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Original Article

Ultrasound/MRI-targeted biopsy versus saturated trans-rectal ultrasound guided biopsy of prostate in patients with primary negative conventional biopsy and still elevated PSA: a prospective randomized clinical trial

Mehdi Dadpour[1], Amir Mohammad Soltani[2], Mahyar Ghafoori[3], Abbas Basiri[2], Nasrin Borumandnia[2], Amirhossein Nayebzade[2], Behzad Narouie[4], Hamed Hasani[1], Nasser Shakhssalim[2]

[1]Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Shahid Labbafinejad Medical Center The Center of Excellence in Urology, Tehran, Iran; [2]Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Iran University of Medical Sciences, Tehran, Iran; [4]Department of Urology, Zahedan University of Medical Sciences, Zahedan, Iran

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Abstract: Introduction: To evaluate and compare the rate of cancer detection by two methods Saturated TRUS guided biopsy and ultrasound/magnetic resonance imaging (US/MRI)-targeted biopsy in patients with primary negative prostate cancer in standard 12 cores biopsy evaluation but still have elevated prostate specific antigen (PSA). Materials and methods: From 105 patients who met our inclusion criteria, 53 patients underwent US/MRI-targeted biopsy and 52 remaining patients underwent Saturated 20 core TRUS guided biopsy in a prospective randomized clinical trial. Results: The mean age (±SD) was 62.2 (±8.2) year. The mean PSA (±SD) was 11.8 (±7.5) ng/ml. The mean prostate volume was 56.1 (±24.8) ml. Adenocarcinoma of prostate was detected in 9/52 (17.3%) patients in groups saturated biopsy and 14/53 (26.4%) patients in US/MRI-targeted biopsy group and there was no difference in cancer detection rate between 2 groups (P=0.252). except four patients with fever (two in each group), there was no other serious complication (Clavien grade 3 or higher) occurred in the patients. In the multivariate analysis, higher pre-procedure PSA, lower size of the prostate, pathology of ASAP and presence of nodule in DRE were independent predictors for cancer detection in second biopsy (P=0.036, P<0.001, P=0.013 and P=0.031, respectively). Conclusion: We didn't find any superiority in cancer detection rate and any different in complication rate between these two methods saturated TRUS guided biopsy and US/MRI-targeted biopsy.

Keywords: Prostate neoplasms, biopsy, magnetic resonance imaging, targeted biopsy, ultrasound transrectal

Introduction

Prostate cancer is the most important reason of elevated prostate specific antigen (PSA) especially in elder men. Trans-rectal ultrasound (TRUS) guided random systematic prostate biopsy is the standard method and most common approach to confirm or rule out prostate cancer in many centers and the diagnostic yield is commonly 40-50%. Traditionally, at least 12 cores of prostate biopsy are taken from all six zones of prostate and prepared for pathologic evaluation. Report of no malignancy in the pathologic evaluation of the samples, can relieve the patients that elevated serum PSA is due to non-cancerous reason including infection and inflammation. Aging, prostatitis, benign prostatic hyperplasia in large prostates, medical procedures on the prostate, urinary tract infection and vigorous exercise are some non-cancerous situations that can increase the serum PSA level [1-3]. Using antibiotics and anti-inflammations for 4 weeks can lower the amount of PSA but further follow up is usually recommended [4]. persistent elevated PSA during follow up can be a worrying subject for the

patients and physicians because of prostate cancer possibility and the problems that may occur due to late detection [5].

Although the use of saturation biopsy techniques, which obtain greater number of prostate cores, in the initial biopsy setting have shown no advantage over standard TRUS-B with respect to cancer detection rate [6, 7], but many studies declare that sampling done with sextant biopsy is not enough and the rate of 12 core TRUS biopsy of prostate false negative is still high and they suggest increasing the number of cores in the repeated biopsy [8-10]. Conventionally, saturated and super extended biopsy with at least 18 core biopsy would improve and optimize cancer detection rate and is recommended in case of persistent elevated PSA. However, it can associated with more complications including bleeding, urinary obstruction, infection and vasovagal reaction [11-13].

Multiparametric Magnetic Resonance Imaging (mpMRI) has been used to improve cancer detection as a promising solution. Todays, the computerized US/MRI-targeted biopsy has been widely used to detect prostate cancer in first time and also repeated prostate biopsy [14-16].

Although Saturated TRUS biopsy is more familiar and costs less, but some studies, which are mentioned above, declare that US/MRI-targeted biopsy has more accuracy and sensitivity to detect prostate cancer [17]. The aim of this study is to compare the rate of cancer detection by two methods Saturated TRUS guided biopsy and US/MRI-targeted biopsy in patients with primary negative prostate cancer in standard 12 cores biopsy evaluation but still have elevated PSA. The secondary objective was to evaluate the risk factors and predictors of cancer detection in second biopsy.

Materials and methods

Patients and setting

This article is a prospective randomized clinical trial that was conducted in the department of Urology, Labbafinejad University hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran from 2018 to 2020. Inclusion criteria was patients with prior negative conventional 12 core TRUS guided prostate biopsy in term of prostate cancer and still elevated amount of PSA (>4 ng/ml) despite medical treatment during six weeks follow up. Exclusion criteria was patients who are not candidate for follow up including obvious sign of cancer spread and who refused participation. After explaining the two methods to the patients, some of them decided which method to choose and they were not interested to participate in the randomized trial.

From 105 patients who met our inclusion criteria, 53 patients underwent US/MRI-targeted biopsy and 52 remaining patients underwent Saturated 20 core TRUS guided biopsy based on the table of random numbers generated by random allocation software in regard to simple random allocation (Random allocation software for parallel group randomized trials). Prostate Imaging Reporting and Data System (PI-RADS) v.2.0 scoring system, a scale of 1-5 to report the overall probability of clinically significant prostate cancer, was used in mpMRI reports [18].

The study was approved by the Ethics Committee of Urology and Nephrology Research Center (ethical number: IR.SBMU.UNRC.1395.45) and each patient gave informed consent prior the study which was performed in accordance with the ethical standards of the 1964 Deceleration of Helsinki as revised in 2000. The study was registered at Iranian Registry of Clinical Trials (IRTC) (registration reference: IRCT20110903007457N19).

Biopsy procedures

All the patients underwent a cleaning enema on the morning of the procedure and receive Ciprofloxacin 500 mg twice a day starting the night before procedure and continued for five days. Generally, procedure was held by local anesthetics (except 2 cases for saturation Biopsy who were conduct by sedation). In the US/MRI-targeted biopsy group, all the 53 patients underwent MRI and assigned Prostate Imaging Reporting and Data System (PI-RADS) v.2.0 scores. The stored 1.5 Tesla MRI with endo-rectal coil and real-time US are superimposed using computer software to enable targeted biopsies. The tracking system of such a device during TRUS allows computer-assisted construction of a 3D representation of the

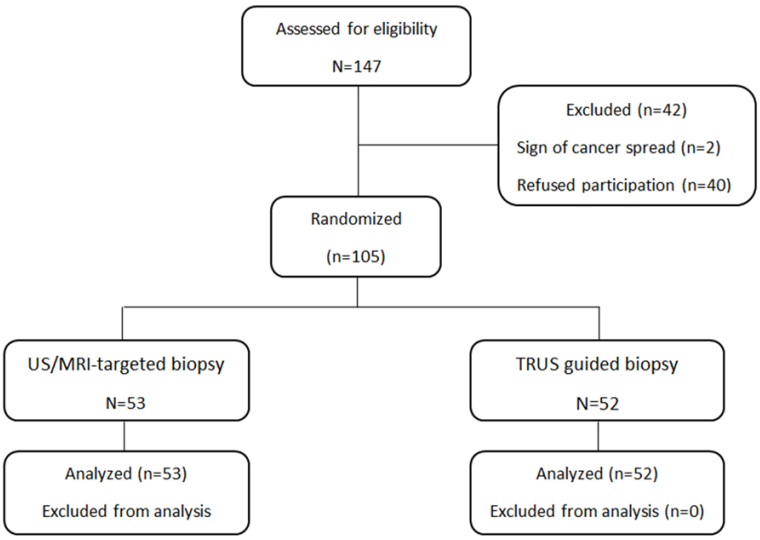

Figure 1. The CONSORT diagram shows the flow of participants.

prostate using individual US image. And finally MRI/US fusion-guided biopsy in addition to standard systematic 12-core biopsy was done. A transrectal ultrasound (TRUS) end-fire probe at a variable frequency of 5-7.5 MHz was used to guide the 18-gauge transrectal needle for prostate biopsy in Saturated TRUS guided biopsy group. US/MRI-targeted biopsy and Saturated 20 core TRUS guided biopsy were performed by an expert interventional radiologist and an expert urologist, respectively with an experience of at least 200 procedures of each group. All the patients discharged in the same day after 2 hours spent in recovery room. All the biopsy cores were evaluated by an expert uro-oncological pathologist with experience of evaluating more than 1000 prostate biopsy samples in our center. For the pathological examination of prostate biopsy samples, the pathologist uses the Gleason score system, in which the most common and the second most common patterns are used. Samples are stained with the H&E technique and with the help of hematoxylin and eosin.

Statistical analysis

Considering the alpha 0.05, power 0.8 and to detect a significant difference 30% between two groups (detection rate of 30% in Saturated TRUS guided biopsy group and 60% in US/MRI-targeted biopsy group), at least 45 samples in each groups were required. Quantitative data are shown as mean (standard deviation). Categorical data were described as frequency (percentage) and were compared between groups using a Chi-square test or Fisher's exact probability test. Quantitative data were compared between the groups by Student's t-test, where applicable. For defining a cutoff point for PSA and prostate volume, the area under the receiver operating characteristic (ROC) curve with 95% confidence interval (CI) was used. We utilized SPSS version 21.0 software (IBM Corporation, Armonk, NY, USA) for statistical analysis. Two-tailed *P*-values <0.05 were considered for the statistical level of significance.

Results

Participants and demographics

The flow of participant through each phase of the trial is shown in **Figure 1**. The mean age (±SD) was 62.2 (±8.2) (range 40 to 75 years). The mean PSA (±SD) was 11.8 (±7.5) ng/ml (range 4.1 to 39.1). The mean prostate volume was 56.1 (±24.8) ml (range 15 to 153). These data is shown between two groups separately in **Table 1** that there was no statistically significance difference between them.

Procedures findings

All the 105 patients with benign pathology of conventional 12 cores TRUS guided biopsy (**Table 1**) and still elevated PSA during follow up, underwent saturated 20 cores TRUS guided biopsy (52 patients) or US/MRI-targeted biopsy (53 patients). Adenocarcinoma of prostate was detected in 9/52 (17.3%) patients in groups saturated biopsy and 14/53 (26.4%) patients in US/MRI-targeted biopsy group and there was no difference in cancer detection rate between 2 groups (P=0.252). All the pathologic information is shown in **Table 2**.

Digital Rectal Exam was performed in all the patients before the procedure and palpable nodule was detected in 5 patients of saturated biopsy group and 4 patients of US/MRI-targeted biopsy group. Malignancy rate was 2/5 (40%) and 2/4 (50%) in groups, respectively (P>0.05).

Table 1. Patients' demographic data

	Saturated TRUS biopsy	US/MRI-targeted biopsy	*P*-value
Age (year)	62.4 (±8.1)	61.9 (±7.9)	0.751
PSA (ng/ml)	10.5 (±6.3)	13.2 (±8.5)	0.07
Prostate volume	56.2 (±22.5)	56.1 (±27.3)	0.983
First Pathology (%) (conventional 12 core TRUS Bx)			0.747
BPH	37 (71.1)	42 (79.2)	
HGPIN	2 (3.8)	2 (3.7)	
ASAP	9 (17.3)	7 (13.2)	
Prostatitis	4 (7.6)	2 (3.7)	

PSA: prostate specific antigen; BPH: benign prostate hyperplasia; ASAP: atypical small acinar proliferation; HGPIN: high-grade prostatic intraepithelial neoplasia.

Table 2. Pathologic data of patients with prostate cancer detected by biopsy

	Saturated TRUS biopsy	US/MRI-targeted biopsy	*P*-value
Adenocarcinoma	9/52	14/53	0.252
Gleason's score (3+3)	3 (33%)	3 (21%)	
Gleason's score (3+4)	3 (33%)	5 (38%)	
Gleason's score (4+3)	1 (11%)	1 (7%)	
Gleason's score (4+4)	1 (11%)	2 (14%)	
Gleason's score (4+5)	1 (11%)	3 (21%)	

The number of 20 cores of biopsy was taken from each patients in group saturated TRUS biopsy while the mean 16.6 cores of biopsy (the mean 4.6 targeted biopsy from suspicious lesions in MRI+12 systematic random biopsy) was taken from patients in group US/MRI-targeted Bx.

Complications

Two patients of group saturated TRUS biopsy (one/two hospitalization) and two in US/MRI-targeted biopsy (one/two hospitalization) developed fever after the procedure and was treated with antibiotic therapy. There was no other serious complication (Clavien grade 3 or higher) occurred including sepsis, rectal injury and uncontrolled hemorrhage, urinary retention or vaso-vagal reaction.

From 53 patients in groups US/MRI-targeted biopsy, there were 4 (7.5%) patients detected with (PIRADS) 2, 22 (41.5%) with PIRADS 3, 22 (41.5%) with PIRADS 4 and 5 (9.4%) remaining with PIRADS 5 in MRI. Cancer detection rate was 0/4 (0%) in PIRADS 2, 5/22 (22.7%) in PIRAD 3, 4/22 (18.1%) in PIRADS 4 and 5/5 (100%) in PIRADS 5 groups.

From the 14 patients in US/MRI-targeted biopsy group whom cancer was detected in them, 6 cases (42%) were merely detected by MRI and targeted biopsy while 2 cases (14%) were diagnosed by only systematic biopsy (P=0.473).

Cancer predictors

In this study, Malignancy was totally detected in 23 from 105 patients. The mean age of patients in malignant group and benign pathology group was 64.7 (±9.7) and 61.5 (±7.7), respectively (P=0.115). The mean pre-procedure PSA was 15.06 ng/ml (±8.4) in malignant pathology and 10.95 ng/ml (±7.1) in benign pathology group (P=0.024). Prostate volume was 37.2 (±17.1) ml and 61.4 (±24.1) ml in malignant and benign group respectively (P<0.001). These data show that patients with malignancy had higher amount of PSA, lower prostate volume but similar age. In the multivariate analysis, higher pre-procedure PSA, lower size of the prostate, pathology of ASAP and presence of nodule in DRE were independent predictors for cancer detection in second biopsy (P=0.036, P<0.001, P=0.013 and P=0.031, respectively) (**Table 3**).

Results of the ROC curve analysis showed that amount of PSA more than 9.66 with a sensitivity of 69.6% and specificity of 64.6%. (AUC=0.693, CI=0.574-0.813, *p* value =0.005) and prostate volume less than 43.5 ml with a sensitivity of 77.3% and specificity of 75.9%. (AUC=0.832, CI=0.061-0.275, *p* value <0.001) have the most specificity and sensitivity to predict cancer detection in second biopsy. All these data are shown separately in two groups in **Table 4**.

Table 3. The multivariate analysis of independent predictors for cancer detection in second biopsy

	Univariable analysis		Multivariable analysis	
	OR (CI)	*P*-value	OR (CI)	*P*-value
Age	1.05 (0.98-1.12)	0.115	1.04 (0.96-1.14)	0.270
PSA	1.06 (1.009-1.13)	0.024	1.10 (1.006-1.21)	0.036
Prostate size	0.93 (0.89-0.96)	<0.001	0.91 (0.87-.95)	<0.001
Pathology				
BPH	Ref.		Ref.	
ASAP	3.63 (1.16-11.28)	0.026	9.58 (1.62-56.69)	0.013
HGPIN	1.55 (0.15-16.00)	0.710	7.30 (0.35-148.75)	0.196
Nodule				
Yes	0.30 (0.07-1.26)	0.101	10.73 (1.23-93.00)	0.031
no	Ref.		Ref.	

PSA: prostate specific antigen; BPH: benign prostate hyperplasia; ASAP: atypical small acinar proliferation; HGPIN: high-grade prostatic intraepithelial neoplasia.

Table 4. Results of the ROC curve analysis

	AUC	*P*-value	Cut off	Sensitivity	Specificity
PSA					
Total cases	0.693	0.005	9.66	0.696	0.646
saturated TRUS Bx	0.729	0.032	8.32	0.889	0.628
US/MRI-targeted Bx	0.649	0.107	9.66	0.714	0.564
Prostate volume					
Total cases	0.832	<0.001	43.5	0.773	0.759
saturated TRUS Bx	0.841	0.001	38	0.778	0.884
US/MRI-targeted Bx	0.829	<0.001	43.5	0.769	0.750

Discussions

In this study, prostate cancer was detected in 23 of 105 (21.9%) patients six weeks after negative traditional 12 cores random TRUS biopsy in term of malignancy and demonstrated the limitation of this conventional method to detect prostate cancer in patients with elevated PSA and the importance of the need for a complementary method in suspicious patients. US/MRI-targeted biopsy and saturated TRUS biopsy are two methods that could improve cancer detection. In a prospective study, Siddiqui et al found that MRI/US-fusion-guided biopsy upgrades and detects prostate cancer of higher Gleason score in 32% of patients compared with traditional 12-core TRUS biopsy alone [19]. Also in a systematic review of the literature since 1995 up to 2011 Maccagnano et al [20] concluded that saturated TRUS biopsy is really necessary in men with elevated PSA and persistent suspicion of Prostate cancer after negative initial 12 core TRUS biopsy.

Although the need of a supplementary method after negative traditional 12 core biopsy and still elevated biopsy in follow up is an accepted fact, but there is no consensus in the next step. Saturated TRUS biopsy and MRI/US fusion-guided biopsy as two well accepted methods in this era have advantages and disadvantages. While the costs of MRI are an understandable concern and need more cores and blind technique of saturated biopsy would also be a concern, but the most important criterion to choose from these two methods is cancer detection rate. More accurate detection of clinically-significant disease may expedite necessary definitive treatment with curative intent would be cost effective [21]. In a review of 12 studies about trans-rectal saturation biopsy and 20 studies of MRI guided biopsy [22]. Meta-regression analysis showed that MRI guided biopsy had significantly higher cancer detection than saturated trans-rectal biopsy. But the emphasized that there is a clear rationale for well-designed prospective studies in a

randomized setting is needed to compare the outcomes of these two approaches. In the current study we didn't find any significant differences in cancer detection rate between two groups and none of them could prove their superiority to the other in this era. So the higher costs and lack of facilities to perform MRI/US fusion-guided biopsy wouldn't be a matter of concern for patients and physicians and saturated TRUS biopsy could be a proper alternative. To our best knowledge, this is the first randomized trial that compared the outcomes of MRI/US fusion-guided biopsy and saturated TRUS guided biopsy.

Yarlagadda et al [23] in the retrospective evaluation of 69 patients who underwent MRI/US fusion-guided biopsy and concurrent systematic 12-core TRUS-guided biopsy, showed that prostate cancer was detected in 45 men, 38 were diagnosed by MRI/US fusion-guided biopsy and 40 by systematic 12-core TRUS-guided biopsy (P=0.39). Delongchamps et al [24] in the evaluation of 108 biopsy naïve patients demonstrated that cancer was detected in 66 (61.1%) and 61 patients (56.5%) by Systematic and targeted biopsies respectively (P>0.05). In the current study, although we found omitting systematic biopsy in US/MRI-targeted biopsy group would miss 14% of prostate cancer but similar to these two studies, it is not significant in cancer detection rate in targeted biopsy compare to systematic random biopsy.

Although the number of core biopsies was lower in MRI/US fusion-guided biopsy group, but there were no differences in the side effects and complications between two groups. Some studies demonstrated that increasing the number of cores taken can lead to increased perioperative bleeding during subsequent radical prostatectomy [25], but unfortunately we didn't have the data of blood loss of the subsequent surgery to evaluate in our study. In the study of Yarlagadda et al [23], the average number of cores taken for MRI-targeted biopsies was 4.42 that was comparable to ours (average of 4.6). Among all 105 patients underwent procedures, fever was developed in four (3.8%) of them and two (1.9%) were hospitalized on night for antibiotic therapy. Similar Studies shows the rate of infection after prostate biopsy is 5%-7% with 1%-3% of patients needing to be hospitalized [26]. Some studies have demonstrated that a higher number of cores of tissue taken correlates with increased rates of fever and sepsis [27, 28], but we didn't get the same result. The rate of post-procedure fever was similar between two groups with different average cores of biopsy.

In addition to there was no differences in cancer detection rate between two groups, there was also no differences in Gleason's score grade in patients whom prostate cancer was detected and there was no superiority between two methods in cancer grading detection. In a systematic review article, Nelson et al [22] evaluated 12 studies about trans-rectal saturation biopsy and 20 studies of MRI guided biopsy. Similar to our study, Fisher's exact test showed that in the pathology of the biopsies, there was no difference in median Gleason's score between the patients underwent prostate biopsy by different strategies.

There are some limitation in this study: First, although it is the first study to compare these two methods of prostate biopsy in a randomized clinical trial setting, it seems that further studies with higher sample size is needed to increase the power of the study and conclusion. Second is that although MRI/US Fusion Targeted Biopsy was held by an experienced uro-radilogist in this study, but even in radiology community there is a lot of controversy regarding interpreting MRI lesions and this can affect our analysis. Third, it would be better to investigate the cost of these two methods of prostate biopsy, beside cancer detection rate and complications.

Conclusion

MRI/US Fusion Targeted Biopsy and Saturated 20 core TRUS guided biopsy are two accepted and valid methods in patients with primary negative prostate cancer in standard 12 cores biopsy evaluation but still have elevated PSA. We didn't find any superiority in cancer detection rate and any different in complication rate between these two methods. We found higher pre-procedure PSA, lower size of the prostate, pathology of ASAP and presence of nodule in DRE as the independent predictors for cancer detection in second biopsy in a multivariable analysis. we also found that the amount of PSA more than 9.66 ng/ml and prostate volume less than 43.5 have the most specificity and

sensitivity to predict cancer detection in second biopsy.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Nasser Shakhssalim, Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, 9th Boostan, Pasdaran Avenue, Tehran, Iran. Tel: +989123278953; ORCID: 0000-0001-8213-531X; E-mail: slim456@yahoo.com

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