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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041427
Article Type:	Protocol
Date Submitted by the Author:	08-Jun-2020
Complete List of Authors:	He, Biming; Changhai Hospital, Li, Rongbing; Shanghai East Hospital Li, Dongyang; Shanghai East Hospital Huang, Liqun; Shanghai East Hospital Wen, Xiaofei; Shanghai East Hospital Yang, Guosheng; Shanghai East Hospital Wang, Haifeng; Changhai Hospital
Keywords:	Prostate disease < UROLOGY, ONCOLOGY, UROLOGY

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Study protocol for a single-centre non-inferior randomized controlled trial on a novel three-dimensional matrix positioning based cognitive fusion targeted biopsy, and software-based fusion targeted biopsy for the detection rate of clinically significant prostate cancer in men without a prior biopsy

Bi-Ming He *, Rong-Bing Li *, Dong-Yang Li, Li-Qun Huang, Xiao-Fei Wen, Guo-Sheng Yang and Hai-Feng Wang

Affiliations:

Department of Urology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

*** Bi-Ming He and Rong-Bing Li contributed equally to this paper.**

Correspondence:

Correspondence should be addressed to Prof. Hai-Feng Wang, Ph.D., M.D., Department of Urology, Shanghai East Hospital, No. 150, Jimo Road, Shanghai, 200120, China. Email: 446720864@qq.com Telephone: +8613681750891.

Abstract

Introduction

The classical pathway for diagnosing prostate cancer is systematic 12-core biopsy under the guidance of transrectal ultrasound, which tends to underdiagnosis the clinically significant tumour and overdiagnosis the insignificant disease. Another pathway named targeted biopsy is using multiparametric magnetic resonance imaging to localizing the tumour precisely and then obtain the samples from the suspicious lesions. Targeted biopsy,

which mainly divided into cognitive fusion method and software-based fusion method, is getting prevalent for its good performance in detecting significant cancer. However, the preferred Targeted biopsy technique in detecting clinically significant Prostate cancer between cognitive fusion and software-based fusion is still beyond consensus.

Methods and analysis

This trial is a prospective, single-centre, randomized controlled, and non-inferiority study in which all men suspicious to have clinically significant prostate cancer. This study aims to determine whether a novel three-dimensional matrix positioning cognitive fusion targeted biopsy is non-inferior to software-based fusion targeted biopsy in the detection rate of clinically significant cancer in men without a prior biopsy. The main inclusion criteria are men with elevated serum PSA above to 4 – 20 ng/ml or with an abnormal DRE and have never had a biopsy before. A sample size of 602 participants allowing for a 10% loss, will be recruited. All patients will undergo a mpMRI examination, and those who fail to be found with a suspicious lesion, with the anticipation of half of the total number, will be dropped. The remaining participants will be randomly allocated to cognitive fusion targeted biopsy (n=137), and software-based fusion targeted biopsy (n=137). The primary outcome is the detection rate of clinically significant prostate cancer for cognitive fusion targeted biopsy, and software-based fusion targeted biopsy in men without a prior biopsy. The clinically significant prostate cancer will be defined as the International Society of Urological Pathology grade group 2 or higher.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China. The results of the study will be disseminated and published in international peer-reviewed journals.

registration details

ClinicalTrials.gov: NCT04271527

Strengths and limitations of this study

►This study is the first trial to compare a novel cognitive fusion targeted biopsy which based on a three-dimensional matrix positioning method, with a software-based fusion targeted biopsy.

►The study will determine the efficacy of the novel cognitive fusion targeted biopsy in the diagnosis of prostate cancer.

►Rigorous randomized design and allocation concealment method will reduce bias, which enables the higher reliability of the results.

►The study performed in the centre that developed the "three-dimensional matrix positioning method" which may overestimate the performance of this method since the operators are experienced.

►This study takes place in one hospital, hence may making the finding less generalizable.

Introduction

Prostate cancer (PCa) is the second most common cancer worldwide which leads the fifth causes of death among men[1]. Men with an elevated serum prostate-specific antigen (PSA) level or an abnormal digital rectal examination (DRE) are usually be considered at risk for PCa and typically be performed a prostate biopsy subsequently to get samples for pathological diagnosis. The common pathway is a systematic 12-core biopsy under the guidance of transrectal ultrasound (TRUS), an approach to randomly get the samples from the whole prostate gland; however, it's blind attribution makes it tends to underdiagnosis the clinically significant tumour and overdiagnosis the clinically insignificant disease[2, 3].

Thanks to the development of multiparametric magnetic resonance imaging (mpMRI) in identifying prostate cancer, another pathway named targeted biopsy is getting prevalent. It aims to first perform a mpMRI for localizing the tumour precisely and then obtain the samples from the suspicious lesions, shows more purposeful and less random compared with the systematic biopsy. Several pieces of evidence have proved the superiority of targeted biopsy in detection rates of clinically significant prostate cancer (csPCa) and avoidance of unnecessary biopsy[4, 5]..

Targeted biopsy can be subdivided into three different methods: in-bore MRI, cognitive fusion and software-based fusion. An in-bore MRI-targeted biopsy is described as to perform a targeted biopsy under real-time MRI guidance. Although this method is accurate in locating the targeted lesions, it is a failure to be widely used in clinical practice for its inconvenience and time-consuming[6]. Compared with in-bore MRI-targeted biopsy, another two methods are more acceptable. Cognitive fusion, a procedure of mental located the target of suspicious lesions in the ultrasound image after a review of MRI, is cost saving due to it needs no extra equipment, aside from the essential requirement for a TURS-biopsy. Software-based fusion is an overlap of the real-time ultrasound image and the previous MRI images by software assistance. Although it is widely adopted by urologists or physicians, the barriers of time-consuming, and excessive price and training for the additional equipment cannot be omitted [7-9]. There is always an interesting topic about whether the ability of cognitive fusion with human brains can achieve the same result as a fusion with intricate fusion software[10]. However, evidence from the comparative trials are few[9, 11-13].
To now, the preferred targeted biopsy technique in detecting csPCa between cognitive fusion and software-based fusion is still beyond consensus.

We have developed a method named three-dimensional matrix positioning to increase the accuracy of cognitive fusion for targeted biopsy detection of csPCa,

which involves several fiducial axes derived from MRI localization of the region of interest, then transposed onto the ultrasound image to help direct the biopsy needle into the right place[14]. This method had shown a reasonable detection rate for clinically significant prostate cancer in a pilot cohort. Hence, we conduct this single-centre randomized controlled trial in order to confirm the finding further.

This trial aims to compare three-dimensional matrix positioning cognitive fusion targeted biopsy and software-based fusion targeted biopsy for the detection rate of clinically significant prostate cancer for men without a prior biopsy localized prostate cancer. The primary objective is to assess whether the cognitive fusion targeted biopsy is non-inferior to software-based fusion targeted biopsy in the detection rate of clinically significant cancer.

Trial design

This prospective, single-centre, randomized controlled, and non-inferiority study will take place at Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China. The primary objective of this study is to identify whether the three-dimensional matrix positioning cognitive fusion targeted biopsy is non-inferior to software-based fusion targeted biopsy in the detection rate of clinically significant cancer in men without a prior biopsy.

The study flow chart is shown in Fig 1. Patients will be initially screened and recruited by the urologists in outpatient. Those who meet the entry criteria and sign the consent form will go for mpMRI within 2 weeks, and only those whose MRI indicate at least one suspicious lesion will proceed to the randomization. With allocation, men will be assigned to cognitive fusion targeted biopsy or to software-based fusion targeted biopsy in a 1:1 ratio while others will drop out of the trial. Men in both arms will be hospitalized one day before the prostate

biopsy. The biopsy procedure, which usually lasts for less than 30 minutes, will be performed under a local anesthetic block in an operation room. In addition to different targeted biopsy methods, a 20-region template guide prostate biopsy (Fig 2) will be performed after the targeted biopsy in each man, which can be a reference to the different targeted techniques. The samples from the biopsy will send to the pathologic apartment for assessment after the procedure. All participants will schedule dismiss the followed day after the biopsy. The pathological assessment will be reported within 2 weeks of post-biopsy. The details and timeframe of the trial are shown in Table 1.

We chose the randomised trial instead of a paired cohort to reduce bias. Because if two biopsies are performed on the same participant, the progress of one may lead to the bleeding and deformation of the prostate, which will affect the progress of the other.

Outcomes

The primary outcome is the detection rate of clinically significant prostate cancer for cognitive fusion targeted biopsy, and software-based fusion targeted biopsy in men without a prior biopsy. The clinically significant prostate cancer will be defined as ISUP grade group 2 or higher, according to the 2014 ISUP classification[15]. .

The main secondary outcomes are as follows:

The detection rate of any prostate cancer for cognitive fusion targeted biopsy, and software-based fusion targeted biopsy

The detection rate of clinically significant prostate cancer for each targeted technique combined with a templated guided biopsy

The detection rate of any prostate cancer for each targeted method combined with a templated guided biopsy

The comparison of the results between the two urologists, including the

detection rate of clinically significant prostate cancer and any prostate cancerThe influence of prostate volume on the difference between the two fusion targeted biopsy

Methods and analysis

Patient population

Patients with a suspicious of harbouring prostate cancer and had no previous biopsy will be considered eligible for registration in this trial if they can meet all inclusion criteria and had no any exclusion criteria. The main criteria include men with elevated serum PSA above to 4 – 20 ng/ml or with an abnormal DRE and have never had a biopsy before. The details of inclusion and exclusion criteria are shown in Table 2. All eligible patients will be informed in detail, and only those who sign the consent form can participate in the trial. Men who are ineligible or do not want to participate in the study will be returned to the regular clinical pathway.

Multi-parametric magnetic resonance imaging

All participants who sign the informed consent will subsequently undergo a 3.0-Tesla mpMRI (Magnetom Skyra, Siemens Medical Solutions, Erlangen, Germany) with an 18-channel phased-array coil. The sequences of examination mainly included T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI, acquired b-values 0,400,1000 and 2000 seconds per mm^2), and dynamic contrast-enhanced imaging (with the setting of temporal resolution less than 7 seconds and 5 minutes acquisition). Images will be evaluated and scored by one of two expert radiologists (20 and 10 yr of experience in prostate MRI) according to Prostate Imaging Reporting and Data System (PI-RADS) version 2.1 criteria. The probability of cancer will be assessed by the score from 1 to 5 (1 - Highly unlikely to be clinically significant cancer, 2 - Unlikely to be clinically significant cancer, 3 - equivocal to be clinically significant cancer, 4 - Likely to be clinically significant cancer, 5 - Highly likely to be clinically

significant cancer). The MRI report will only be marked as 'no abnormal' or 'less than 3' when scoring 1 or 2 while a specific score will be recorded at a score 3, 4 or 5.

Randomization

Only participants with a PI-RADS score 3, 4 or 5 will be allocated 1:1 to cognitive fusion targeted biopsy group or software-based fusion targeted biopsy group by using block-randomization. The random sequence will be generated by PROC PLAN statement of SAS program which keep by one research nurse and blind to other researchers. A random number will be revealed only when one participant being randomising.

Interventions

Biopsy

All biopsies in both arms will be performed via the perineum by two urologists (Haifeng Wang with an experience more than 10 years and Biming He with an experience more than 5 years) with an UltraView 800 ultrasound device (BK Ultrasound, USA) and a bi-planar transrectal ultrasound (TRUS) probe (8848, BK Ultrasound) under a local anesthetic block. Before performing the biopsy, one urologist will read the report and the image of MRI to identify the location of target lesions while another one will be blinded to the MRI result.

Cognitive fusion targeted biopsy arm

Each participant in this arm will undergo a cognitive fusion targeted biopsy first. A novel three-dimensional matrix positioning based cognitive fusion targeted biopsy will be performed under the guidance of a bi-plane TURS probe after reviewing the mpMRI finding. Three cores of biopsy will be taken for each suspicious lesion which is showed in mpMRI that PI-RADS score of 3 to 5. The details of the cognitive fusion targeted biopsy was described in our previous research[14]. After the targeted biopsy, a 20-region template guided biopsy will

be subsequently performed by another urologist who blinded to the MRI results [18].

Software-based fusion targeted biopsy arm

The software-based fusion targeted biopsy will be performed with the MIM symphony software by taking two-dimensional (2D) mpMRI images to create a three-dimensional (3D) map then be fused with the ultrasound images. Each suspicious area with a PI-RADS score equal or more than 3 will be performed a 3 cores biopsy by one urologist, which will be followed with a 20-region template guided biopsy by another.

Histology

A pathology group, which blind to all clinical data including the technique of biopsy, will evaluate the samples. The pathologic finding will be reported within 2 weeks post biopsy. Clinically significant cancer defined as the International Society of Urological Pathology grade group 2 or higher.

Statistical analysis

Continuous variables will be reported by using means with standard deviations (SD) or median with interquartile range (IQR), while categorical variables will be shown by using frequencies with proportions.

The primary analysis in this trial will follow the intention-to-treat principle, including all patients who have undergone randomization. The primary outcome is the detection rate of clinically significant prostate cancer for cognitive fusion targeted biopsy and software-based fusion targeted biopsy. The absolute difference between these two arms will be calculated with a 95% confidence interval (CI) by estimating with a generalized linear model. The cognitive fusion targeted biopsy will be described as non-inferior if the lower bound of the 95%CI of the difference in the clinically significant cancer detection rate of the cognitive fusion targeted biopsy arm compared with the software-based fusion targeted

biopsy arm (cognitive fusion arm minus software-based arm) is higher than -10%.

The second outcomes will be analysed with 95%CI and Pearson chi-square test. All reported P values were two-sided in this trial.

Sample size

A retrospective data review for cognitive fusion targeted biopsy performed at our institution during 2017 showed a clinically significant cancer detection rate of 52.8%[19] while a literature from Germany revealed a clinically significant cancer detection rate of 45% for software-based fusion targeted biopsy. The patients with PI-RADS score $\geqslant$3 account for 60.6% in all patients who had undergone a mpMRI examination at our institution.

For the non-inferiority hypothesis, using a 10% noninferiority margin, using 80% power and 5% one-sided α, assuming a detection rate of clinically significant cancer for cognitive fusion targeted biopsy of 50% and a detection rate for software-based fusion targeted biopsy of 45%, using allocation ratio of 1:1, 137 men per arm will be required. Assuming that 50% has at least one suspicious lesion on mpMRI, 548 men are needed. Account for 10% withdraw/loss, a total of 602 participants are required for inclusion.

Harms and adverse events

A research nurse will record all harms or adverse events relevant or not relevant to the procedure of biopsy. Adverse events will be assessed by Common Terminology Criteria for Adverse Events (CTCAE). The serious adverse events include (1) death; (2) life-threatening; (3) hospitalization and (4) disability or permanent damage will be recorded immediately and then sent to the ethics committee and the monitoring board within 24 hours. All harms and adverse events will be recorded from the registration to one-week after the biopsy.

Data collection

The data will be collected from the patient/relative of a patient at registration, and the medical record on two weeks and six weeks. The demographic information (age, height, weight, BMI), PSA, and family history will be recorded on registration, as well as the digital rectal examination will be performed. On two weeks after the registration, an MRI result will be recorded, including a PI-RADS score, prostate volume, and suspicious lesion volume. Both prostate volume and suspicious lesion volume will be measured by mpMRI on the T2WI sequence. The data of pathological assessment will be recorded on six weeks (two weeks post-biopsy) including an overall Gleason score and a separate Gleason score for each biopsy core. Besides, the length and percent of tumour in each biopsy core will also be reported.

Monitoring

A team of independent clinical research associate (CRA) with all more than five years of experiences is responsible for being familiar with the trial protocol and monitoring all researchers and all participants involved in the whole processes of this trial. The CRA's role is to (1) monitoring the trial plan, the record forms, and the case report form before the start of the trial; (2) monitoring participants' informed consent and enrolment rates; (3) monitor the compliance of participants and investigators with the protocol, and monitoring data quality and authenticity.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai East Hospital. The results of this study will be disseminated for international peer-reviewed journal and disseminated for presentation at international or national academic conference.

Trial status

This RCT was first registered online at ClinicalTrials.gov on 13 February 2020.

The study is expected to start on 1 September 2020. Recruitment is anticipated to continue until 1 September 2021 with 6-week follow-up to be completed in November 2020.

Patient and public involvement

This trial protocol was written without patient or public involvement. The participants were not involved in the contribution of the design, recruitment or conduction of the study. Each participant will be informed of the latest results at follow-up and received a summary of the main finding at the end of the trial.

Authors' contributions

Conceptualization: He B, Li R and Wang H.

Data curation: He B, Li R, Li D, Huang L and Wang H.

Formal analysis: He B, Li R, Li D and Huang L.

Investigation: He B, Li R, Li D, Huang L and Wang H

Supervision: Wen X and Yang G

Original draft: He B and Wang H

Review and editing: Li R, Wen X and Yang G.

Funding

This trial is supported by National key research and development program，(2019YFC0119100), Shanghai Science and technology innovation action plan(18441910900), National Natural Science Foundation of China, youth project (81602220) and The Special Diseases Program of Pudong New Area Health System(PWZzb2017-06).

Declaration of interests

None of the authors have any conflicts of interest to declare.

Table 1. Participant timeline in the study

	Contact with patient			
	Vist 1	Vist 2	Vist 3	Vist 4
	0	0~2 weeks	2~4 weeks	5~6 weeks
Consent	×			
Screening	×			
Baseline characteristic	×			
PSA	×			
MRI		×		
Randomization		×		
Prostate biopsy			×	
Cognitive fusion targeted biopsy + 20 region templated guide biopsy (cognitive fusion arm)			×	
Software fusion targeted biopsy + 20 region templated guide biopsy (Software fusion arm)			×	
Pathological assessment				×
Withdrawal	Complete as required at any time following registration			
SAE	Complete as required at any time following registration			

Table 2. Patients inclusion and exclusion criteria

Inclusion criteria
Age over 18 years old
PSA increase to 4–20 ng/ml and/or abnormal DRE;
Without previous prostate biopsy
Fully understand the clinical trial protocol and sign the informed consent
Exclusion criteria
Previous history of prostate biopsy
Evidence of acute or chronic prostatitis
Contraindications to prostate biopsy (e.g. fever, evidence of urinary tract infection)
Contraindications to MRI (e.g. metal implant, contrast agent allergy)
The investigator judges that patients who are not suitable for this clinical trial
Any other conditions that investigator judges that participations who are not suitable for this trial

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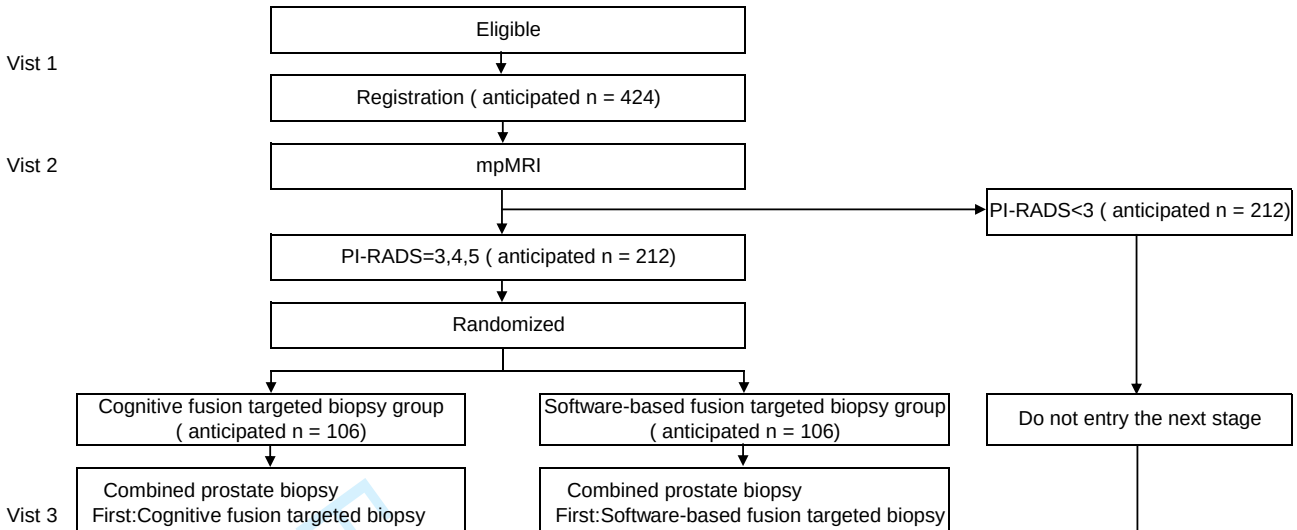

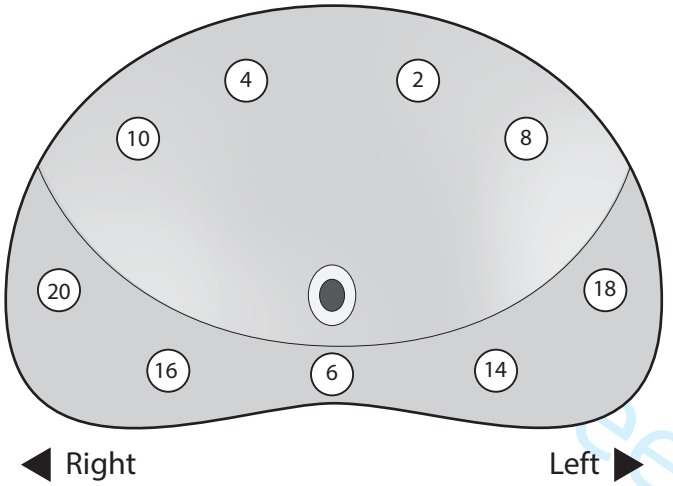

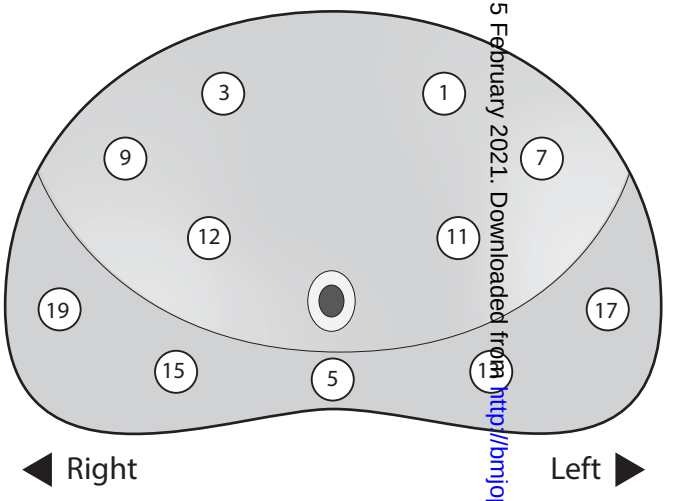

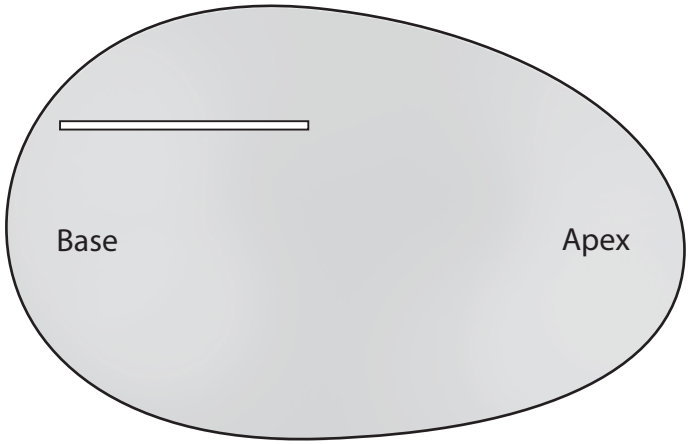

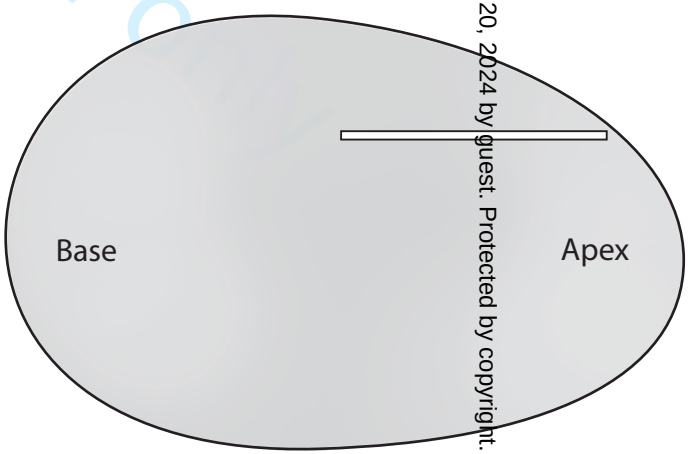

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041427.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Aug-2020
Complete List of Authors:	He, Biming; Changhai Hospital, Li, Rongbing; Shanghai East Hospital Li, Dongyang; Shanghai East Hospital Huang, Liqun; Shanghai East Hospital Wen, Xiaofei; Shanghai East Hospital Yang, Guosheng; Shanghai East Hospital Wang, Haifeng; Changhai Hospital
Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology, Diagnostics
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Bi-Ming He *, Rong-Bing Li *, Dong-Yang Li, Li-Qun Huang, Xiao-Fei Wen, Guo-Sheng Yang and Hai-Feng Wang

Affiliations:

Department of Urology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

*** Bi-Ming He and Rong-Bing Li contributed equally to this paper.**

Correspondence:

Correspondence should be addressed to Prof. Hai-Feng Wang, Ph.D., M.D., Department of Urology, Shanghai East Hospital, No. 150, Jimo Road, Shanghai, 200120, China. Email: 446720864@qq.com Telephone: +8613681750891.

Abstract

Introduction

The classical pathway for diagnosing prostate cancer is systematic 12-core biopsy under the guidance of transrectal ultrasound, which tends to underdiagnosis the clinically significant tumour and overdiagnosis the insignificant disease. Another pathway named targeted biopsy is using multiparametric magnetic resonance imaging to localizing the tumour precisely and then obtain the samples from the suspicious lesions. Targeted biopsy,

which mainly divided into cognitive fusion method and software-based fusion method, is getting prevalent for its good performance in detecting significant cancer. However, the preferred Targeted biopsy technique in detecting clinically significant Prostate cancer between cognitive fusion and software-based fusion is still beyond consensus.

Methods and analysis

This trial is a prospective, single-centre, randomized controlled, and non-inferiority study in which all men suspicious to have clinically significant prostate cancer. This study aims to determine whether a novel three-dimensional matrix positioning cognitive fusion targeted biopsy is non-inferior to software-based fusion targeted biopsy in the detection rate of clinically significant cancer in men without a prior biopsy. The main inclusion criteria are men with elevated serum PSA above to 4 – 20 ng/ml or with an abnormal DRE and have never had a biopsy before. A sample size of 602 participants allowing for a 10% loss, will be recruited. All patients will undergo a mpMRI examination, and those who fail to be found with a suspicious lesion, with the anticipation of half of the total number, will be dropped. The remaining participants will be randomly allocated to cognitive fusion targeted biopsy (n=137), and software-based fusion targeted biopsy (n=137). The primary outcome is the detection rate of clinically significant prostate cancer for cognitive fusion targeted biopsy, and software-based fusion targeted biopsy in men without a prior biopsy. The clinically significant prostate cancer will be defined as the International Society of Urological Pathology grade group 2 or higher.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China. The results of the study will be disseminated and published in international peer-reviewed journals.

registration details

ClinicalTrials.gov: NCT04271527

Strengths and limitations of this study

►This study is the first trial to compare a novel cognitive fusion targeted biopsy which based on a three-dimensional matrix positioning method, with a software-based fusion targeted biopsy.

►The study will determine the efficacy of the novel cognitive fusion targeted biopsy in the diagnosis of prostate cancer.

►Rigorous randomized design and allocation concealment method will reduce bias, which enables the higher reliability of the results.

►This study takes place in one hospital, hence may making the finding less generalizable.

►The study is performed in the centre that developed the guiding method, which may over-estimate its performance as compared to less experienced readers.

Introduction

Prostate cancer (PCa) is the second most common cancer worldwide which leads the fifth causes of death among men[1]. Men with an elevated serum prostate-specific antigen (PSA) level or an abnormal digital rectal examination (DRE) are usually be considered at risk for PCa and typically be performed a prostate biopsy subsequently to get samples for pathological diagnosis. The common pathway is a systematic 12-core biopsy under the guidance of transrectal ultrasound (TURS), an approach to randomly get the samples from the whole prostate gland; however, it's blind attribution makes it tends to underdiagnosis the clinically significant tumour and overdiagnosis the clinically insignificant disease[2, 3].

Thanks to the development of multiparametric magnetic resonance imaging (mpMRI) in identifying prostate cancer, another pathway named targeted biopsy is getting prevalent. It aims to first perform a mpMRI for localizing the tumour precisely and then obtain the samples from the suspicious lesions, shows more purposeful and less random compared with the systematic biopsy. Several pieces of evidence have proved the superiority of targeted biopsy in detection rates of clinically significant prostate cancer (csPCa) and avoidance of unnecessary biopsy[4, 5]..

Targeted biopsy can be subdivided into three different methods: in-bore MRI, cognitive fusion and software-based fusion. An in-bore MRI-targeted biopsy is described as to perform a targeted biopsy under real-time MRI guidance. Although this method is accurate in locating the targeted lesions, it is a failure to be widely used in clinical practice for its inconvenience and time-consuming[6]. Compared with in-bore MRI-targeted biopsy, another two methods are more acceptable. Cognitive fusion, a procedure of mental located the target of suspicious lesions in the ultrasound image after a review of MRI, is cost saving due to it needs no extra equipment, aside from the essential requirement for a TURS-biopsy. Software-based fusion is an overlap of the real-time ultrasound image and the previous MRI images by software assistance. Although it is widely adopted by urologists or physicians, the barriers of time-consuming, and excessive price and training for the additional equipment cannot be omitted [7-9]. There is always an interesting topic about whether the ability of cognitive fusion with human brains can achieve the same result as a fusion with intricate fusion software[10]. However, evidence from the comparative trials are few[9, 11-13].
To now, the preferred targeted biopsy technique in detecting csPCa between cognitive fusion and software-based fusion is still beyond consensus.

We have developed a method named three-dimensional matrix positioning to

increase the accuracy of cognitive fusion for targeted biopsy detection of csPCa, which involves several fiducial axes derived from MRI localization of the region of interest, then transposed onto the ultrasound image to help direct the biopsy needle into the right place[14]. This method had shown a reasonable detection rate for clinically significant prostate cancer in a pilot cohort. Hence, we conduct this single-centre randomized controlled trial in order to confirm the finding further.

This trial aims to compare three-dimensional matrix positioning cognitive fusion targeted biopsy and software-based fusion targeted biopsy for the detection rate of clinically significant prostate cancer for men without a prior biopsy localized prostate cancer. The primary objective is to assess whether the cognitive fusion targeted biopsy is non-inferior to software-based fusion targeted biopsy in the detection rate of clinically significant cancer.

Trial design

This prospective, single-centre, randomized controlled, and non-inferiority study will take place at Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China. The primary objective of this study is to identify whether the three-dimensional matrix positioning cognitive fusion targeted biopsy is non-inferior to software-based fusion targeted biopsy in the detection rate of clinically significant cancer in men without a prior biopsy.

The study flow chart is shown in Fig 1. Patients will be initially screened and recruited by the urologists in outpatient. Those who meet the entry criteria and sign the consent form will go for mpMRI within 2 weeks, and only those whose MRI indicate at least one lesion with a PI-RADS v2.1 $\geq$ 3 will proceed to the randomization. With allocation, men will be assigned to cognitive fusion targeted biopsy using the three-dimensional matrix positioning method or to

software-based fusion targeted biopsy using the MIM symphony software in a 1:1 ratio while others will drop out of the trial. Men in both arms will be hospitalized one day before the prostate biopsy. The biopsy procedure, which usually lasts for less than 30 minutes, will be performed under a local anesthetic block in an operation room. In addition to different targeted biopsy methods, a 20-region template guide prostate biopsy (Fig 2) will be performed after the targeted biopsy in each man, which can be a reference to the different targeted techniques. The samples from the biopsy will send to the pathologic department for assessment after the procedure. All participants will schedule dismiss the followed day after the biopsy. The pathological assessment will be reported within 2 weeks of post-biopsy. The details and timeframe of the trial are shown in Table 1.

We chose the randomised trial instead of a paired cohort to reduce bias. Because if two biopsies are performed on the same participant, the progress of one may lead to the bleeding and deformation of the prostate, which will affect the progress of the other.

Outcomes

The primary outcome is the detection rate of clinically significant prostate cancer for cognitive fusion targeted biopsy, and software-based fusion targeted biopsy in men without a prior biopsy. The clinically significant prostate cancer will be defined as ISUP grade group 2 or higher, according to the 2014 ISUP classification[15]. .

The main secondary outcomes are as follows:

The detection rate of any prostate cancer for cognitive fusion targeted biopsy, and software-based fusion targeted biopsy

The detection rate of clinically significant prostate cancer for each targeted technique combined with a templated guided biopsy

The detection rate of any prostate cancer for each targeted method combined with a templated guided biopsy

The comparison of the results between the two urologists, including the detection rate of clinically significant prostate cancer and any prostate cancer in the targeted biopsy, template biopsy and combined biopsy

The influence of prostate volume on the difference between the two fusion targeted biopsy

Methods and analysis

Patient population

Patients with a suspicious of harbouring prostate cancer and had no previous biopsy will be considered eligible for registration in this trial if they can meet all inclusion criteria and had no any exclusion criteria. The main criteria include men with elevated serum PSA above to 4 – 20 ng/ml or with an abnormal DRE and have never had a biopsy before. The details of inclusion and exclusion criteria are shown in Table 2. All eligible patients will be informed in detail, and only those who sign the consent form can participate in the trial. Men who are ineligible or do not want to participate in the study will be returned to the regular clinical pathway.

Multi-parametric magnetic resonance imaging

All participants who sign the informed consent will subsequently undergo a 3.0-Tesla mpMRI (Magnetom Skyra, Siemens Medical Solutions, Erlangen, Germany) with an 18-channel phased-array coil. The sequences of examination mainly included T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI, acquired b-values 0,400,1000 and 2000 seconds per mm^2), and dynamic contrast-enhanced imaging (with the setting of temporal resolution less than 7 seconds and 5 minutes acquisition). Images will be evaluated and scored by one of two expert radiologists (20 and 10 yr of experience in prostate MRI) according to Prostate Imaging Reporting and Data System (PI-RADS)

version 2.1 criteria[16]. The probability of cancer will be assessed by the score from 1 to 5 (1 - Highly unlikely to be clinically significant cancer, 2 - Unlikely to be clinically significant cancer, 3 - equivocal to be clinically significant cancer, 4 - Likely to be clinically significant cancer, 5 - Highly likely to be clinically significant cancer). The MRI report will only be marked as 'no abnormal' or 'less than 3' when scoring 1 or 2 while a specific score will be recorded at a score 3, 4 or 5.

Randomization

Only participants with a PI-RADS score 3, 4 or 5 will be allocated 1:1 to cognitive fusion targeted biopsy group or software-based fusion targeted biopsy group by using block-randomization. The random sequence will be generated by PROC PLAN statement of SAS program which keep by one research nurse and blind to other researchers. A random number will be revealed only when one participant being randomising.

Interventions

Biopsy

All biopsies in both arms will be performed via the perineum by two urologists (Haifeng Wang with an experience more than 10 years and Biming He with an experience more than 5 years) with an UltraView 800 ultrasound device (BK Ultrasound, USA) and a bi-planar transrectal ultrasound (TRUS) probe (8848, BK Ultrasound) under a local anesthetic block. Before performing the biopsy, one urologist will read the report and the image of MRI to identify the location of target lesions while another one will be blinded to the MRI result.

Cognitive fusion targeted biopsy arm

Each participant in this arm will undergo a cognitive fusion targeted biopsy first. A novel three-dimensional matrix positioning based cognitive fusion targeted biopsy will be performed under the guidance of a bi-plane TURS probe after

reviewing the mpMRI finding. Three cores of biopsy will be taken for each suspicious lesion which is showed in mpMRI that PI-RADS score of 3 to 5. The details of the cognitive fusion targeted biopsy was described in our previous research[14]. After the targeted biopsy, a 20-region template guided biopsy will be subsequently performed by another urologist who blinded to the MRI results [17]. The urologist who performs the targeted biopsy will be determined by a random number generated by PROC PLAN statement of SAS program.

Software-based fusion targeted biopsy arm

The software-based fusion targeted biopsy will be performed with the MIM symphony software by taking two-dimensional (2D) mpMRI images to create a three-dimensional (3D) map then be fused with the ultrasound images. Each suspicious area with a PI-RADS score equal or more than 3 will be performed a 3 cores biopsy by one urologist, which will be followed with a 20-region template guided biopsy by another. Also, who performs the targeted biopsy will be randomized.

Histology

A pathology group, which blind to all clinical data including the technique of biopsy, will evaluate the samples. The pathologic finding will be reported within 2 weeks post biopsy. Clinically significant cancer defined as the International Society of Urological Pathology grade group 2 or higher.

Statistical analysis

Continuous variables will be reported by using means with standard deviations (SD) or median with interquartile range (IQR), while categorical variables will be shown by using frequencies with proportions.

The primary analysis in this trial will follow the intention-to-treat principle, including all patients who have undergone randomization. The primary outcome is the detection rate of clinically significant prostate cancer for cognitive fusion

targeted biopsy and software-based fusion targeted biopsy. The absolute difference between these two arms will be calculated with a 95% confidence interval (CI) by estimating with a generalized linear model. The cognitive fusion targeted biopsy will be described as non-inferior if the lower bound of the 95%CI of the difference in the clinically significant cancer detection rate of the cognitive fusion targeted biopsy arm compared with the software-based fusion targeted biopsy arm (cognitive fusion arm minus software-based arm) is higher than -10%.

The second outcomes will be analysed with 95%CI and Pearson chi-square test. All reported P values were two-sided in this trial.

Sample size

A retrospective data review for cognitive fusion targeted biopsy performed at our institution during 2017 showed a clinically significant cancer detection rate of 52.8%[18] while a literature from Germany revealed a clinically significant cancer detection rate of 45%[19] for software-based fusion targeted biopsy. The patients with PI-RADS score $\geqslant$3 account for 60.6% in all patients who had undergone a mpMRI examination at our institution.

For the non-inferiority hypothesis, using a 10% noninferiority margin, using 80% power and 5% one-sided α, assuming a detection rate of clinically significant cancer for cognitive fusion targeted biopsy of 50% and a detection rate for software-based fusion targeted biopsy of 45%, using allocation ratio of 1:1, 137 men per arm will be required. Assuming that 50% has at least one suspicious lesion on mpMRI, 548 men are needed. Account for 10% withdraw/loss, a total of 602 participants are required for inclusion.

Harms and adverse events

A research nurse will record all harms or adverse events relevant or not relevant

to the procedure of biopsy. Adverse events will be assessed by Common Terminology Criteria for Adverse Events (CTCAE). The serious adverse events include (1) death; (2) life-threatening; (3) hospitalization and (4) disability or permanent damage will be recorded immediately and then sent to the ethics committee and the monitoring board within 24 hours. All harms and adverse events will be recorded from the registration to one-week after the biopsy.

Data collection

The data will be collected from the patient/relative of a patient at registration, and the medical record on two weeks and six weeks. The demographic information (age, height, weight, BMI), PSA, and family history will be recorded on registration, as well as the digital rectal examination will be performed. On two weeks after the registration, an MRI result will be recorded, including a PI-RADS score, prostate volume, and suspicious lesion volume. Both prostate volume and suspicious lesion volume will be measured by mpMRI on the T2WI sequence. The data of pathological assessment will be recorded on six weeks (two weeks post-biopsy) including an overall Gleason score and a separate Gleason score for each biopsy core. Besides, the length and percent of tumour in each biopsy core will also be reported.

Monitoring

A team of independent clinical research associate (CRA) with all more than five years of experiences is responsible for being familiar with the trial protocol and monitoring all researchers and all participants involved in the whole processes of this trial. The CRA's role is to (1) monitoring the trial plan, the record forms, and the case report form before the start of the trial; (2) monitoring participants' informed consent and enrolment rates; (3) monitor the compliance of participants and investigators with the protocol, and monitoring data quality and authenticity.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai East Hospital. The results of this study will be disseminated for international peer-reviewed journal and disseminated for presentation at international or national academic conference.

Trial status

This RCT was first registered online at ClinicalTrials.gov on 13 February 2020. The study is expected to start on 1 September 2020. Recruitment is anticipated to continue until 1 September 2021 with 6-week follow-up to be completed in November 2021.

Patient and public involvement

This trial protocol was written without patient or public involvement. The participants were not involved in the contribution of the design, recruitment or conduction of the study. Each participant will be informed of the latest results at follow-up and received a summary of the main finding at the end of the trial.

Authors' contributions

Conceptualization: He B, Li R and Wang H.

Data curation: He B, Li R, Li D, Huang L and Wang H.

Formal analysis: He B, Li R, Li D and Huang L.

Investigation: He B, Li R, Li D, Huang L and Wang H

Supervision: Wen X and Yang G

Original draft: He B and Wang H

Review and editing: Li R, Wen X and Yang G.

Funding

This trial is supported by National key research and development program，(2019YFC0119100), Shanghai Science and technology innovation action

plan(18441910900), National Natural Science Foundation of China, youth project (81602220) and The Special Diseases Program of Pudong New Area Health System(PWZzb2017-06).

Declaration of interests

None of the authors have any conflicts of interest to declare.

Table 1. Participant timeline in the study

	Contact with patient			
	Vist 1	Vist 2	Vist 3	Vist 4
	0	0~2 weeks	2~4 weeks	5~6 weeks
Consent	×			
Screening	×			
Baseline characteristic	×			
PSA	×			
MRI		×		
Randomization		×		
Prostate biopsy			×	
Cognitive fusion targeted biopsy + 20 region templated guide biopsy (cognitive fusion arm)			×	
Software fusion targeted biopsy + 20 region templated guide biopsy (Software fusion arm)			×	
Pathological assessment				×
Withdrawal	Complete as required at any time following registration			
SAE	Complete as required at any time following registration			

Table 2. Patients inclusion and exclusion criteria

Inclusion criteria
Age over 18 years old
PSA increase to 4–20 ng/ml and/or abnormal DRE;
Without previous prostate biopsy
Fully understand the clinical trial protocol and sign the informed consent

Exclusion criteria

Previous history of prostate biopsy

Evidence of acute or chronic prostatitis

Contraindications to prostate biopsy (e.g. fever, evidence of urinary tract infection)

Contraindications to MRI (e.g. metal implant, contrast agent allergy)

The investigator judges that patients who are not suitable for this clinical trial

Any other conditions that investigator judges that participations who are not suitable for this trial

Figure legend

Fig 1 Trial flow chart

Fig 2 20-region template guided prostate biopsy

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