

STUDY PROTOCOL

Title:

Randomized-controlled trial: whether transperineal prostate biopsy under local-anaesthesia using a transperineal-access system is superior to standard transrectal biopsy to detect prostate cancer in biopsy-naïve men

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Introduction

The incidence of prostate cancer (PCa) has increased considerably in recent years [1, 2]. The reported lifetime risk for men in Hong Kong to be diagnosed with PCa is 1 in 31 before the age of 75, and is currently the third commonest cancer Hong Kong men according to the Hong Kong Cancer Registry [3]. This highlights the importance of thorough and fundamentally a safe investigation technique to correctly identify patients with PCa. Such test should be able to sensitively detect PCa, and provide early diagnosis. Critically, such test is required to provide accurate disease risk stratification, which is absolutely crucial in guiding level of appropriate treatment is necessary in patients diagnosed with PCa.

According to recommendations from the National Institute for Health and Care Excellence (NICE) guidelines, current standard clinical practice considers histological diagnosis of PCa a necessity in majority of patients presented with localized disease who are eligible for treatment [4]. This, alongside with prostate specific antigen (PSA) level, digital rectal examination (DRE) findings, and increasingly the use of multi-parametric MRI (mpMRI) imaging, collectively allows risk stratification of PCa.

The current pathway to obtain prostate tissue for histological diagnosis of CaP is by transrectal ultrasound-guided systematic biopsy (TRUSB) of the prostate, usually following the detection of a raised serum PSA level and/or suspicious rectal examination findings. TRUSB has been the standard prostate tissue sampling technique for men suspected with PCa for over 30 years. It is an office-based procedure carried out under local anaesthesia (LA), with 10 to 12 biopsy cores directed towards the lateral peripheral zones of the prostate thought to harbour majority of cancers [7]. However, there are still various well-known cancer detection limitations and patient safety problems associated with TRUSB.

Firstly, a very significant portion of tumours are being missed with the TRUSB technique [8]. It has been well-known that over 30% of patients with low risk PCa on TRUSB have been found to harbour clinically significant PCa [9]. Many of these tumours missed on TRUSB are located in the anterior and apical regions of the prostate, which TRUSB is difficult to access, in particular in patients with a large prostate volume

Secondly, TRUSB requires the biopsy needle to penetrate through the bowel (rectum). This results in high risk of developing sepsis following biopsy, despite all patients undergoing the procedure being started on antibiotics prophylactically. This is a serious complication which can potentially be life-threatening. Our previous study has already demonstrated a high prevalence of fluoroquinolone-resistant and ESBL-producing rectal flora in our local population in Hong Kong [10]. The risk of developing post-biopsy sepsis in Hong Kong is high.

Transperineal prostate biopsy (TPB) has been developed to provide a more comprehensive biopsy method to improve cancer detection rate by directing biopsy cores through the perineal skin. Theoretically, TPB enables access to sample the entire prostate, in particular the anterior and apical regions which are not easily accessible through the standard TRUSB method. By sampling the prostate using

biopsy needles directly inserted through the perineal skin rather than bowel, the risk of sepsis is reduced. However, this technique requires multiple needles traversing through the perineum, and requires to be carried out under general anaesthesia (GA). Another disadvantage is a stabilising stepping unit is required to provide a consistent alignment of the ultrasound probe against the prostate in order to carry out the biopsies. Such stabilising stepping units are costly.

A novel but simple transperineal access system device known as PrecisionPoint (Perineologic, Cumberland, MD, USA) has been developed to tackle the aforementioned limitations of TPB. This revolutionary device utilises a single access needle cannula mounted directly on to the ultrasound probe, which acts as an access point traversing through the perineal skin. This design minimises the number of needle punctures through the skin, enabling TPB to be carried out under LA. A stabilising stepping unit is not required with this technique. The device has gained the United States Food and Drug Administration (FDA) approval [11], and results from small contemporary series have already been published with very promising results in terms of cancer detection rate and safety [12].

TRUSB has a poor cancer detection rate and is associated with potentially fatal septic risk. TPB, if able to be carried out under LA as an office-based procedure, can potentially provide a better cancer detection rate with significantly reduced sepsis risk. It has fundamentally a very high potential to become the new gold standard in obtaining prostate tissue for histological diagnosis of PCa.

With an increasing number of men in Hong Kong with elevated serum PSA suspicion of PCa needing prostate biopsy, we strongly feel that it is fundamental to carry out a study to determine the most effective, safe and tolerable prostate biopsy technique which fits with the clinical practice in Hong Kong.

Aim of study

To evaluate whether TPB using a novel transperineal access system under LA is superior to standard 12-cores TRUSB in detecting prostate cancer (PCa), in patients with clinical suspicion of PCa with no prior prostate biopsy.

Other objectives of the study include:

- To assess whether LA TPB has reduced post-biopsy sepsis rate
- To assess whether patient tolerability with LA TPB is non-inferior to standard TRUSB

Study design and method

All patients referred with a raised serum PSA or abnormal DRE will be seen in the urology specialist unit outpatient clinic (OPD), where patients will be screened and assessed for eligibility for the study. All patients must satisfy all inclusion criteria and none of the exclusion criteria outlined in the table below.

| Inclusion criteria | Exclusion criteria |
|--|--|
| 1. Patients between ages 40 – 80 | 1. Patients who are unable to provide written informed consent |
| 2. Serum PSA \leq 20ng/mL | 2. Known history of prostate cancer |
| 3. Suspected tumour clinical stage \leq T2 on DRE | 3. Contraindication to prostate biopsy |
| 4. No previous history prostate biopsy | 4. Had pre-biopsy mpMRI |
| 5. Medically fit to undergo procedures according to study protocol | 5. Rectal abnormality precluding transrectal ultrasound |

If eligible, informed consent will be obtained. Baseline characteristics will be recorded, such as age, height, weight, allergies, past medical history, family history of PCa, drug history, presenting PSA and DRE findings. Baseline urine and blood samples will be taken. Baseline IPSS, EQ-5D-5L and IIEF questionnaires will be filled by each participant. Eligible patients will be randomized to either the LA TRUSB arm or the LA TPB arm. Randomisation will be executed per participant with a third-party statistical software using a computer-generated randomization tool, following completion of informed consent procedure. Equal allocation between both arms will be performed, using random permuted blocks of varying size. In order to ensure allocation concealment, block sizes will not be disclosed and randomisation codes will be obtained through a web-based application.

Procedures will be carried out within 30-60 days following first visit. Procedure in each arm will be carried out according to protocols described below within 60 days of randomisation. All patients on anticoagulants will be advised to stop 7 days prior to biopsy.

For the superiority hypothesis, based on assumptions from results from previous preliminary studies, a sample size of 330 subjects (165 per group) will achieve 80% power to detect superiority of LA TPB over TRUSB. The calculation used a one-sided Z test assuming superiority margin of 10% and the significance level at 0.05. Estimating up to 10% of patients will withdraw from the study or loss to follow-up, 364 patients will need to be recruited for the study (182 patients per arm).

Patient recruitment and enrollment will take place at urology outpatient clinics at a tertiary university teaching hospital. In 2017, on average 16 biopsy-naïve men with raised serum PSA underwent TRUSB per month. It is therefore estimated that the study will complete within 26 months of commencement. The start date of the study will be 1st April 2019, and the estimated completion date for recruitment will be 1st June 2021.

Statistical analysis

Primary outcome analysis will be based on intention to treat sample as well as per protocol sample.

Primary endpoint is difference in proportion of patients with PCa detected between the two cohorts based on histopathological analysis. Absolute differences in PCa detection rate will be calculated with 95% CIs. If lower bound of 97.5% CI for the difference in cancer detection rates of LA TP biopsy compared with TRUS biopsy is greater than -5%, then TP biopsy will be deemed non-inferior. If lower bound is greater than 0, TP will be deemed superior. Comparisons will be made concerning the basic characteristics between the two arms of participants. If any imbalance were identified, a multivariable logistic regression analysis will be carried out, with clinically significant PCa as the dependent variable and group as the independent variable. Any baseline characteristics imbalance will be used as a covariate.

Effect sizes concerning secondary outcomes will be presented with 95% CIs. For binary outcomes, differences between the two arms will be calculated with 95% CIs. Any imbalance between the two arms will again be accounted for with a multivariable logistic regression analysis. For continuous outcomes, mean differences in outcomes between the two study arms will be calculated with 95% CIs. Imbalances identified between the two groups will be accounted for in a multivariable linear regression analysis. Non-parametric test will be used if any secondary outcomes were found not normally distributed. All statistical analysis will be carried out using the SPSS software.

Primary end-point

Primary outcome is proportion of participants identified with PCa, assessed on a per patient basis from each individual's biopsy histopathological analysis report (i.e. comparison of absolute cancer detection rate). Definition of PCa is presence of any PCa regardless of grade on histopathology. Definition of clinically significant PCa is any core containing Gleason grade 3+4 disease or above. Timeframe for

assessment will be when histopathology reports are available, usually expected to be within 14 days following biopsy procedures.

Secondary end-points

Secondary outcomes, tools for assessment, and their corresponding timeframe for assessment are summarized in table below.

| Secondary outcomes | Assessment tool (if applicable) | Timeframe for assessment |
|---|---|---|
| Procedure tolerability | Visual Analogue Scale (VAS) | Immediately following test |
| Health-related quality of life and patient satisfaction | EQ-5D-5L questionnaire, IPSS, IIEF | Baseline, 24 hours post-biopsy, and 30 days post-biopsy |
| Proportion of men developing sepsis | Either: 1) admission to hospital for urosepsis; or 2) Presence of nitrites in urine at <1 month | 1 week to 30 days post-biopsy |
| Detection rates of patients with clinically significant PCa (Gleason 3+4 or higher) | Histopathology report | When histopathology results available, expected to be within 14 days following biopsy |
| Maximum cancer core length (MCCL, mm) | Histopathology report | When histopathology results available, expected to be within 14 days following biopsy |
| Proportion of men go on to undergo definitive curative treatment for local disease (including surgery and radiotherapy) | Clinical records, patient interview | After treatment decision, expected to be within 30 days following biopsy |
| Procedure times (minutes) | Time from start of ultrasound probe insertion to probe removal | During test |
| Cost per diagnosis of cancer (HKD) | | 30 days post-biopsy |

Data Access and Handling

To protect patient privacy, all research data will be handled in line with Hospital Authority's or Hospital's policy in handling/storage/destruction of patients' medical records. They would be locked in cabinets where the department/ward keep patients' medical records. Electronic data would be saved in secured computer of the hospital with restricted access. USB Device would not be used for patient information for personal data.

Personal data (name, HKID, address and any other personal identifiable information) will not be recorded on the projects' data sheets or electronic files. A study code will be used.

Any documents or electronic files containing personal identifiable information would be considered as part of the medical record and will be dealt with the same stringent regulations of security according to the hospital policies. The principal investigator/co-investigator will be responsible for the execution of data protection.

This study will fully comply with the requirements of ICH-GCP.

Ethics

There is no conflict of interest in this study.

Financing and Insurance

A grant has been applied (HMRF) to help funding in the purchase of required equipments to carry out this study. No additional insurance requirements will be necessary.

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