cores). Specifically, csPCa was diagnosed in 28 patients (18%, n-28/154). PDS-Tx missed 12 patients with csPCa (30%) and diagnosed 3 csPCa that were missed by MRI-Tx. PDS identified 58% (21/36) of MRI-HSL's and was unable to recognize any MRI-SL.

Modified SBx detected csPCa in 34 cores or in 21 patients (13%, n – 21/154): 20 of these patients were also diagnosed by MRI and/or PDS guided biopsies, and 1 patient was diagnosed only by modified SBx. The detection rate for csPCa by SBx was 1.4 (32 out of 2464 cores). SBx missed all csPCa in the in the anterior aspect of middle gland that were detected by MRI-TBx. Combination of PDS-TBx + SBx detected csPCa in 35 patients: 31 patients with csPCa diagnosed by MRI-TBx and in 4 additional patients that otherwise were missed by MRI. This combination misses 5 patients with csPCa (15% of 40 patients with csPCa).

Discussions

The concept of ideal strategy for prostate biopsy incorporates the detection of significant cancers in one session by

Table 1 Patients PSA, age, BMI and clinically significant prostate cancer detection rates

	MRI-HSL	MRI-SL	PDS-TBx	only modified SBx	P
Age	62.1 ± 3.5	67.6 ± 3.8	61 ± 2.4	68 ± 2.3	<0.05
PSA	5.3 ± 2.1	6.3 ± 1.6	6.1 ± 3.8	5.8 ± 2.5	>0.05
BMI	27.3 ± 1.8	29.6 ± 2.4	27 ± 3.7	28 ± 3.3	>0.05
csPCa detected	33 patients	3 patients	28 patients	21 patients	<0.05
Detection rate for csPCa by Bx	91%	25%	28%	1.4%	<0.05

MRI-HSL-MRI highly suspicious lesions (PIRADS>3); MRI-SL-MRI suspicious lesions (PIRDS = 3); PDS-TBX-Power Doppler targeted biopsies; modified SBx-,modified systematic biopsies; BMI-body mass index; csPCa-clinically significant prostate cancer; Bx-biopsy

Table 2 Logistic regression analysis showed 3 strongest predictors for csPCa detection

Dependent Variable	B	S.E	Wald	df	Sig.	Exp(B)
MRI-HSL	2.771	1.044	7.045	1	0.008	15.980
PDS hypervascular lesions	0.076	0.34	4.795	1	0.019	1.078
Anterior Bx	1.23	0.657	3.502	1	0.037	2.546
PSA	0.276	1.142	0.058	1	0.809	1.317
Prostate Volume	0.212	1.097	0.37	1	0.847	0.809

decreased number of cores. In the light of the above mentioned, MRI-TBx might be considered as a beneficial approach [2, 6]. Some studies dedicated to MRI-US fusion prostate biopsy found it to be one of the most promising technique of MRI-TBx, while other had shown that the results of cognitive MRI- TBx were equal [4, 6, 7]. Our results indicated that cognitive MRI- TBx showed the highest detection rates for csPCa. In addition, 92% of biopsies targeted to the HSL diagnosed csPCa. Previous studies had already emphasized the important role of PI-RADS scores in detection of csPCa [8]. However, in our study biopsies targeted to the MRI-HSL missed 10% of csPCa that were successfully diagnosed with PDS and modified SBx. This problem was highlighted in previous studies that discussed the potential sources of errors [5, 14]. These false negative results of MRI-TBx can be explained by failure to properly adjust MRI and TRUS images and technical or anatomic problems to accurately target the lesions [14]. However, even with the all deficiencies of MRI-HSL targeted biopsies, in our study it was one of the strongest predictors of csPCa and showed a high association with the presence of csPCa.

PDS identified 58% (21/36) of MRI-HSL's and in all these lesions csPCa was diagnosed. However, its detection rate for csPCa was 28%, which is comparative only with 25% achieved by MRI-SL targeted biopsies. Although the same overlay between inflammatory and malignant processes was also reported for PDS, our results showed that PDS-TBx had diagnosed three of four csPCa missed by MRI-TBx. In addition, PDS hypervascular lesions were amongst the three strongest predictive factors for csPCa detection. Furthermore, the Pearson's chi-square test showed strong association between PDS hypervascular lesions and MRI-HSL, in addition to strong association with csPCa. This is in a concurrence with the previous studies, which showed that PDS findings helped to direct biopsies to more aggressive cancer [15–17]. Nevertheless, PDS-TBx alone missed 12 patients with csPCa (30%) and cannot be considered as autonomous biopsy approach in patient who cannot undergo MRI.

Previous studies had already indicated a 33%–40% increase in cancer detection rate when TRUS-biopsies were taken from lateral and anterior aspects [18–21]. In our study the detection rate for csPCa by SBx was 1.4, that was the lowest. SBx missed all csPCa in the in the anterior aspect of middle gland that were detected by MRI-TBx. This low yield of SBx in our study might be explained by the analysis of csPCa distribution in radical prostatectomy specimens made in previous studies, which had shown that the majority of csPCa in the anterior areas tend to invade the anterior half of the gland at the apex to mid-prostate levels, but rarely extend to the posterior gland [20, 21]. Our analysis of cancer-bearing lesions detected by targeted biopsies showed that 65% of these lesions were in the anterior and utmost lateral aspects of prostate, while no sPCa was detected in the base. This can explain why biopsies from anterior zone were included in 3 strong predictors of csPCa and had strong association with the presence of csPCa, while systematic biopsies from the lateral aspect (which also included posterior base) showed the low probability to detect csPCa. The above mentioned taught us that the sampling area of SBx should include a wider expanse of anterior aspect (from apex to midland), anterior lateral hones and utmost lateral aspect, while base can be avoided in re-biopsy. In this way, combination of PDS-TBx with systematic biopsies targeted to the extended anterior aspect and utmost lateral aspects would diagnose csPCa in 38 of 40 (95%) patients with csPCa of our study.

Conclusions

In candidates for re-biopsy who cannot undergo MRI, PDS-TBx cannot alone substitute for MRI-TBx. Modified systematic biopsies in these patients have also a low diagnostic power. However, combination of PDS targeted biopsies to

Table 3 Pearson's chi-square analysis of the association between csPCa and MRI-HSL, PDS and SBx from anterior aspect of prostate

Ch—Square test	Asymp.Sig.(2-sided)	Fisher's Exact test (2-sided)	Fisher's Exact test (1-sided)
MRI -SL/csPCa	0.488	0.562	0.334
MRI-HSL/csPCa	0.001	0.001	0.001
PDS/csPCa	0.003	0.005	0.003
PDS/MRI-HSL	0.001	0.002	0.002
SBx anterior/csPCa	0.004	0.005	0.003
SBx lateral/csPCa	0.86	0.395	0.282

hypervascular lesions and re-modified systematic biopsies can be very accurate in candidates for re-biopsies. The latter should include anterior aspect of apex, midland, lateral horns of midland and utmost lateral aspects of apex and midland.

Compliance with Ethical Standards

Conflict of Interest We state that there is no conflict of interest to any of the authors.

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