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Magnetic Resonance / Transrectal Ultrasound Guided Biopsy of the Prostate Compared to Standard Transrectal Ultrasound Guided Biopsy for Diagnosis of Prostate Cancer

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Abstract: Background: Multiparametric magnetic resonance imaging (mp-MRI) may improve the detection of prostate cancer (PCa). **Objective**: To compare mp-MRI transrectal ultrasound (TRUS)-fusion targeted biopsy with standard 12-coreTRUS-guided random biopsy for overall and clinically significant PCa detection among biopsy- naïve patient with suspected PCa. **Patients and Methods:** This ethical committee-approved, single-center, prospective, randomized clinical study (April 2018 to December 2019) included 98 biopsy-naïvepatients referred for prostate biopsy based on prostate specific antigen (PSA) values (PSA > 4 ng/ml) and/or suspicious digital rectal examination (DRE). Patients were randomized 1:1 to the mp-MRI or control group. Patients in the mp-MRI group underwent prebiopsymp-MRI followed by 12-core TRUS guided random biopsy and cognitive MRI/TRUS fusion targeted biopsy from each detected lesion. The control group underwent TRUS-guided random biopsy alone. **Results**: Overall, 40 patients were evaluable in both the mp-MRI and control groups. The overall PCa detection rate and the clinically significant cancer detection rate were similar between the mp-MRI and control groups, respectively (42.5% [17 of 40] vs40% [16 of 40], p = 0.820, and 35% [14 of 40] vs 30% [12 of 40], p = 0.633). **Conclusions**: MP-MRI/TRUS-fusion targeted biopsy did not improve PCa detection rate.
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1. Introduction

The standard diagnostic pathway for Prostatic carcinoma (PCa) based on systematic 12-core transrectal ultrasound (TRUS) guided needle biopsies following suspicious digital rectal examination (DRE) and/or elevated prostatic specific antigen (PSA) (1).

Systematic TRUS guided biopsy carries a considerable risk of sampling error, which can lead to over diagnosis and overtreatment (by nearly 45%) of clinically insignificant prostate cancer (CI-PCa), missing about 30% of clinically significant disease (CS-PCa) and imprecise risk stratification. Thus, refinement of the diagnostic pathway for PCa is an urgent need to control these mishaps (2).

Multiparametric magnetic resonance imaging (mpMRI) of the prostate detects suspicious malignant lesions as it delineates anatomical and functional data for prostate enables targeted biopsies. These biopsies can be done either by MRI□ultrasound fusion biopsy or cognitive fusion biopsy (CFB), with similar cancer detection rate. CFB doesn't need expensive hardware, and done by the TRUS operator(3).

With the development of reporting systems PI-RADS version 2, the targeting biopsy for PI-RADS 3-5 lesion increases CS-PCa detection rate and decrease CI-PCa detection rate in comparison to the systematic TRUS biopsy (3).

The aim of this study was to evaluate the diagnostic accuracy of the mpMRI pathway to itself and in comparison with the standard pathway in biopsy-naive men.

2. Patients and Methods

During the period of this study, starting from April 2018 to December 2019, 98 patients attended the urology clinic in Fayoum University Hospital with PSA > 4 ng/dL and were assessed for eligibility. After exclusion of 7 cases, 91 cases were randomized and allocated to either MRI group or control group. Further 11 cases left the study resulting in 40 cases in each arm for analysis. The following flow chart in figure-1describes the trial profile.

Sample size was calculated using (G power version 3). Each group had to contain at least 33 patients to get alpha level 0.05, power level 0.80 and difference in detection rate of PCa of 30% (60% for MR group and 30% for TRUS group) (4,5).To avoid the problem of patient loss during the follow up, each study group was

increased by 10% to reach 36 patients in each group.

Inclusion criteria were: 1) Age between 40 and 70 years, 2) Suspicious DRE, 3) Double-checked, elevated PSA > 4 ng/ml confirmed not to be due to urinary tract infection or recent prostatic manipulation, 4) Informed written consent. Exclusion criteria were: 1) Previous prostatic biopsy, 2) Known prostatic cancer, 3) Follow up after prostatic cancer treatment, 4) Contraindicated for MRI (e.g. with metallic implants or cardiac pace-maker). 5) Contraindicated for prostatic biopsy (e.g. coagulopathy, severe immune-suppression, acute prostatitis and sever anal stenosis).

This prospective study was composed of 2 groups, **MRI Group** and **TRUS (control) Group**. An independent statistician carried out a computer-generated randomization list using block sizes of 2 and distributed the cases with 1:1 distribution ratio into either group. The study protocol was approved by our institutional ethics council and conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

MRI preparation and imaging:

Pre-MRI preparation included: abstinence from ejaculation > 3 days to maintain seminal vesicles distended, evacuation of the rectum and intake of sublingual hyoscyamine sulfate 1 hour before the exam to reduce motion artifact from bowel peristalsis.

Patients were examined in supine position by using **(Vantage Titan 1.5T, Toshiba Medical Systems, Tochigi, Japan)** equipment and pelvic phased-array surface coil. The mp-MRI sequences used for patients were: T1WI, axial T2WI, T2 FAT SAT, coronal T2WI, sagittal T2WI, axial DWI with ADC map, and axial DCE-MRI. The volume of the prostate gland was measured using the prolate ellipse formula: Volume = height x width x length x 0.52. Assessment, reporting and mapping of lesions was done using Prostate Imaging Archiving and Reporting Data System (PI-RADS™ v2) (6) by a dedicated senior radiologist (Magdy A.M.) with an 8-year experience in prostate MRI reading.

TRUS preparation and imaging:

Patients had 1gm ceftriaxone prophylaxis and a cleansing enema at home the night before the biopsy.

Transrectal prostatic imaging was carried out using a 6 MHz, 150^0 end-firing probe **(PVG-630V)** mounted on ultrasound device (**Toshiba Famio-5 SSA-510A; Toshiba Medical Systems Corporation, Tochigi, Japan**). The prostate volume was calculated using the same formula used in MRI. The gland, including seminal vesicles (SV) and ejaculatory ducts (ED), was then scanned systemically in axial and sagittal planes. Abnormalities viewed in both planes for confident analysis.

Biopsy technique & collection:

A local prostatic block was done using 1% to 2% lidocaine, injected under TRUS guidance in the hyperechoic fat pad at the vesiculo-prostatic junction bilaterally.

In control group, 12 systematic random transrectal cores (RBs) were taken, each preserved in separate container. For suspicious lesions, 2 cores were taken and preserved in a separate container.

In MRI group, patients underwent systematic biopsies (RBs) plus cognitively-targeted transrectal biopsies (TBs) from PI-RADS III, IV, V lesions with 2 cores from each lesion, preserved separately. In case of PI-RADS I and II, only systematic biopsies were taken. Targeted biopsies were taken by one urologist followed in the same session by systematic biopsies performed by a separate urologist blinded to the MRI result.

Post biopsy, the patients were prescribed a 5-day course of levofloxacin 500mg and complications were reported using modified Clavien-Dindo classification.

Pathological Processing and Reporting:

Histopathologic examination was conducted by pathology team who were not blinded to the patient data. The biopsy Gleason score (GS), number of total and positive cores, total and maximum cancer core length (CCL), and maximum cancer core invasion (CCI) rate were recorded.

In this study, clinically significant PCa (csPCa) was defined as biopsy GS >7 (3+4), more than 2 cores involved or any CCL longer than 5 mm. Intermediate and high risk PCa was defined according to modified criteria of International Society of UroPathology (ISUP 2014) as tumors > ISUP grade 2.

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using SPSS software (Statistical Package for the Social Sciences) version 22 (SPSS Inc, USA). Quantitative data were presented as mean ± SD**,** or median and Inter quartile range (IQR). Student-t test and One-way ANOVA test were used as test of significance to compare between two and three groups, respectively. Qualitative data were presented as numbers and percentages. Chi square (χ^2) or Fischer exact test was used as a test of significance. A probability value (P-value) < 0.05 was considered to be a statistically significant.

3. Results

A. Study Population:

The characteristics of both groups of this study are shown in table-1 regarding age, total and free PSA levels and data of DRE and TRUS examination. Both study groups present a good match as there are insignificant differences between them.

B. Cancer detection rate:

The detection rate of PCa, csPCa and intermediate/high risk PCa in MRI vs TRUS groups were 17/40 (42.5%) vs 16/40 (40%), 14/40 (35%) vs 12/40 (30%) and 9/40 (22.5%) vs 8/40 (20%) respectively. The statistical difference was insignificant.

C. Prostatic cores analysis:

In this study, 1036 core biopsies were collected for analysis including 544 and 492 cores from MRI and TRUS groups respectively. The cancer detection rate amongst both groups was not significantly different (P=0.652). Similarly, other histopathologic characteristics of the retrieved cores showed insignificant difference between them as shown in table-3.

D. Comparison between MRI targets and TRUS targets:

In MRI group, 29 cases had 32 lesions scored as PI-RADS 3-5 where 64 cores were targeted (by cognitive fusion). In TRUS group, 6 cases had 6 hypoechoic lesions where 12 cores were targeted (by TRUS). Detection rates of PCa in TBs of both groups regarding cases and lesions are shown in table-4.

E. Complications:

The complication rate and grade in the both groups were trivial. Two cases in both groups had self-limited hematuria (grade 1). Only, 2 cases in the MRI group had epidydimo-orchitis (grade 2) that resolved with medical treatment with no need for hospital admission.

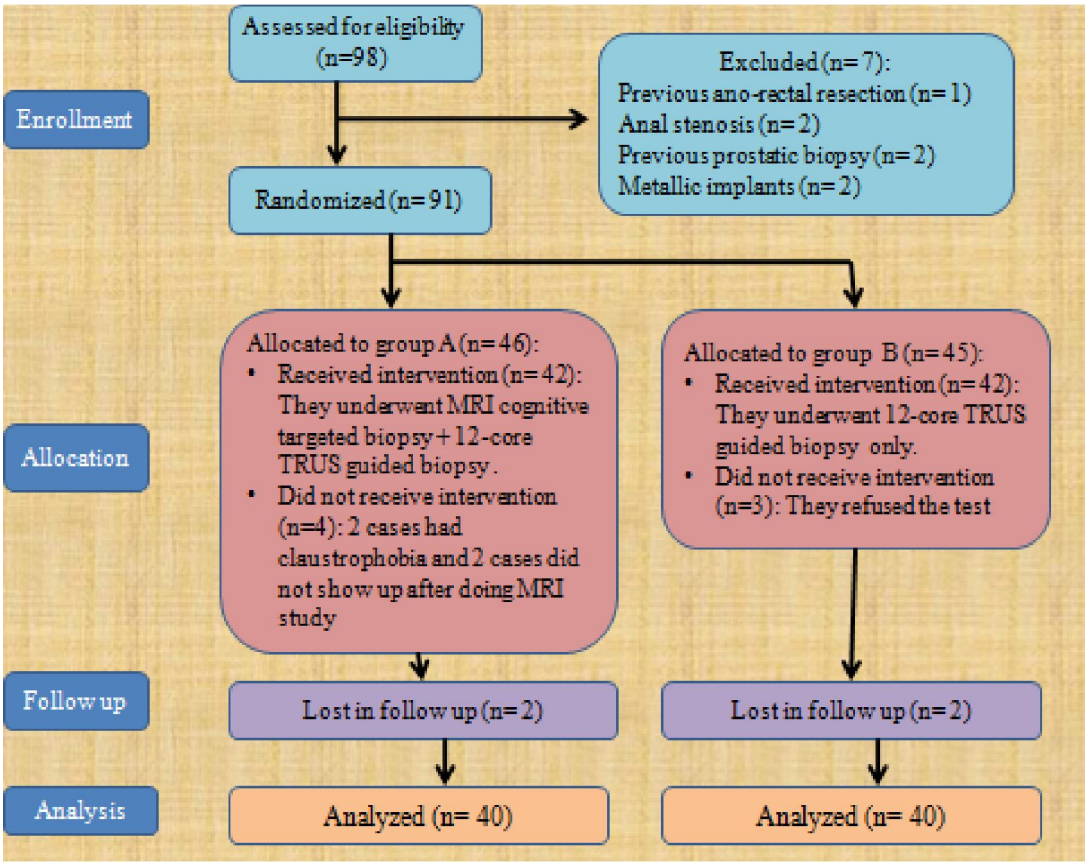

Fig 1: Flow chart of study population

Table (1): Patients` Characteristics

Variable	MRI group (n = 40)	TRUS group (n = 40)	P-value
Age (yrs)(Mean + SD)	65 + 6.6 years	66.4 + 6.8 years	0.355
Total PSA (ng/mL) (Median, IQR)	12.5 ng/mL (7.8-16.4)	11.8 ng/mL (8.9-17.3)	0.673
TRUS Prostate volume (cc) (Median, IQR)	82.3 cc (58.1-116)	76 cc (51-94.3)	0.127
DRE lesion N (%)	8 (20%)	5 (12.5%)	0.363

Table (2): Cancer Detection rate

	MRI Group	TRUS Group	p-value
Group size N (%)	40 (100%)	40 (100%)	-
Overall detection of PCa N (%)	17 (42.5%)	16 (40%)	0.820
Detection of csPCa N (%)	14 (35%)	12 (30%)	0.633
Detection ratio of csPCa/PCa (%)	14/17 (82.4%)	12/16 (75%)	0.927
Detection of Intermediate and High risk PCa (>ISUP 2) N (%)	9 (22.5%)	8 (20%)	0.785
Detection ratio of Intermediate and High risk PCa/PCa (>ISUP 2) (%)	9/17 (52.9%)	8/16 (50%)	0.865

Table (3): Analysis of prostatic cores

	MRI	TRUS	p-value
Total Number of Cores	544	492	-
PCa detection rate N (%)	111/544 (20.4%)	106/492 (21.5%)	0.652
No. of PCa Cores per patient (Median, IQR)	4.0 (3-12)	6 (4-8)	0.973
PCa cores detection ratio per patient(Median, IQR)	28.5 % (21.4-75.0)	50.0 % (28.5-66.0)	0.708
Total Cancer Core Length (Median, IQR)	34.2 (24.5-93.1)	30.0 (10.4-63.0)	0.306
Maximum Cancer Core Length(Median, IQR)	11.0 (9.0-12.0)	7.5 (4.2-12.0)	0.274
% of Maximum Cancer Core Invasion (Median, IQR)	28.6 (12.2-37.5)	25.0 (15.7-38.5)	0.812

Table (4): Comparison between TBs from lesions scored PI-RADs 3-5 in MRI group and targets in TRUS group

Variable	MRI lesions (PI-RADS 3-5)	TRUS lesions	P-value
No. cases	29	6	-
No. lesions	32	6	-
Cases with prostate cancer N (%)	15/29 (51.7%)	2/6 (33.3%)	0.708
Lesions with prostate cancer N (%)	17/32 (53.1%)	2/6 (33.3%)	0.764
Cases with clinically significant prostate cancer N (%)	8/29 (27.6%)	2/6 (33.3%)	0.289
Lesions with clinically significant prostate cancer N (%)	10/32 (31.2%)	2/6 (33.3%)	0.189

4. Discussion

Currently, targeting a predefined lesion seems logical to overcome the problem of overdiagnosis and overtreatment encountered in PCa. Cognitive targeting using prebiopsymp-MRI is the simplest way in this regard. The evidence about impact of MRI in repeated biopsy cases is undeniable however in biopsy-naïve cases, it is controversial (1).

In our series, the detection rates of PCa and csPCa were slightly better by the MRI-pathway versus the standard TRUS pathway with no statistically significant difference. This study is in agreement with prior studies addressing this comparison which have shown a modest benefit of the MRI-stratified pathway. Tonttila et al. reported a detection rate of PCa and csPCa to be 64% and 55% in the mpMRI arm versus 57% and 45% in the TRUS-guided biopsy arm, respectively (P = 0.5 and P = 0.8) (7). Also, Baco et al. found insignificant differences in detection of any PCa between both groups (54% vs 59%, respectively, P = 0.4) or for csPCa (49 vs 44%, respectively, P = 0.5) (8). Bryant et al. in observational cohort study reported insignificant difference between both techniques regarding overall detection of PCa (57.6% vs 56.7%, P = 0.7), csPCa or number of positive cores (P > 0.5 in each) (9).

Conversely, other studies have demonstrated significant benefit of the mp-MRI pathway in PCa diagnosis. Porpiglia et al. in RCT found that detection of any PCa and csPCa were higher in MRI group than in TRUS group (50.5 vs 29.5% and 43.9 vs 18.1%, respectively, all P < 0.002) (5). Panebianco et al. revealed that detection of any PCa was higher in the mpMRI group (73%) versus (38%) in TRUS group (10). In the PRECISION study, Kasivisvanathan et al reported that mpMRI-targeted biopsy aided diagnosis of csPCa in 38% of men, compared with 26% for TRUS-guided biopsy (P = 0.005) (11). The discrepancy between the results of those studies and ours may be attributed to differences regarding patient selection criteria, MRI settings (like use of 3-Tesla magnets and endorectal coil), presence of more than one experienced reader to interpret the MRIs (>2 radiologists), using different navigation method (software fusion), taking higher number of cores per MRI target (>3cores). In this study we tried to compare MRI with TRUS from another prospective. Hypoechoic lesions detected in the TRUS arm were compared to PI-RADS 3-5 lesions detected in MRI. Again, there were no significant statistical differences between both study arms. These results have been noticed by some authors like Herlemann et al and Garcia-Reyes. The first author noticed diagnosis rate of prostatic carcinoma in 38% in TRUS arm versus 47% in MRI arm and the second author reported 34% vs 47% diagnosis of prostatic carcinoma in TRUS hypoechoic lesions versus MRI lesions scored PI-RADS 3-5 (12, 13).

The main strength of this study was its prospective RCT design, in accordance with good clinical practice guidelines. The mpMRI was performed according to standardized protocols, and its results were reported using the PI-RADS classification by expert radiologist.

On the other hand, our study has some limitations. The results of a single center trial may not reproducible as those of multicenter trials. It is possible that the use of a 3-T MRI would have resulted in even better diagnostic performance of mpMRI, although a recent systematic review did not support this hypothesis(14). Finally, histopathological examination of prostate biopsies was done by different pathologists.

Conclusion

Targeted prostatic biopsy based on cognitive fusion of mp-MRI and TRUS is safe, efficient technique in the urologist armamentarium for prostate cancer diagnosis and is as reliable as systematic 12-core TRUS biopsy. However, it is early for mp-MRI to replace the systematic 12-core biopsy in diagnosis of prostate cancer in biopsy-naïve cases.

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