Aus der Klinik für Urologie

Diakonie-Klinikum Stuttgart

Is It Appropriate to Use Only Magnetic Resonance Imaging/transrectal Ultrasound (MRI/TRUS) Fusion Targeted Biopsy for Diagnosis of Prostate Cancer in Patients with Positive mpMRI Results?

Inaugural-Dissertation

zur Erlangung des Doktorgrades

der Medizin

der Medizinischen Fakultät

der Eberhard Karls Universität

zu Tübingen

vorgelegt von

Lei, Ye

2018

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Tag der Disputation:	27. 11. 2018

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Abbreviations

Abbreviation	Full name
ADT	Androgen Deprivation Therapy
AFS	Anterior Fibromusclar Zone
AMACR	Alpha-Methylacyl-CoA Racemase
AS	Active Surveillance
ASAP	Atypical Small Acinar Proliferation
AUA	Americian Urological Association
BPH	Benign Prostatic Hyperplasia
95%CI	95% Confidence Interval
CK34ßE12	High Molecular Weight Cytokeratin 34ßE12
csPCa	Clinically Significant Prostate Cancer
CZ	Central Zone
D	Diameter
DCE	Dynamic Contrast-enhanced
DHT	Dihydrotestosterone
DWI	Diffusion-weighted Imaging
EAU	European Association of Urology
FDA	Food and Drug Administration
GS	Gleason Score
HE	Hematoxylin-eosin
HGPIN	High Grade Prostatic Intraepithelial Neoplasia
IDC-P	Intraductal Prostatic Carcinoma
IQR	Interquartile Range
ISUP	International Society of Urological Pathology
MCCL	Maximum Cancer Core Length
ml	milliliter
mpMRI	Multiparametric Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging

Abbreviations

ng	nanogram
OR	Odds Ratio
PAP	Prostatic Acid Phosphatase
PCa	Prostate Cancer (Carcinoma)
PI-RADS	Prostate Imaging-Reporting and Data System
PSA	Prostate-specific Antigen
PSAD	Prostate-specific Antigen Density
PZ	Peripheral Zone
ROI	Region of Interest
SB	Systematic Biopsy
SPSS	Statistical Package for Social Science
START	Standards of Reporting for MRI-targeted Biopsy Studies
TB	Targeted Biopsy
T1WI	T1-weighted Imaging
T2WI	T2-weighted Imaging
TRUS	Transrectal Ultrasound
TZ	Transitional Zone
UTI	Urinary Tract Infection
WHO	World Health Organisation

1 Introduction

1.1 Anatomy and physiology of prostate

Prostate, a masculine unique organ, made up of glandular tissue and muscle tissue, is located in pelvic cavity. The normal size of prostate is 4cm × 3cm × 2cm. It has four major physiological functions. Firstly, as a exocrine gland, prostate could secrete the prostatic fluid, which is a crucial constituent of semen and has an important influence on the normal physiological function of sperm. Meanwhile, due to its endocrine function, prostate is involved in the generation of 5α-reductase, which promotes the transformation of dihydrotestosterone (DHT) from testosterone. With 5α-reductase inhibited, the hyperplastic prostate tissue would atrophy and this is the reason why 5α-reductase inhibitors are widely used to treat benign prostatic hyperplasia (BPH) in the clinical practice. In addition, its circular smooth muscle tissues participate in the formation of internal urethral sphincter so that prostate might be able to control urination. Besides, urethra and two ejaculation tubes pass through the prostate, therefore prostate manifests, to a large extent, the feature of basic transportation.

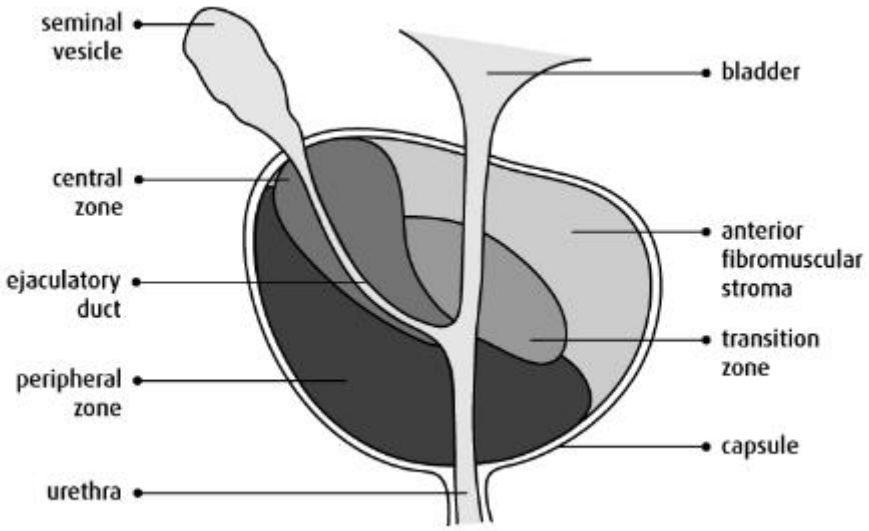


Figure 1. Anatomical divisions and zones of the Prostate (source from the chapter of prostate cancer from Canadian Cancer society)

As shown in Figure 1, clinically, prostate is divided into four regions: peripheral zone (PZ), transition zone (TZ), central zone (CZ) and the anterior fibromuscular stroma

(AFS) [1]. The peripheral zone taking up over 70% part of the prostate is close to rectum. Prostate cancer often occurs in the peripheral zone, so digital rectal examination (DRE) is hugely helpful for the diagnosis of prostate cancer. The urethra is partially surrounded by transition zone, which constitutes 25% of the prostate and BPH often occurs at this site. As a result of the limitation of prostatic capsule, BPH patients are always suffering from the symptoms of urinary tract obstruction.

1.2 Epidemiology and pathology of prostate cancer

Prostate cancer (PCa) is one of the most commonly diagnosed malignant tumor among men all over the world, especially in European countries and the numbers of estimated new cases and estimated deaths always account for the first place and the second place after lung cancer in all male malignancies, respectively [2,3]. Hence, prostate cancer has already become the main culprit for men's health. Understanding the pathogenesis of prostate cancer has always been the focus of attention among urologists, biologists and oncologists.

Unlike other solid tumors, prostate cancer is a highly heterogeneous and multifocal malignancy, which leads to the complexity of the pathological diagnosis of prostate cancer [4,5]. Based on the latest 2016 WHO classification of prostate cancer, more than ten pathological types are referred to, even if the main pathological classifications of prostate cancer are still acinar adenocarcinoma, squamous cell carcinoma, neuroendocrine tumor and miscellaneous tumor [6]. In this new classification version, some unusual pathological types, such as intraductal carcinoma, need to be specifically mentioned in the routine pathological report as well. In terms of the pathological grade of prostate cancer, Gleason grading system has been introduced as one of the most valuable references in making clinical decision for patients with prostate cancer [7, 8]. With the acquisition of exceeding number of evidence-based medical evidence, International Society of Urologic Pathology (ISUP) updated the Gleason grading system in 2014 and its new Grade group was put forward along with some modifications of Gleason patterns (Figure 2). It is attributed to the diversity on histological morphology of prostate cancer cells, besides

Hematoxylin-eosin (HE) staining, immunohistochemical technique is strongly recommended for the pathological diagnosis of prostate cancer. Antibodies against CK34ßE12, P63 and AMACR known as P504S, are often used to aid diagnosis of ambiguous biopsy samples.

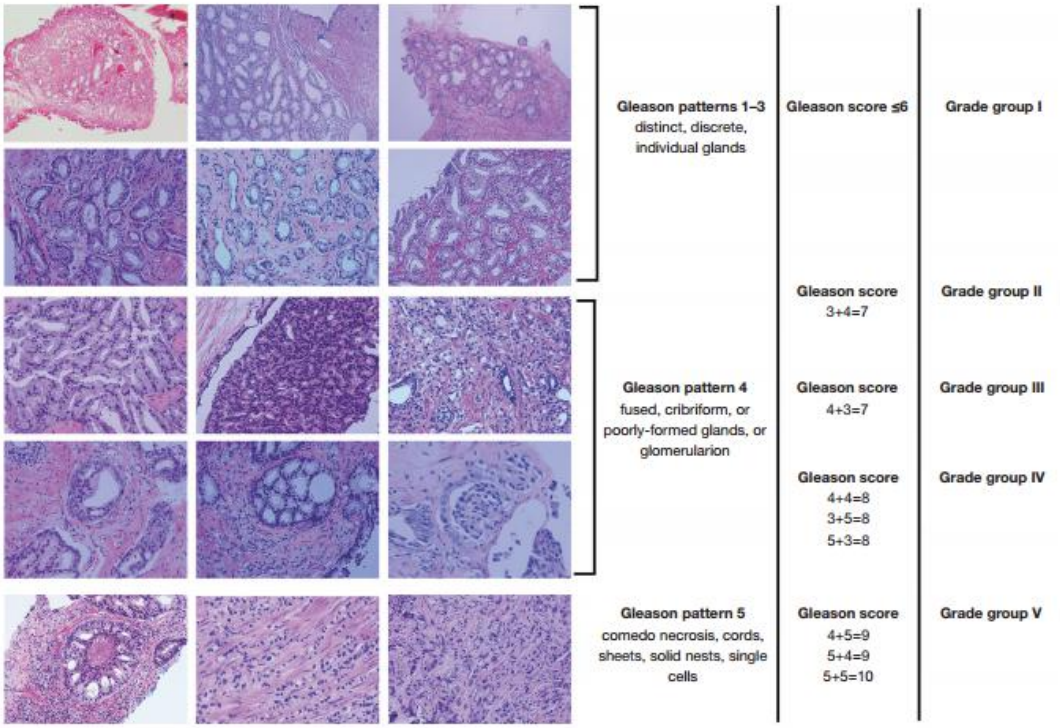


Figure 2. Newly Gleason grading system of prostate cancer (source from Chen N, et al [7])

1.3 Contemporary diagnosis in prostate cancer

1.3.1 Prostate-specific antigen

Prostate-specific antigen (PSA) testing, has been used as a screening and monitoring method since 1980s [9]. PSA, a chymotrypsin-like protease, belonging to the family of serine protease, only exists in the cytoplasm of prostatic acinus and ductal epithelial cells and is overexpressed in the serum of patients with prostate cancer [10]. The higher PSA value, the greater the possibility of having prostate cancer. However, PSA is not a tumor-specific indicator. PSA value could be affected by a variety of factors including age and prostate volume, etc. [11]. Some other non-neoplastic diseases, even medical approaches, which traumatically interfere with the structure and function of the prostate, for instance, BPH, prostatitis, urine retention as well as

catheterisation, could also make the concentration of PSA go up. Accordingly, PSA level exceeding threshold doesn't signify it is certainly a prostate malignancy and influencing factors above should be also taken into consideration. Notably, while prostate cancer mortality rate is declining with the routine use of PSA screening, this PSA-based testing strategy increases risks of unnecessary prostate biopsy and overtreatment of prostate cancer [12, 13]. United States Preventive Services Task Force (USPSTF) once opposed PSA screening being used for all healthy crowed without any hazards of prostate cancer. Benefits and potential harms of PSA determination need to be discussed with every patient. American Urological Association (AUA) guidelines specify that men ages from 55 to 69 years old might be the optimal population to proceed PSA screening with greatest benefits [14].

1.3.2 Digital rectal examination

Together with PSA testing, digital rectal examination (DRE) is another recognised test which could improve the early detection rate of prostate cancer. Jones and colleagues [15] reported that the sensitivity and specificity of DRE in detection of prostate cancer for symptomatic patients was 28.6 and 90.7%, respectively. DRE for the detection of prostate cancer is also positively correlated with PSA level [16]. Prostate cancer with Gleason score greater than 7 is more likely to be found in patients with suspicious DRE [17]. DRE is more useful for detecting prostate cancer in peripheral zone, but it is less powerful and effective for detecting tumors in transitional zone and central zone because of the limitation of palpation distance, especially in patients with very big prostate. Thereby, DRE is a relatively subjective measure which could be easily influenced by experience and manipulative skills of clinicians.

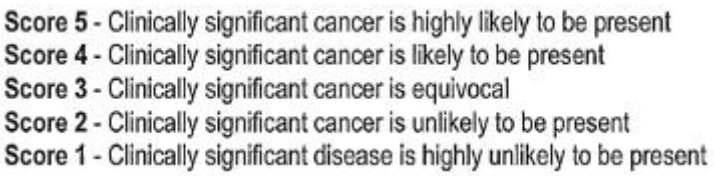
1.3.3 Transrectal ultrasound

Typical prostate cancer appearing in transrectal ultrasound (TRUS) is characterised by hypoechoic nodule [18], but there are still some prostate cancers verified in the specimens of radical prostatectomy which are visualised as isoechoic (39%) and hyperechoic (1%) lesions [19]. Sensitivity and specificity of TRUS for the detection

of prostate cancer are also somewhat low and unsatisfying [20]. Currently, TRUS modality is more set to guide prostate biopsy. The procedure of transrectal ultrasound-guided prostate biopsy will be described in detail in the section of Material and Methods.

1.3.4 Multiparametric magnetic resonance imaging (mpMRI)

In recent years, with the rapid development of imaging technologies, multiparametric magnetic resonance imaging (mpMRI) was involved in the diagnosis and treatment of prostate cancer. mpMRI is an imaging modality, employing not only conventional T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) but also some functional sequences mainly containing diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE). DWI is the predominant reference sequence for PZ tumor, while T2WI is applied as the primary distinguishing technique for TZ tumor [21]. DCE findings which illustrate early and focal enhancement in malignant lesions are also instructive and meaningful, offering considerable additional diagnostic messages when interpreting and analysing with the results of T2WI and DWI sequences. Prostate Imaging-Reporting and Data System (PI-RADS), an assessment system of 5-point scale ranging from score 1 to score 5 based on the likelihood of developing clinically significant prostate cancer (Figure 3), is introduced and widely accepted to standardise mpMRI interpretation and reporting as well as to eliminate disaccord and misreading between radiologists and urologists. 36 sections for prostate, two for seminal vesicles and one for urethra should be assessed and reported separately in mpMRI report (Figure 4).



Figrue 3. 5-point assessment scale in PI-RADS v2 (source from Moore CM et al [22])

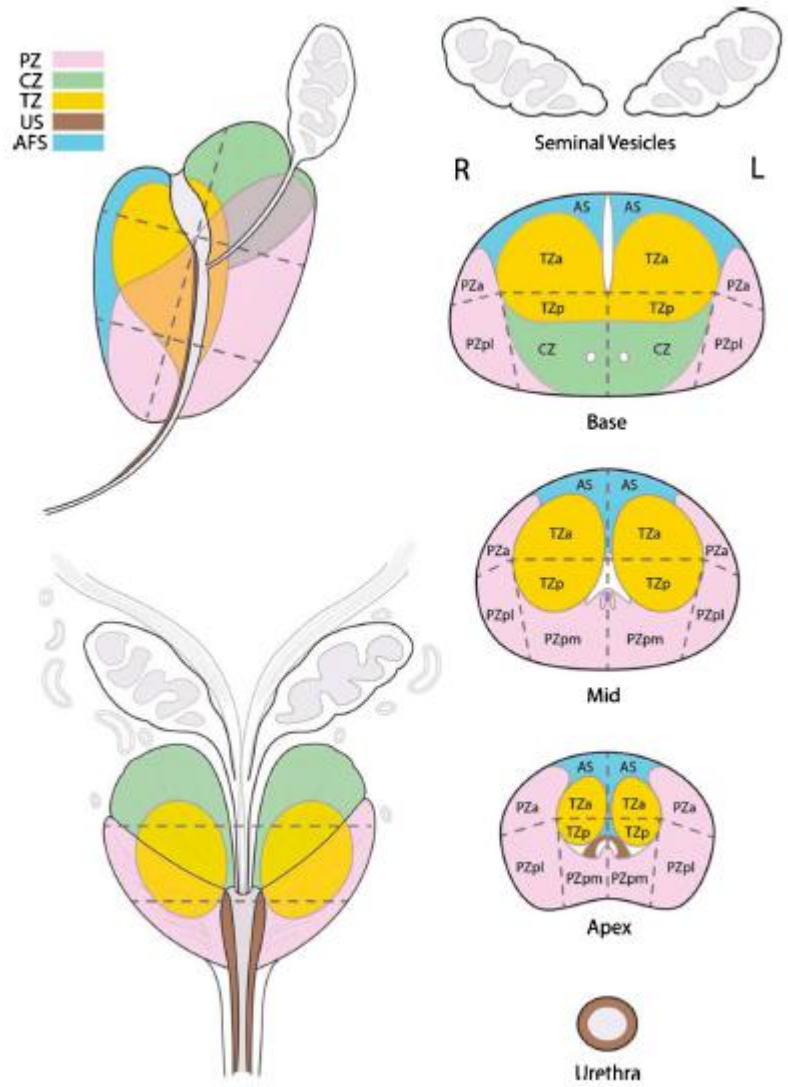


Figure 4. Sector map in PI-RADS v2 (source from Weinreb JC, et al [21])

Several studies have highlighted that mpMRI is able to help define the clinically significant prostate cancer and scrap unnecessary prostate biopsy, in particularly, for patients with PSA level between 4 and 10 ng/ml [23-25]. mpMRI appears to perform pretty high sensitivity (0.85) and pooled specificity (0.71) for the detection of prostate cancer [26]. Furthermore, when changes on mpMRI are integrated into the follow-up regime of active surveillance (AS) for cases with localised prostate cancer, pathological progression rate would not rise compared with re-biopsy follow-up strategies [27, 28]. mpMRI used to be the most cutting-edge imaging means of detecting abnormality to select appropriate patients for further biopsy, but now is

becoming a new measure to locate and illustrate lesions during targeted prostate biopsy, which will be introduced in detail later on.

1.3.5 Overview of prostate biopsy and precision medicine

1.3.5.1 Systematic biopsy (SB)

It is truth universally acknowledged that pathological results are the gold standard for diagnosis of tumor. Of course, to diagnose prostate cancer is no exception. The indications of prostate biopsy depend on elevated PSA level, abnormal DRE findings, questionable lesions on TRUS and suspected imaging on mpMRI. Prostate biopsy is often performed via either transperineal access or transrectal access. There is no significant difference between this two approaches over the detection rate of prostate cancer [29, 30]. However, compared with transperineal procedure, transrectal protocol owns several outstanding merits: less painful, no need to undergo spinal and general anesthesia for patients as well as easy to master for clinicians [31, 32]. With regards to potential complications, except rectum bleeding, the risk of fever, urethral bleeding and urine retention in transrectal approach is also equivalent to it in transperineal way. Thus, transrectal procedure is more fashionable and convenient (Figure 5).

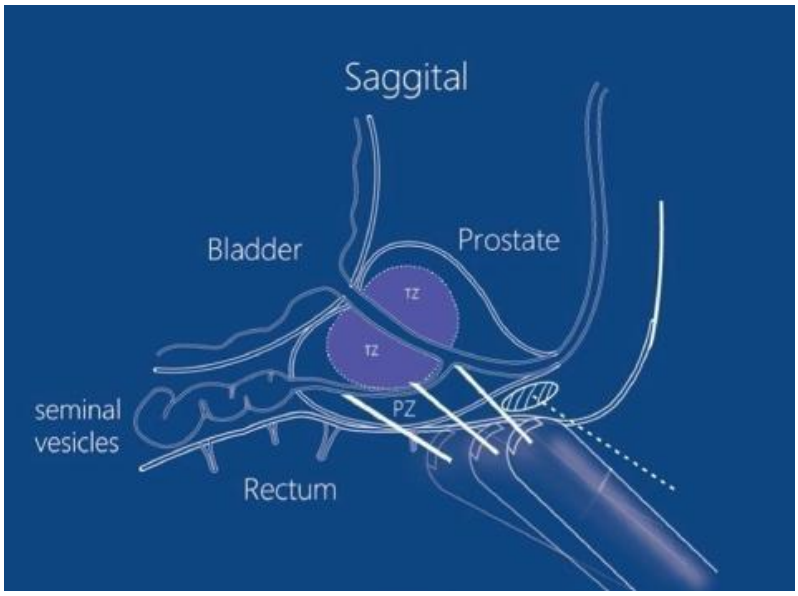


Figure 5. Diagram of transrectal prostate biopsy approach (source from Guo LH et al [33])

As mentioned previously prostate cancer possessing the characteristics of multifocal

growth and significant heterogeneity at various levels from genomic alterations to morphological, spatial, and clinical diversity, so multi-core sampling strategy should be utilised in prostate biopsy [5]. At present, 12-core systematic biopsy which schematically samples the medial and lateral areas of three planes from apex to base in both left side and right side of prostate is strongly recommended (Figure 6).

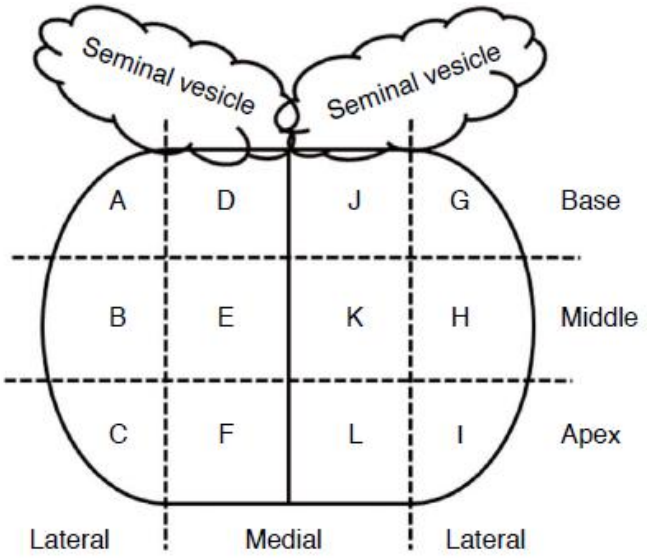


Figure 6. Diagram of 12-core systematic biopsy (source from You MW, et al [34])

1.3.5.2 Precision medicine and deficiency of systematic biopsy

The concept of precision medicine is that health care is tailored to individuals [35]. Briefly speaking, as US former president Obama said, precision medicine conveys right medical decisions to the right patients in right time instead of delivering universal standards of either diagnosis or treatment to every patient. As a result, modern medicine is becoming more precise and personal. During my doctoral study, I have advanced some new reflections and ideas concerning the application of liquid biopsy for patients with renal cancer, which has been published in the platinum journal, European Urology, and also concentrated on the feasibility of non-whole-gland HIFU, as a type of focal therapy including hemiablation and zonal ablation, for management of localised prostate cancer, which have been submitted to Journal of Endourology and now is in the status of major revision. Both of them are the embodiment of precision medicine and individual medicine (Appendix 1, 2). As

mentioned above, it is the standard procedure that 12 cores are taken from the prostate when conducting a transrectal systematic biopsy in the diagnostic pathway of prostate cancer. This fashion is apparently a randomised, non-targeted, and imprecise approach. Additionally, it is difficult for the needle of systematic biopsy to arrive at the apex and anterior part of the prostate resulted from the restriction of puncture angle as well as the volume of prostate. This leads to some apex tumors to be easily missed in systematic biopsy path. The drawbacks of systematic biopsy can be inferred from the diagram of this procedure (Figure 5). The detection rate of prostate cancer could increase by 9.3% if additional dorsal apex is examined during the procedure of systematic biopsy [36]. Likewise, in addition to apex and anterior areas, lesions located in midline and extreme base are also easily to be missed and undersampled in 12-core systematic biopsy [37]. Another bias which cannot be ignored is that there may be a slight difference among operators for sampling the same area. What is more worthy mentioning is that systematic biopsy might detect more indolent and clinically insignificant prostate cancers which is not supposed to be radically treated and is associated with overdiagnosis and overtreatment [38, 39].

1.3.5.3 MRI/TRUS fusion targeted biopsy (TB)

With mpMRI integrated into biopsy protocol, mpMRI/TRUS fusion targeted biopsy is becoming appealing and available. mpMRI makes identification of prostate cancer precise rather than blind and aimless. MRI/TRUS fusion targeted biopsy is a new method that uses software to fuse the preoperative mpMRI imaging with real-time transrectal ultrasound to target related lesions and areas for patients who have suspected mpMRI imaging. The specific protocol of MRI/TRUS fusion targeted biopsy will be further elaborated in the part of Material and Methods. MRI/TRUS fusion targeted biopsy has shown very good prospects in several trials. Prostate MRI Imaging Study [40], also called PROMIS, a multicentric, paired-cohort, prospective study, took template prostate mapping biopsy as reference and compared underlying mpMRI-based biopsy strategy with transrectal systematic biopsy strategy, finding that mpMRI-based targeted biopsy appeared to be more sensitive (93% vs 48%), but less

specific (41% vs 96%) for detecting clinically significant prostate cancer (csPCa). Based on this, 27% of patients could be avoided to undergo prostate biopsy and 5% of clinically insignificant prostate cancers would be ruled out if using mpMRI as triage test among biopsy-naive patients. Moreover, MRI/TRUS fusion targeted biopsy pathway has been demonstrated to have higher detection rate of clinically significant prostate cancer than systematic biopsy in patients undergone repeated biopsy after previous negative biopsy, and over 38.9% of pathological upgrading were also observed in MRI/TRUS fusion targeted biopsy in contrast with systematic biopsy [41]. Therefore, MRI/TRUS fusion targeted biopsy is a reliable method and sounds like the ideal fashion for diagnosis of prostate cancer.

1.4 Controversies over biopsy strategies in patients with positive mpMRI results

Obviously, patients with negative results on preoperative mpMRI, but continually under suspicion of prostate cancer would undergo systematic biopsy. However, if the patients are suspected with concerning lesions on mpMRI, the strategy of using mpMRI fusion targeted biopsy will arouse some disputes on whether a concurrent systematic biopsy should be performed in the same session. A very enthralling randomised clinical trial, PRECISION [42] presented in EAU early this year, provides the evidence that only performing MRI/TRUS fusion targeted biopsy has great superiority for detecting clinically significant prostate cancer, indicating that patients with positive mpMRI results could only undergo MRI/TRUS fusion targeted biopsy. Another randomised clinical trial, omitting systematic biopsy and only conducting MRI/TRUS fusion targeted biopsy achieves 50.5% of detection rate of overall prostate cancer and 43.9% of detection rate of clinically significant prostate cancer versus 29.5% and 18.1% in standard pathway based on systematic biopsy, respectively [43]. Besides, psychological burden of patients cannot be neglected when adding a 12-core systematic biopsy in MRI-based diagnostic strategy. A significant number of patients with positive lesions on mpMRI who come to our clinic are always afraid of the number of needle cores to be taken from prostate and the potential severe

post-biopsy complications, and wondering whether they could only undergo MRI/TRUS fusion targeted biopsy, but without missing any malignancies, at least under the same diagnostic potency. Hence, MRI/TRUS fusion targeted biopsy alone scheme will be an ideal method if it could embrace as comparable the cancer detection rate as MRI/TRUS fusion targeted biopsy with systematic biopsy. However, other studies suggest that the efficiency of MRI/TRUS fusion targeted biopsy has been overestimated and it does not increase the detection rate of both overall prostate cancer and clinically significant prostate cancer [44, 45]. In addition, it is remarkable that MRI/TRUS fusion targeted biopsy also has defect to reach apex lesions, especially in dorsolateral region, and even more than 16% of clinically significant prostate cancers will be missed in MRI/TRUS fusion targeted biopsy. Surprisingly, 80% of cribriform cancers (Gleason pattern 4) are not identifiable in MRI/TRUS fusion targeted biopsy fashion [46-48]. They assert that MRI/TRUS fusion targeted biopsy cannot shake and replace systematic biopsy in the diagnosis of prostate cancer for patients with positive mpMRI results and incorporating with systematic biopsy could yield better outcomes than only performing MRI/TRUS fusion targeted biopsy [49]. This is the reason why most urologists are still conservative and adopt MRI/TRUS fusion targeted biopsy together with 12-core systematic biopsy in patients with positive results on mpMRI, so is our department.

1.5 Scientific questions of the study

In summary, the biopsy strategies for patients with positive mpMRI results are still unclear and controversial. Is MRI-based diagnostic pathway really superior to standard pathway in the aspect of oncological outcomes and complications? Can we omit the systematic biopsy for patients with positive mpMRI results? If it is not applicable in all cases, is it possible to only carry out MRI/TRUS fusion targeted biopsy for special cases from the point of view of mpMRI parameters of lesions? What influence factors are together contributing to the detection rate of clinically significant prostate cancer in MRI/TRUS fusion targeted biopsy approach or MRI/TRUS fusion targeted biopsy combined with systematic biopsy approach? How

to balance the detection rate of clinically significant prostate cancer and the detective risk of clinically insignificant prostate cancer for those patients?

1.6 Objectives and framework of the study

Based on the current clinical strategy of prostate biopsy, to evaluate the possibility of omitting systematic biopsy and verify whether only performing MRI/TRUS fusion targeted biopsy is sufficient for the diagnosis of prostate cancer in particular cases with positive mpMRI results, I propose to: (1) analyse the techniques itself of both MRI/TRUS fusion targeted biopsy and systematic biopsy; (2) explore the oncological efficacy and agreement, as well as complications of patients between MRI-based biopsy pathway (MRI/TRUS fusion targeted biopsy plus systematic biopsy) and standard biopsy pathway (systematic biopsy only) in order to verify the effectiveness and safety of MRI-based biopsy strategy; (3) identify the relative contributions of MRI/TRUS fusion targeted biopsy alone (TB), systematic biopsy alone (SB) and combined scheme (TB+SB) for the detection of prostate cancer as well as clinically significant prostate cancer in all patients who underwent MRI/TRUS fusion targeted biopsy combined with 12-core systematic biopsy; (4) assess the relevancy between MRI parameters and the detection rate of clinically significant prostate cancer in MRI/TRUS fusion targeted biopsy alone scheme and combined scheme, relatively; (5) establish multivariate logistic regression models for the purpose of determining all the possible influence factors contributing to the detection of clinically significant prostate cancer in MRI/TRUS fusion targeted biopsy alone approach and MRI/TRUS fusion targeted biopsy along with systematic biopsy approach individually. In summary, we hope to sketch out some rough criteria which might be the reference to select suitable patients with suspicious lesions on mpMRI to undergo the MRI/TRUS fusion targeted biopsy without additional 12-core systematic biopsy.

2 Material and Methods

2.1 Patients selection

A consecutive series of cases suspected with prostate cancer who underwent prostate biopsy from January 2017 to March 2018 in our centre, Diakonie Klinikum Stuttgart, were considered as targeted population in this retrospective study. Patients without diagnosis of prostate cancer previously can be enrolled in this study. Patients were excluded if they had evidence of metastases at diagnosis. All the participants at least met one of the following indications of prostate biopsy: raised serum PSA level (≥ 4ng/ml); abnormal digital rectal examination; imaging abnormality on either TRUS or mpMRI. In total, 272 patients fulfilling the criteria above were recruited in this retrospective study, of which 139 patients with positive mpMRI results underwent MRI/TRUS fusion targeted biopsy followed by a 12-core systematic biopsy approach (MRI group), and the rest of 133 patients without suspicious mpMRI scan only underwent 12-core systematic biopsy approach (Standard group). In addition to mpMRI-related outcomes in MRI group, serum PSA value, prostate volume, PSA density (PSAD), family history of prostate cancer and prior negative biopsy status were also assessed as basic demographics in both MRI group and standard group. Of note, prostate volume was calculated by ultrasound system automatically through elliptic evaluation (diameter of height × diameter of width × diameter of length × 0.52) in my study.

2.2 The procedure of systematic biopsy

All the patients had a physical examination, a blood testing as well as an urine testing, and signed the informed consent prior to the prostate biopsy. Patients with blood coagulation disorders, acute infectious disease, etc. were not the suitable candidates for prostate biopsy. Oral antibiotic prophylaxis (ciprofloxacin 500mg) and a certain extent of bowel preparation one day before the prostate biopsy are helpful and necessary for patients. At the beginning of the procedure, the patient was placed in the left lateral position and the digital rectal examination was performed to evaluate the

tone of rectum and the texture of prostate as well as relax the anal sphincter slightly. After ultrasound probe was inserted into the rectum, we could get access to the prostatic ultrasonic imaging and measure the volume of prostate as well. After that, under periprostatic local anesthesia with 10ml scandicaine, a reusable biopsy gun with 18-gauge spring-driven needle (Bard, Arizona, USA) was used to perform the biopsy. The whole procedure was guided and monitored by real-time transrectal ultrasound with the imaging of both sagittal and axial plane of the prostate. 12 cores were obtained according to the standard scheme which has been depicted in Figure 6. Prostate biopsy cores from different areas were separately labeled and fixed with formalin solutions in small containers, and then embedded with paraffin. Once more digital rectal examination would also be routinely performed after the whole procedure. Oral antibiotic ciprofloxacin needed to be taken for another three days in our protocol.

2.3 Multiparametric Magnetic Resonance Imaging

mpMRI was performed mostly with 3Tesla scanner without using endorectal coils (Siemens, Erlangen, Germany), only eight patients was scanned with 1.5 Tesla MRI. T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) sequences were normally interpreted and reported compliant with Prostate Imaging-Reporting and Data System (PI-RADS) guideline in each patient who underwent mpMRI scan. The mpMRI imaging was interpreted by three experienced senior attending radiologists (Oberarzt) who have been engaged in MRI diagnosis of prostate cancer for at least four years. The suspicious regions of interest (ROIs) were marked and assigned with PI-RADS score individually by radiologists.

2.4 The procedure of MRI/TRUS fusion targeted biopsy

MRI/TRUS fusion targeted biopsy was performed with software registration method (Hi-RVS/Hitachi, Tokyo, Japan). The lesions scored of PI-RADS 3, 4, or 5 would be carried out with MRI/TRUS fusion targeted biopsy. Preoperative preparation, posture,

and anesthesia of patients were the same with 12-core systematic biopsy. After mpMRI imaging was imported into ultrasound machine, anatomical landmarks including lower margin of pubic bone and membranous urethra could be used to help urologists overlap the imaging of preoperative mpMRI imaging with the imaging of real-time TRUS. Typically, at least two cores would be taken from each suspicious ROI contoured by radiologists on preoperative mpMRI imaging, except seven ROIs sampled with only one needle core. MRI/TRUS fusion targeted biopsy was prior to 12-core systematic biopsy in all patients with positive mpMRI results.

2.5 Pathology

Prostate specimens were reviewed by dedicated pathologists in the same clinic. Each core was reported dividedly and had its own diagnosis in the pathological report. General assessment including gross length of single core and its location, as well as microscopic examination were performed in each patient. When it comes to the diagnosis of prostate cancer, some precancerous pathological lesions containing high grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) involved in the core should also be described if we cannot entirely diagnose it as benign tissue. In addition to pathological type, Gleason score (GS) consisting of primary and secondary Gleason grade, Gleason group based on ISUP 2014 consensus, and the number of positive core as well as cancer involvement per core needed to be recorded in tumor patients. In the current study, clinically significant prostate cancer (csPCa) was defined using the following three criteria: PROMIS criterion (GS ≥ 4+3 or maximum cancer core length (CCL) ≥ 6 mm) [40]; START criterion (GS ≥7 or cancer core length (CCL) ≥5 for GS =6) [22]; PI-RADS criterion (GS ≥ 7) [21, 50]. The definition of clinically insignificant cancer is GS = 6 or ISUP =1.

2.6 Outcomes assessment

2.6.1 Oncological outcomes

The detection rate of prostate cancer and the detection rate of clinically significant

prostate cancer were calculated in this study. Based on this, diagnostic efficiency and consistency were mainly assessed to compare different prostate biopsy strategies for diagnosis of prostate cancer. Moreover, MRI parameters involved in the detection of prostate biopsy would also be evaluated individually in this study. Furthermore, all the predictors related to the detection rate of clinically significant prostate cancer in each prostate biopsy approach were also identified in the analysis.

2.6.2 Complications

All the patients were observed for underlying biopsy-related complications including macrohematuria, urinary tract infection, fieber, urine retention and vasovagal reaction. For macrohematuria, we did not count transient mild hematuria, only one time after biopsy procedure, as macrohematuria. Patients were told that they did not necessarily come to ambulance if hematuria was just one time without other symptoms after prostate biopsy. Analyses on complications were carried out for patients in both MRI group and standard group.

2.7 Statistical analysis

The mean differences of continuous variables between three groups or between different biopsy schemes were compared using One-way ANOVA in current study. T-test was performed to assess the difference of continuous variables between two groups, while Chi-square or Fisher exact test was used for comparison of proportions of categorical variables between two groups. In addition, we fitted two binary logistic regresssion models with the thresholds of $\alpha_{entry}=0.05$ and $\alpha_{removal}=0.1$ to evaluate the correlation between potential risk factors and the detection rate of clinically significant prostate cancer respectively in different biopsy strategies. All data were analysed using SPSS software 21.0. *p* value no more than 0.05 was considered statistically significant.

3 Results

3.1 The length of single core in systematic biopsy

From January 2017 to March 2018, a total of 272 patients undergone prostate biopsy in Diakonie Klinikum Stuttgart fulfilling the inclusive criteria were enlisted in this research. MRI/TRUS fusion targeted biopsy followed by systematic biopsy was used in 139 patients with suspicious areas on mpMRI and systematic biopsy alone was applied in 133 cases without positive mpMRI results. We first analysed the biopsy technique itself from the perspective of the length of single core taken from the prostate for the purpose of optimising the biopsy strategy, for Iczkowski and his colleagues have addressed the length of single core sampled by biopsy played an important role on the detection of prostate cancer [51]. Figure 6 and Figure 7 exhibited the length of single core for systematic biopsy in standard group and the average length of four cores in apex, middle and base level for systematic biopsy in standard group, respectively. Apart from the needle core of right apex, there was no statistically significant difference in the length of single core between the other 11 cores (p=0.089). In addition, we found a very interesting phenomena that the length of apex core was shorter than the length of middle or the length of base core no matter in medial or lateral line on both lobes, though its difference was not statistically significant. The average length of four apex cores including right apex, right apex lateral, left apex and left apex lateral was obviously shorter than that in the middle plane (p=0.000) or that in the base plane (p=0.001). Nevertheless, the average length of cores in the middle level was comparable to that in the base level (p=0.068).

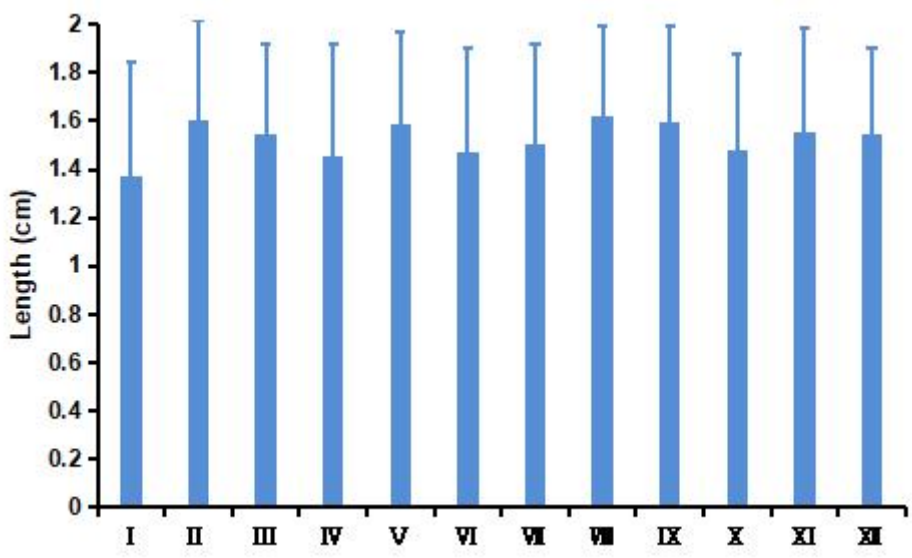


Figure 7. Gross length of each core for systematic biopsy in standard group. I: right apex; II: right middle; III: right base; IV: right apex lateral; V: right middle lateral; VI: right base lateral; VII: left apex; VIII: left middle; IX: left base; X: left apex lateral; XI: left middle lateral; XII: left base lateral. I to III represent cores taken from the right medial line and VII to IX are the cores sampled from the left medial line.

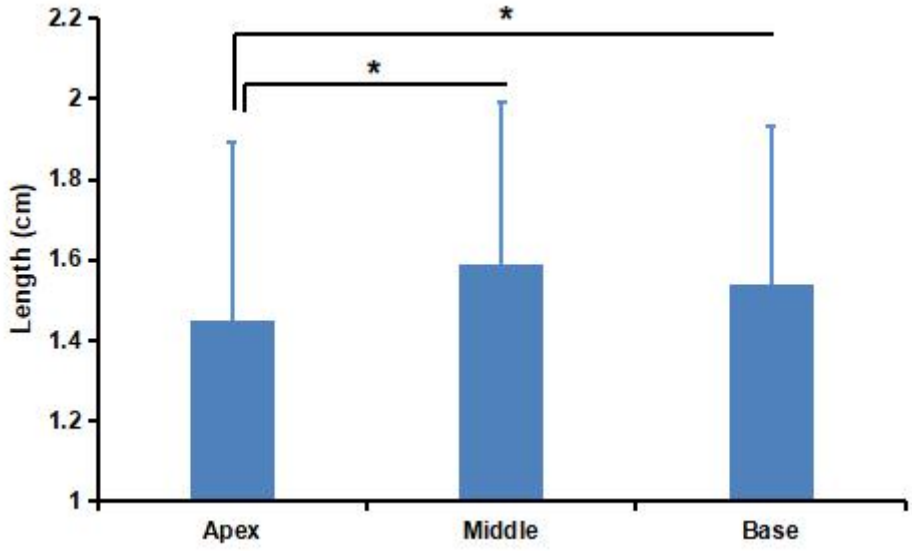


Figure 8. Average length of cores in three planes of prostate in standard group

We further expanded the sample size to all patients who underwent the systematic biopsy in both MRI group and standard group, and the results were the same as the analyses concerning only the patients from the standard group. The length of single core in right apex, right apex lateral or left apex lateral was markedly below the length of single core in any other nine sites, and the length of these nine cores was similar to

each other (p=0.086) (Figure 8). Equally, the average length of either the middle cores (p=0.000) or the base cores (p=0.000) was longer than the length of the apex cores, but no statistical differences were shown between the average length of middle cores and the base cores (p=0.675) (Figure 9).

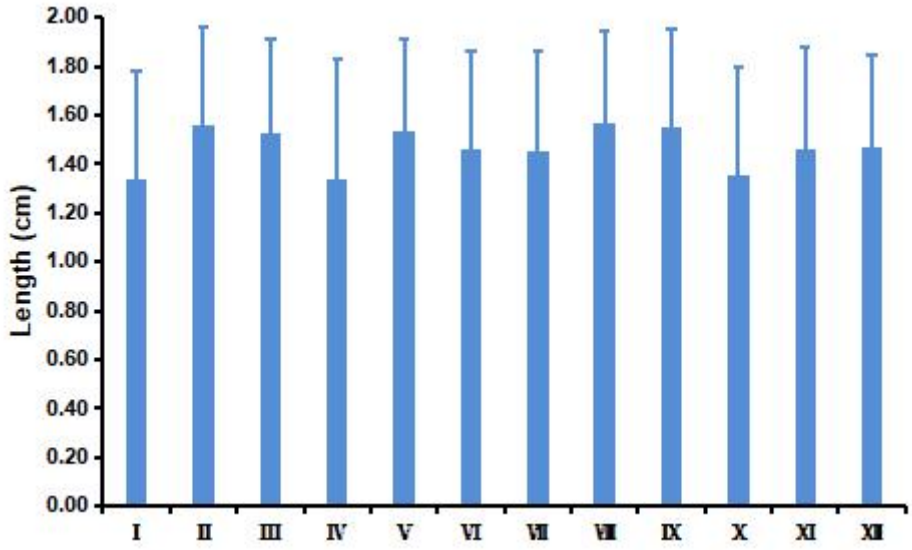


Figure 9. Gross length of each core for systematic biopsy in all patients. I: right apex; II: right middle; III: right base; IV: right apex lateral; V: right middle lateral; VI: right base lateral; VII: left apex; VIII: left middle; IX: left base; X: left apex lateral; XI: left middle lateral; XII: left base lateral. I to III represent cores taken from the right medial line and VII to IX are the cores sampled from the left medial line.

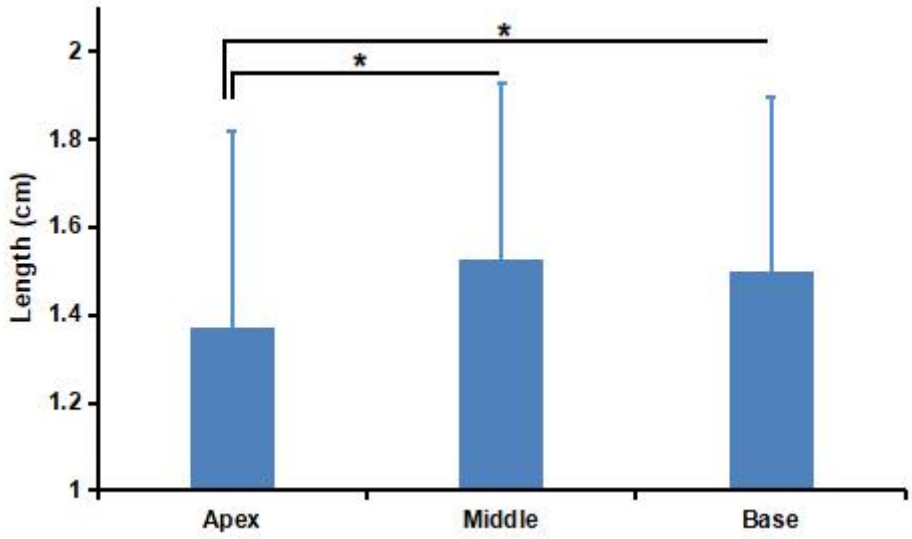


Figure 10. Average length of cores in three planes of prostate in all patients

3.2 Baseline characteristics, oncological outcomes and complications of patients

3.2.1 Baseline characteristics

The demographics of patients in MRI group and standard group were listed in Table 1. Age at biopsy (p=0.052), PSA (p=0.919), prostate volume (p=466), PSAD (p=0.490), family history of prostate cancer (p=0.768) and digital rectal examination (p=0.489) did not differ between MRI group and standard group. However, more patients in MRI group seem to have previously experienced a negative biopsy than patients in standard group (27.3% versus 17.3%; p=0.047).

Table 1. Baseline characteristics for patients in MRI group and standard group

Variables	Standard group	MRI group	*p* value
Number	133	139	
Age at biopsy (year)	69.62±8.01	67.76±7.73	0.052
PSA (ng/ml)	10.24±9.90	10.12±9.23	0.919
Prostate volume (ml)	51.38±23.78	53.62±26.57	0.466
PSA density	0.23±0.23	0.22±0.20	0.490
Family history of prostate cancer (%)			0.768
Yes	3 (2.3)	5 (3.6)	
No	130 (97.7)	134 (96.4)	
Digital rectal examination (%)			0.489
Suspect	62 (46.6)	59 (42.4)	
Normal	71 (53.4)	80 (57.6)	
Prior negative biopsy (%)			**0.047**
Yes	23 (17.3)	38 (27.3)	
No	110 (82.7)	101 (72.7)	

3.2.2 Oncological outcomes

The oncological outcomes were summarised in Table 2. The detection rates of benign tissue, atypical small acinar proliferation (ASAP), high grade prostatic intraepithelial neoplasia (HGPIN) and malignancy were comparable between this two groups (p=0.294), with 36.8%, 3.8%, 4.5% and 54.9% of 133 patients belonging to the standard group, respectively and 27.9%, 2.1%, 4.3% and 65.7% of 139 cases in the MRI group, respectively. It was in line with the paralleled findings of detection rate of overall prostate cancer between this two groups (54.9% versus 66.2%; p=0.057). Of

them, only one patient in MRI group presented both precancerous lesion ASAP and precancerous lesion HGPIN. Detected prostate cancers classified by Gleason score were also comparable between these two groups (p=0.145). The detection rate of clinically significant prostate cancer identified in MRI group based on PROMIS criterion (p=0.043) or START criterion (p=0.038) was apparently higher than it recorded in standard group, though no statistical difference was found between these two groups according to PI-RADS criterion (p=0.084). In terms of clinically insignificant prostate cancer, 14.4% of clinically insignificant prostate cancers were reported in MRI group, which was similar to 13.5% of it in standard group. Other pathological factors like the number of positive cores per patient and the total number of cores per patient in MRI group were certainly more than that in standard group due to more cores sampled in MRI group (p=0.022; p=0.000). Nevertheless, the average length of cores in MRI group was shorter than it in standard group (p=0.000). No significant differences were found regarding total cores positive for cancer (p=0.327) and maximum length of cancer core (p=0.335) when comparing these two groups. Accordingly, MRI/TRUS fusion targeted biopsy together with systematic biopsy could achieve excellent oncological results for patients in MRI group.

Table 2. Oncological outcomes for patients in MRI group and standard group

Variables	Standard group	MRI group	*p* value
Prostate biopsy outcome (%)			0.294
Benign tissue	49 (36.8)	39 (27.9)	
ASAP	5 (3.8)	3 (2.1)	
HGPIN	6 (4.5)	6 (4.3)	
Malignancy	73 (54.9)	92 (65.7)	
Gleason score (%)			0.145
3+3 (ISUP1)	18 (24.7)	20 (21.7)	
3+4 (ISUP2)	17 (23.3)	21 (22.8)	
4+3 (ISUP3)	8 (11.0)	23 (25.0)	
8 (ISUP 4)	12 (16.4)	15 (16.3)	
> 8 (ISUP 5)	18 (24.7)	13 (14.1)	
Total cancer detection (%)	73 (54.9%)	92 (66.2)	0.057
Clinically significant cancer[#1] (%)	48 (36.1)	67 (48.2)	**0.043**
Clinically significant cancer[#2] (%)	56 (42.1)	76 (54.7)	**0.038**
Clinically significant cancer[#3] (%)	55 (41.4)	72 (51.8)	0.084
Clinically insignificant cancer[*] (%)	18 (13.5)	20 (14.4)	0.839

Average length of core (mm)	15.26±2.17	14.30±2.05	**0.000**
Maximum length of cancer core (mm)	8.17±6.69	7.26±4.97	0.335
Number of positive cores per patient	2.59±3.53	3.68±4.22	**0.022**
Total number of cores per patient	12.19±0.85	16.29±1.93	**0.000**
Total core positive for cancer (%)	344/1621 (21.2)	511/2267(22.5)	0.327

[#1]PROMIS criterion (GS ≥ 4+3 or maximum cancer core length (CCL) ≥ 6 mm); [#2]START criterion (GS ≥7 or cancaer core length (CCL) ≥5 for GS =6); [#3]PI-RADS criterion (GS ≥7); [*]Criteria (GS =6)

3.2.3 Complications of patients

Adding systematic biopsy in MRI group actually did not increase the total incidence of complications compared to standard group (p=0.431). Complications in MRI group and standard group were reported in Table 3. Macrohematuria was the most common complication in standard group, while urinary tract infection occurred mostly in MRI group. Besides, macrohematuria and fever were observed simultaneously in one case in each group. There was also one patient combining urinary tract infection with fever in both groups. One patient developed an acute epididymitis in standard group because of severe urinary tract infection. It must be noticed that vasovagal reaction occurred in two cases in standard group and one case in MRI group, even vasovagal syncope appearing in one case during the biopsy procedure, but all of them recovered after urologist stopped operating and carried out cardio-pulmonary resuscitation (CPR). Thus, the complications for the strategy of MRI/TRUS fusion targeted biopsy followed by systematic biopsy were acceptable compared with standard biopsy strategy.

Table 3. Complications of patients in MRI group and standard group

Variables	Standard group	MRI group	*p* value
Number of complications (%)	12 (9.0)	9 (6.5)	0.431
Macrohematuria	4	1	
Urinary tract infection	3	3	
Fever	2	2	
Urine retention	1	2	
Vasovagal reaction	2	1	

3.3 Efficiency of TB, SB, and TB+SB scheme for patients in MRI group

Among 139 patients with positive mpMRI results who were initiated on MRI/TRUS

fusion targeted biopsy followed by systematic biopsy, a separate analysis was conducted over the contribution of targeted biopsy alone (TB), systematic biopsy alone (SB) and targeted biopsy plus systematic biopsy (TB+SB) to the detection of prostate cancer, respectively. All the data were presented in Table 4. For the detection rate of overall prostate cancer, TB combined with SB was superior to TB alone or SB alone scheme (p=0.050). The detection rate of clinically significant prostate cancer was not statistically distinguishable among these three schemes based on three different criteria of clinically significant prostate cancer in my study, though TB+SB scheme is generally held to be able to detect more clinically significant prostate cancers than TB alone or SB alone scheme. It at least hints that besides the small elevated section of clinically significant prostate cancer, an increase in the detection of overall prostate cancer in the scheme of TB plus SB might be resulted from the detection of a large number of clinically insignificant prostate cancers. Interestingly, the discrimination of clinically insignificant prostate cancer among these three schemes were observed neither between TB and TB+SB nor SB and TB+SB, only between TB alone and SB alone. It indicates that SB scheme was more likely to discover clinically insignificant tumor which was indolent, undesired and less progressive compared with TB alone scheme (16.5% versus 6.5%), yet statistically, the union of TB and SB would not enhance the detection rate of clinically insignificant prostate cancer in comparison with TB alone or SB alone scheme in the study. In addition, no statistical difference was shown with respect to the maximum length of cancer core between these three schemes (p=0.080), whereas TB combined with SB could obtain more positive cores in patients with prostate cancer than SB alone or TB alone scheme (3.68 versus 2.40 versus 1.27; p=0.000). Furthermore, TB alone scheme could achieve a relatively longer average length of core than SB alone or TB incorporated with SB procedure (15.78mm versus 14.10mm versus 14.29mm; p=0.000), with the advantage of fewer cores taken from the prostate (4.31 versus 12.00 versus 16.31; p=0.000). In TB alone scheme, it also displayed higher detective efficiency (29.5%), with 177 positive cores taken from gross 599 cores, than SB alone scheme (20.0%), with 334 positive cores obtained from total 1668 cores or TB

consolidated with SB scheme (22.5%), with 511 positive cores sampled from overall 2267 cores. Hence, TB alone scheme might be regarded as an alternative way to TB plus SB scheme in patients with positive mpMRI results according to the oncological efficacy.

Table 4. Oncological efficacy of three schemes for patients in MRI group

Variables	SB alone	TB alone	TB+SB	*p* value
Number	139	139	139	
Prostate biopsy outcome (%)				**0.047**
Benign tissue	47 (33.1)	63 (45.3)	39 (27.9)	
ASAP	5 (3.5)	1 (0.7)	3 (2.1)	
HGPIN	7 (4.9)	3 (2.2)	6 (4.3)	
Malignancy	83 (58.5)	72 (51.8)	92 (65.7)	
Gleason socre (%)				0.469
3+3 (ISUP1)	23 (27.7)	9 (12.5)	20 (21.7)	
3+4 (ISUP2)	15 (18.1)	22 (30.6)	21 (22.8)	
4+3 (ISUP3)	19 (22.9)	21 (29.2)	23 (25.0)	
8 (ISUP 4)	14 (16.9)	11 (15.3)	15 (16.3)	
> 8 (ISUP 5)	12 (14.5)	9 (12.5)	13 (14.1)	
Total cancer detection (%)	83 (59.7)	72 (51.8)	92 (66.2)	**0.050**
Clinically significant cancer[#1] (%)	55 (39.6)	57 (41.0)	66 (47.5)	0.364
Clinically significant cancer[#2] (%)	68 (49.6)	67 (48.2)	84 (60.4)	0.083
Clinically significant cancer[#3] (%)	60 (43.2)	63 (45.3)	72 (51.8)	0.324
Clinically insignificant cancer[*] (%)	23 (16.5)	9 (6.5)	20 (14.4)	**0.028**
Average length of core (mm)	14.10±2.17	15.78±3.62	14.29±2.06	**0.000**
Maximum length of cancer core (mm)	3.58±5.01	3.60±4.61	4.80±5.30	0.080
Number of positive cores per patient	2.40±3.10	1.27±1.54	3.68±4.22	**0.000**
Total number of cores per patient	12.00±0.00	4.31±2.00	16.31±2.00	**0.000**
Total core positive for cancer (%)	334/1668 (20.0)	177/599 (29.5)	511/2267 (22.5)	**0.000**

[#1]PROMIS criterion (GS ≥ 4+3 or maximum cancer core length (CCL) ≥ 6 mm); [#2]START criterion (GS ≥7 or cancaer core length (CCL) ≥5 for GS =6); [#3]PI-RADS criterion (GS ≥7); [*]Criteria (GS =6).

3.4 Consistency of TB and TB+SB scheme for patients in MRI group

Cancer detection and distribution of Gleason score in TB scheme as well as TB plus SB scheme were listed in Table 5. It can be clearly seen that 20 patients identified with prostate cancer in TB plus SB scheme would be missed using only TB scheme, of which nine cases were encountered with clinically significant prostate cancer (Table 6). Among 92 patients with prostate cancer found by TB scheme, six patients with GS 7a, seven patients with GS 7b and three patients with GS 8 were examined to have an upgraded GS after the addition of SB scheme. However, if the patients have been demonstrated with clinically insignificant prostate cancer in TB scheme, additional SB scheme would not upgrade the GS for patients in the same session. Consequently, when adding systematic biopsy after the MRI/TRUS fusion targeted biopsy, the detection rate of clinically significant prostate cancer would increase by 6.5%, but as much as 7.9% risk of more clinically insignificant prostate cancers would be diagnosed at the same time.

Table 5. Cancer yield and GS distribution between TB and TB+SB scheme for patients in MRI group

TB scheme	TB+SB scheme					
	No cancer	GS=6	GS=7a	GS=7b	GS=8	GS>8
No cancer	47	11	5	4	0	0
GS=6	0	9	0	0	0	0
GS=7a	0	0	16	5	0	1
GS=7b	0	0	0	14	6	1
GS=8	0	0	0	0	9	3
GS>8	0	0	0	0	0	8

Table 6. Cancer yield and categorisation by clinical significance between TB and TB+SB scheme for patients in MRI group

TB scheme	TB+SB scheme		
	No cancer	Clinically insignificant Cancer*	Clinically significant cancer#
No cancer	47	11	9
Clinically insignificant cancer	0	9	0
Clinically significant cancer#	0	0	63

#PI-RADS criteria (GS ≥7); *Criteria (GS =6)

3.5 The basic features of all the mpMRI suspicions in MRI group

Of all 139 patients in MRI group, a total of 212 lesions were found on preoperative multiparametric magnetic resonance imaging (mpMRI), including 51 lesions scored for PI-RADS 3, 118 lesions for PI-RADS 4, and 43 lesions for PI-RADS 5 (Table 7). One suspicious region of interest (ROI) was visible in 87 patients and suspicious ROIs ranging from two to four were identified in 34, 15 and 3 patients, respectively. Four lesions were located in anterior fibromusclar zone and ten lesions were measured in central zone. 133 and 65 lesions visualized on mpMRI were sorted to peripheral zone and transitional zone, respectively.

Table 7. Lesions identified by mpMRI in MRI group

Variables	Value
mpMRI PI-RADS score (%)	212
3	51 (24.0)
4	118 (55.7)
5	43 (20.3)
Number of ROI (%)	139
1	87 (62.6)
2	34 (24.5)
3	15 (10.8)
4	3 (2.1)
Location of MRI target (%)	212
AFS	4 (1.9)
CZ	10 (4.7)
TZ	65 (30.7)
PZ	133 (62.7)

AFS: anterior fibromusclar zone; CZ: central zone; TZ: transitional zone; PZ: peripheral zone.

3.6 Efficiency and consistency of TB and TB+SB scheme for all lesions in MRI group

As displayed in Figure 11 and 12, we carried out a similar analysis over the detection of prostate cancer using TB or TB plus SB scheme for all the 212 lesions on mpMRI imaging. Gleason score upgrading was determined in 51 lesions implemented by TB plus SB scheme in comparison with TB alone scheme, about a quarter of the total suspicions on mpMRI (Table 8 and Table 9). TB followed by SB scheme could

increase the detection rate of overall prostate cancer by 24.1% and the detection rate of clinically significant prostate cancer by 12.7% compared to TB alone scheme. However, as much as 11.3% of clinically insignificant prostate cancers were overdiagnosed in TB plus SB scheme as well, which was not expected.

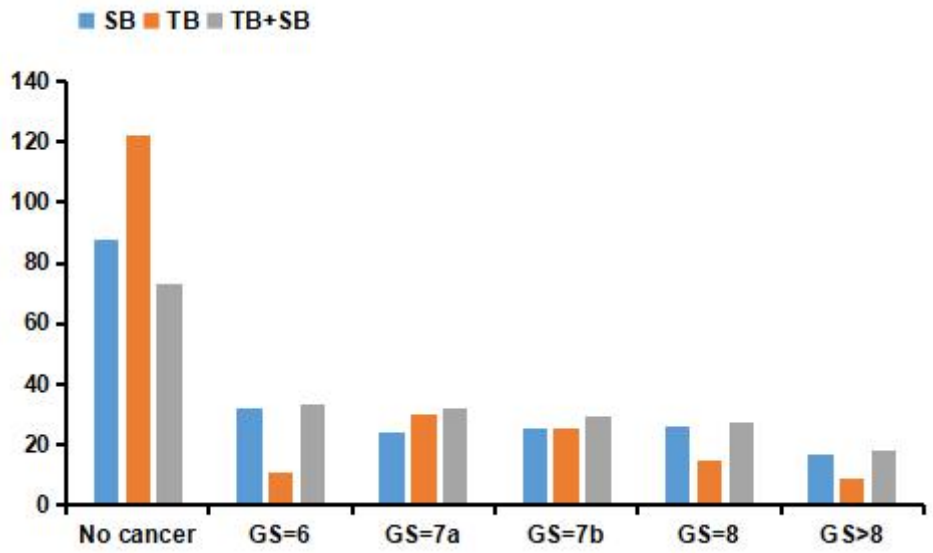


Figure 11. Cancer yield and GS distribution between the three schemes for all lesions in MRI group

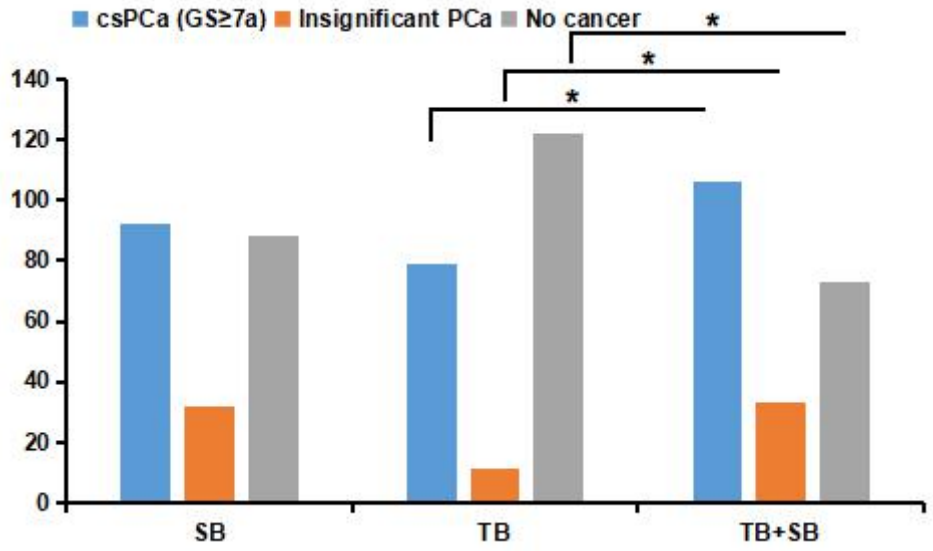


Figure 12. Tumor clinical significance detected between the three schemes for all lesions in MRI group

Table 8. Cancer yield and GS distribution between TB and TB+SB scheme for all lesions in MRI group

TB scheme	TB+SB scheme					
	No cancer	GS=6	GS=7a	GS=7b	GS=8	GS>8
No cancer	73	24	12	6	5	2

GS=6	0	9	1	0	1	0
GS=7a	0	0	19	8	1	2
GS=7b	0	0	0	15	8	2
GS=8	0	0	0	0	12	3
GS>8	0	0	0	0	0	9

Table 9. Cancer yield and categorisation by clinical significance between TB and TB+SB scheme for all lesions in mpMRI group

TB scheme	TB+SB scheme		
	No cancer	Clinically insignificant Cancer*	Clinically significant cancer#
No cancer	73	24	25
Clinically insignificant cancer	0	9	2
Clinically significant cancer	0	0	79

#PI-RADS criteria (GS ≥7); *Criteria (GS =6)

3.7 Relevancy between mpMRI results and the detection of prostate cancer

As discussed above, TB plus SB scheme could definitely detect more prostate cancers, in particular, clinically significant prostate cancers in the same session in MRI group compared with TB alone scheme, but it also bears the risk of detecting considerable numbers of clinically insignificant prostate cancer, which greatly discounts its advantages. As for TB alone scheme, though it is powerful enough for the detection of prostate cancer, it would still miss some cases harbouring clinically significant prostate cancer. Helping to investigate whether in some certain cases TB could be used as an alternative scheme to achieve the identical diagnostic efficiency without missing any clinically significant prostate cancers compared with TB plus SB scheme, we carried out a correlation analysis between mpMRI findings of lesions and the detection of prostate cancer.

The pathological outcomes of patients with one suspicious ROI, two suspicious ROIs, and three or more suspicious ROIs in TB alone scheme and TB plus SB scheme were graphed in Figure 13 and Figure 14. The distribution of Gleason score and detection rate of clinically significant prostate cancer as well as clinically insignificant prostate cancer between TB and TB plus SB scheme were not different from each other no

matter how many ROIs a patient had. It illustrates that the number of ROIs per patient does not appear to be a major affecting factor in picking the optimal biopsy strategy for patients with positive mpMRI results.

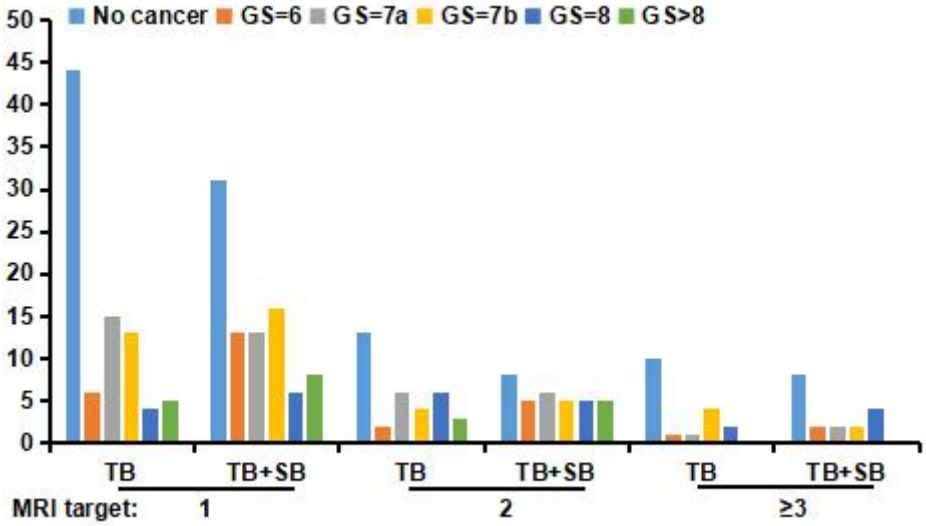


Figure 13. Pathological outcomes classified by the number of ROIs between TB and TB+SB scheme for patients in MRI group

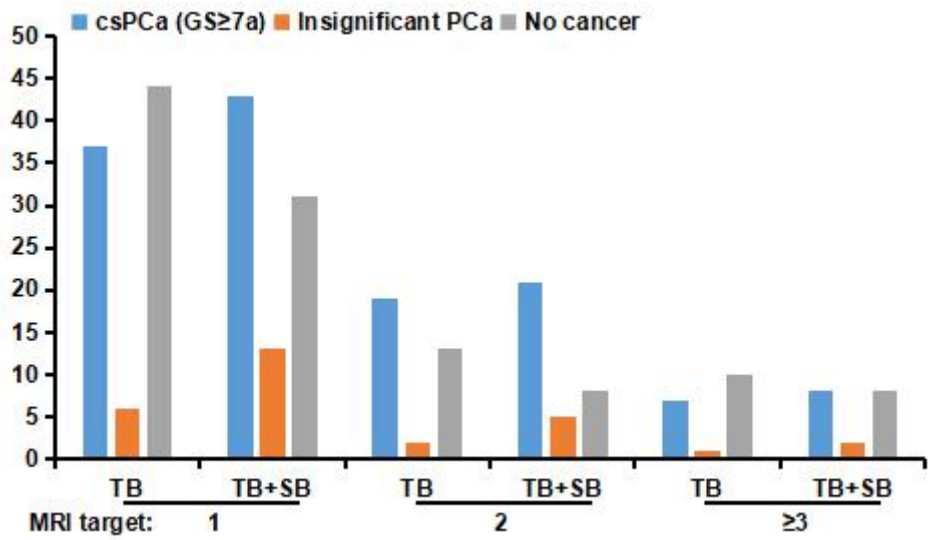


Figure 14. Tumor clinical significance detected in TB and TB+SB scheme in subgroups of number of ROIs for patients in MRI group

Next, an association analysis was made between PI-RADS score of lesions on mpMRI and the detection of prostate cancer (Figure 15 and 16). In lesion with PI-RADS score of 5, TB+SB scheme did not show statistical superiority in the detection rate of overall prostate cancer and the detection rate of clinically significant

prostate cancer compared to TB alone scheme, whilst it did not increase the detection rate of clinically insignificant prostate cancer. Using this combined approach, 14.4% (17 cases) more cases would be identified with clinically significant prostate cancer in PI-RADS 4 subgroup, but 10.2% (12 cases) more patients with clinically insignificant prostate cancer would also be confirmed at the same time. For 51 lesions with PI-RADS score of 3, the detection rate of clinically significant prostate cancer was similar between TB alone and TB plus SB scheme. However, additional systematic biopsy following targeted biopsy could increase the detection rate of clinically insignificant prostate cancer by 13.8% (7 cases) compared with TB alone scheme. Therefore, TB alone scheme has proved pretty good diagnostic efficiency for lesions with PI-RADS 3. To sum it up, when only PI-RADS score was taken into consideration, TB alone scheme could be simply performed for patients with PI-RADS score of 3 and 5, but for patients with PI-RADS score of 4, the selection of biopsy scheme depends on the individual case.

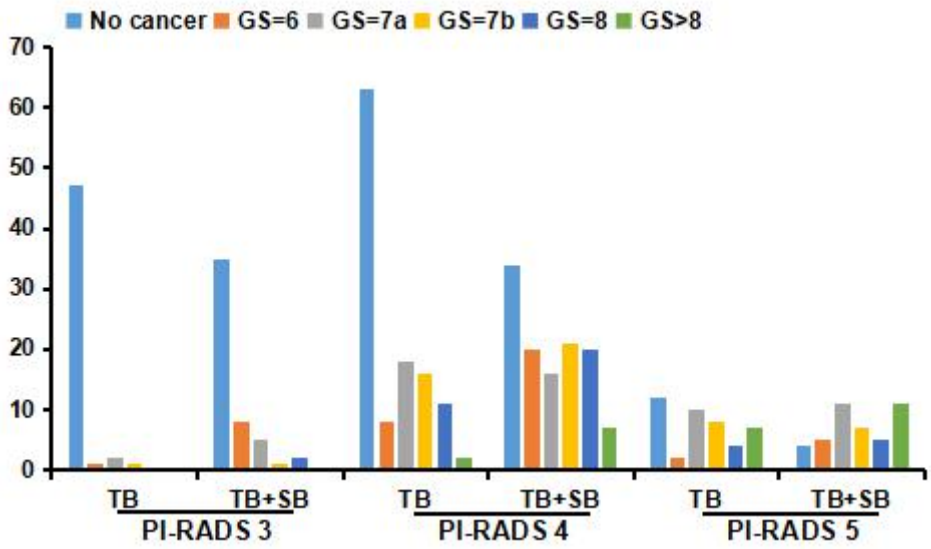


Figure 15. Pathological outcomes classified by PI-RADS score between TB and TB+SB scheme for all lesions in MRI group

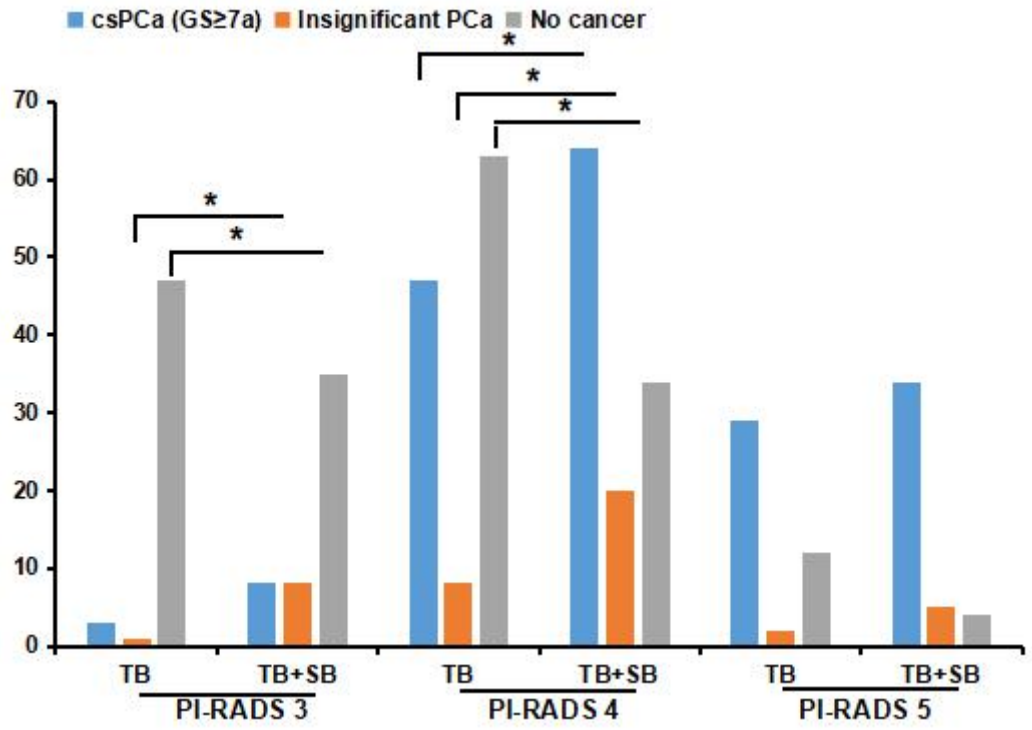


Figure 16. Tumor clinical significance between TB and TB+SB scheme in subgroups of PI-RADS score for all lesions in MRI group

Figure 17 and Figure 18 present the individual diagnostic efficiency of TB alone and TB+SB scheme for lesions located in different prostate regions on mpMRI. For lesions located in central zone or anterior fibromusclar zone, there was no significant difference between TB alone and TB+SB scheme in the detection rate of overall prostate cancer as well as the detection rate of clinically significant prostate cancer. But we cannot genuinely conclude that TB over TB plus SB approach was comparable in dealing with lesions in central zone or anterior fibromusclar zone due to such a small sample size. Of 133 lesions in peripheral zone included in the analysis, combined scheme could detect more prostate cancers than TB alone scheme, with more cases (15 cases; 11.3%) with clinically significant prostate cancer and more patients with clinically insignificant prostate cancer (10 cases; 7.5%) diagnosed, despite that the detection rate of clinically significant prostate cancer and the detection rate of clinically insignificant prostate cancer were not statistically significant between the two schemes. Besides, results were also obtained for lesions in transitional zone. Here clinically significant prostate cancer was found more often in

TB+SB scheme than in TB alone scheme (32.3% versus 15.4%; $p<0.05$) as well as clinically insignificant prostate cancer (18.5% versus 4.6%; $p<0.05$). In conclusion, both TB alone scheme and TB plus SB scheme have their own advantages and disadvantages for the detection of prostate cancer among lesions positioned in peripheral zone or transitional zone. The more clinically significant prostate cancer was detected, the more clinically insignificant prostate cancer would also be detected in the same session. However, TB alone scheme seems to be powerful enough to use for lesions in peripheral zone.

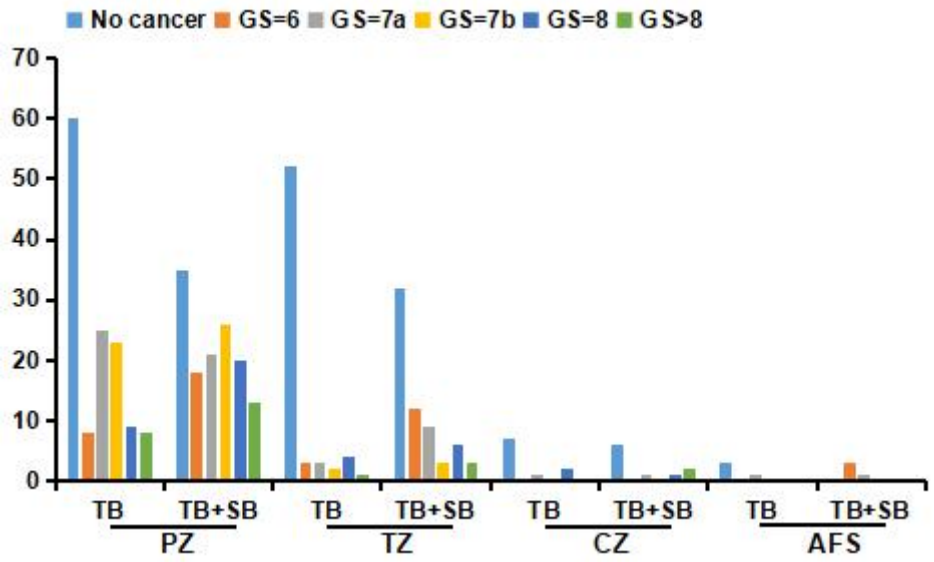


Figure 17. Pathological outcomes classified by location between TB and TB+SB scheme for all lesions in mpMRI group. AFS: anterior fibromusclar zone; CZ: central zone; PZ: peripheral zone; TZ: transitional zone.

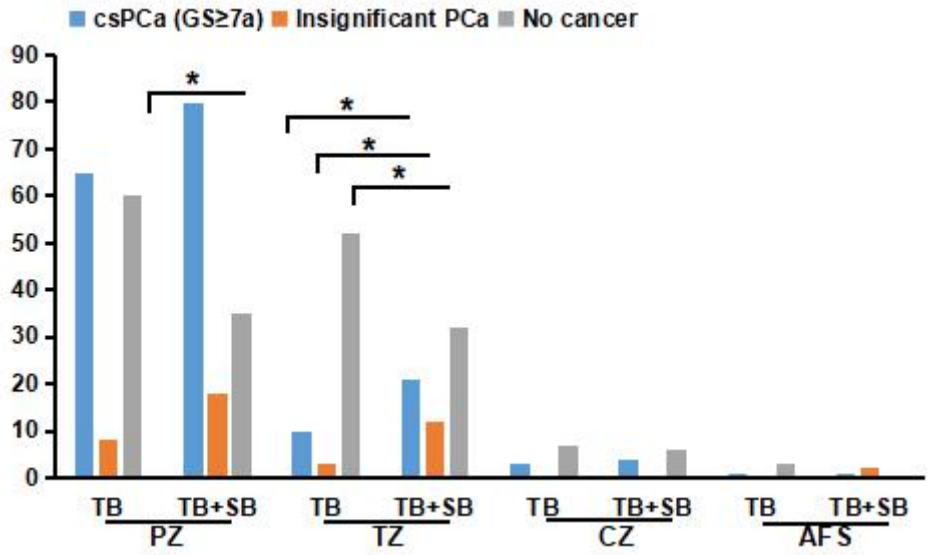


Figure 18. Tumor clinical significance between TB and TB+SB scheme in subgroups of

location for all lesions in mpMRI group. AFS: anterior fibromusclar zone; CZ: central zone; PZ: peripheral zone; TZ: transitional zone.

Further, the influence of the diameter of lesion on the detection of prostate cancer was estimated in both TB and TB+SB scheme as well (Figure 19 and Figure 20). The lesions on mpMRI were divided into three groups based on their diameter: no more than 10mm group, between 10mm and 20mm group, and no less than 20mm group. In group of lesion diameter between 10mm and 20mm, the detection rate of prostate cancer in TB+SB scheme did not differ from it in TB alone scheme from a statistical point of view, with 53 of 76 lesions found in TB+SB scheme and 39 of 76 lesions found in TB alone scheme. The detection rate of clinically significant prostate cancer was also comparable between these two schemes, with 44 of 76 lesions verified in TB+SB scheme and 33 of 76 lesions verified in TB alone scheme. When it comes to the group of lesion diameter no more than 10mm, clinically insignificant prostate cancer was found in 17 (15.6%) out of 109 lesions in combined scheme, while it was found in 4 (3.7%) out of 109 lesions in TB alone scheme ($p<0.05$). Nevertheless, the detection rate of clinically significant prostate cancer in TB+SB scheme would not be higher than the one in TB alone approach. For lesion diameter no less than 20mm, TB scheme was also not inferior to TB+SB approach concerning the detection rate of clinically significant prostate cancer. On the contrary, TB scheme could reduce the detection rate of clinically insignificant cancer compared to TB+SB scheme. In summary, the lesion diameter as a predictor for the detection rate of prostate cancer as well as clinically significant prostate cancer was not different between these two schemes. Added SB approach after TB procedure would just improve the detection rate of clinically insignificant prostate cancer instead of increasing the detection rate of clinically significant prostate cancer when diameter of lesion was subjected to analysis. Accordingly, the diameter of lesion was not a key factor in judging biopsy strategy in patients with positive mpMRI results.

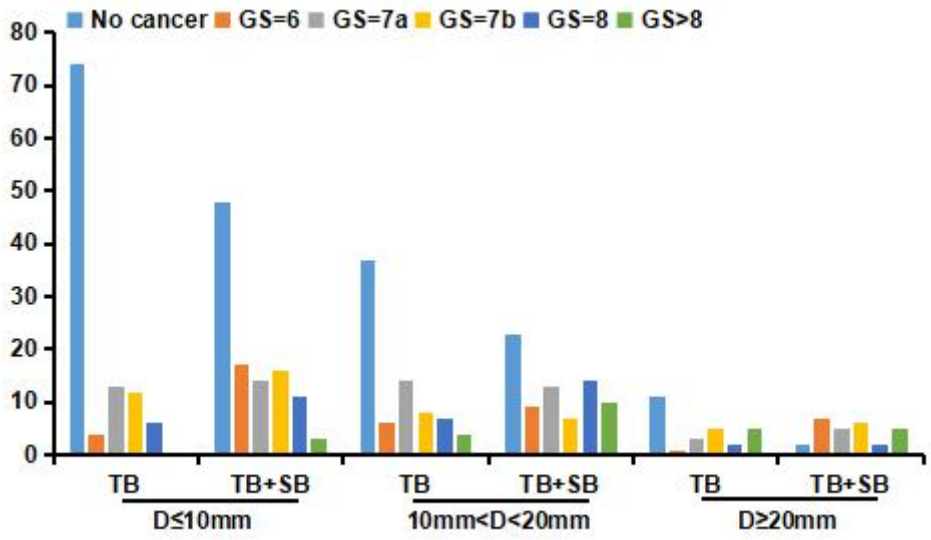


Figure 19. Pathological outcomes classified by diameter of lesion between TB and TB+SB scheme for all lesions in mpMRI group

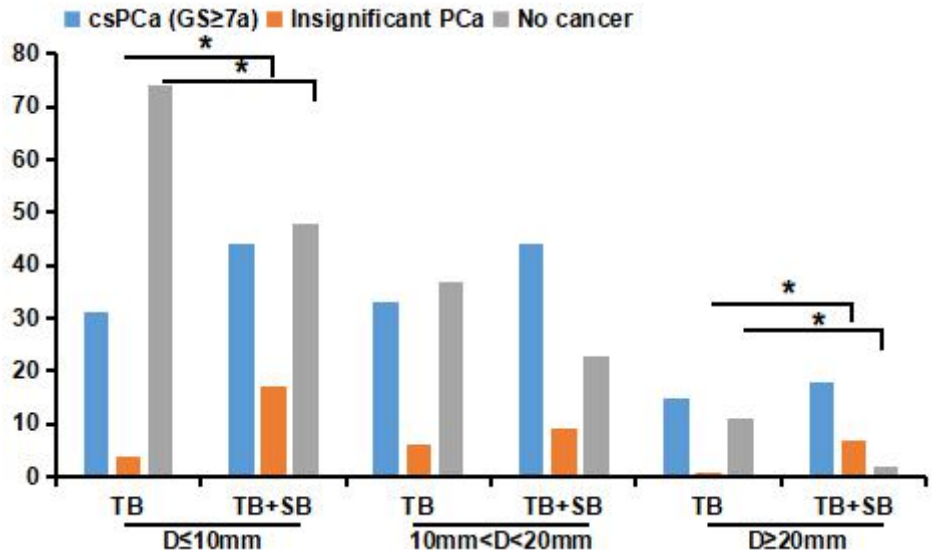


Figure 20. Tumor clinical significance between TB and TB+SB scheme in subgroups of diameter of lesion for all lesions in mpMRI group

3.8 Multivariate logistic regression model for TB and TB+SB scheme

Ultimately, we investigated the predictors for the detection of clinically significant prostate cancer in TB alone and TB plus SB scheme respectively using multivariate logistic regression analysis (Table 10 and Table 11). Out of mpMRI parameters, only PI-RADS score and lesion location, which were different between TB alone scheme and TB+SB scheme to the detection of clinically significant prostate cancer in univariate analysis, were chosen for the multivariate logistic regression analysis. The

multivariate logistic regression analysis showed that the age at biopsy, PSAD, family history of prostate cancer, prior negative biopsy status, PI-RADS score, and the location of lesion were the independent predictors for the detection rate of clinically significant prostate cancer in TB alone scheme, whereas the age at biopsy, PSAD, digital rectal examination, prior negative biopsy status, PI-RADS score, and the location of lesion were independently associated with the detection rate of clinically significant prostate cancer in TB+SB scheme. We could find that digital rectal examination was not identified as an independent predictor in TB alone scheme for the detection of clinically significant prostate cancer, whereas the family history of prostate cancer was not included in the logistic regression model in TB+SB scheme. Apart from the lesions located in peripheral zone, other lesion locations in transitional zone, anterior fibromusclar zone, and central zone were demonstrated to be paralleled for the detection rate of clinically significant prostate cancer between these two schemes. Based on the logistic regression model for TB scheme, lesions with PI-RADS score of 5 (OR=35.787; 95%CI: 6.576-194.739; p=0.000) had higher possibility of being found to harbour clinically significant prostate cancer than lesions with PI-RADS score of 4 (OR=6.567; 95%CI: 1.512-28.516; p=0.012). In TB+SB scheme, there was also a statistically significant increase in the risk of having clinically significant prostate cancer for lesions of PI-RADS score of 5 (OR= 21.918; 95%CI: 5.271-91.148; p=0.000) compared with lesions of PI-RADS score of 4 (OR=3.049; 95%CI: 1.082-8.589; p=0.035). In brief, when we apply prostate biopsy to sample patients with positive mpMRI results, family history of prostate cancer should be given more weight other than digital rectal examination in TB alone scheme. However, digital rectal examination was more likely to account for the detection of clinically significant prostate cancer than family history of prostate cancer in TB+SB scheme.

Table 10. Regression analysis for factors associated with the detection of csPCa in TB scheme

Variables	B coefficient	OR (95% CI)	*p* value
Age at biopsy (year)	0.107	1.113 (1.058-1.170)	0.000
PSAD	2.999	20.061 (2.0655-194.870)	0.010
Family history of prostate cancer			

No	Reference (OR=1.000)		
Yes	2.473	11.853 (1.479-95.011)	0.020
Prior negative biopsy			
Yes	Reference (OR=1.000)		
No	1.219	3.382 (1.383-8.272)	0.008
mpMRI PI-RADS score			0.000
PI-RADS 3	Reference (OR=1.000)		
PI-RADS 4	1.882	6.567 (1.512-28.516)	0.012
PI-RADS 5	3.578	35.785 (6.576-194.739)	0.000
Location of MRI target			0.006
AS	Reference (OR=1.000)		
CZ	1.529	4.613 (0.199-106.881)	0.340
PZ	2.530	12.559 (0.924-170.650)	0.057
TZ	0.879	2.409 (0.164-35.412)	0.521
Constant	-13.538	0.000	0.000

AFS: anterior fibromusclar zone; CZ: central zone; PZ: peripheral zone; TZ: transitional zone.

Table 11. Regression analysis for factors associated with the detection of csPCa in TB+SB scheme

Variables	B coefficient	OR (95% CI)	*p* value
Age at biopsy (year)	0.110	1.116 (1.056-1.180)	0.000
PSAD	3.973	53.130 (4.052-696.718)	0.002
Digital rectal examination			
Normal	Reference (OR=1.000)		
Suspect	0.977	2.692 (1.247-5.661)	0.011
Prior negative biopsy			
Yes	Reference (OR=1.000)		
No	1.749	5.747 (2.408-13.716)	0.000
mpMRI PI-RADS score			0.000
PI-RADS 3	Reference (OR=1.000)		
PI-RADS 4	1.115	3.049 (1.082-8.589)	0.035
PI-RADS 5	3.087	21.918 (5.271-91.148)	0.000
Location of MRI target			0.074
AS	Reference (OR=1.000)		
CZ	1.728	5.628 (0.261-121.262)	0.270
PZ	2.781	16.133 (1.287-202.278)	0.031
TZ	2.155	8.627 (0.646-115.178)	0.103
Constant	-13.644	0.000	0.000

AFS: anterior fibromusclar zone; CZ: central zone; PZ: peripheral zone; TZ: transitional zone.

4 Discussion

4.1 Development of prostate biopsy

It is well known that the prostate is an organ deeply located in the pelvic cavity. Prostate cancer is one of the malignancies lacking of early symptoms and pain. PSA screening is commonly used to predict the possibility of having prostate cancer before identifying the palpable prostate nodule [52-54]. However, histopathology still is the gold standard of tumor diagnosis. The location and volume of the prostate determines the difficulties in obtaining samples. The number and position of needle cores in prostate biopsy has gone through several changes for the sake of better oncological outcomes and less complications. Research and debates concerning the biopsy instruments and the strategy of biopsy are still ongoing. Early in 1988, Ragde and colleagues [55] already addressed that 89 percent of prostate cancers could be detected using a biopsy gun which has been employed as the standard device nowadays, while aspiration biopsy only found 51 percent of cancers in all the specimens of prostate. Prostate biopsy mapping with six cores under the guidance of transrectal ultrasound advanced by Hodge [56] in 1989 firstly provided the concept of "systematic sampling". Systematic sampling was able to reduce observer- and sampling-related errors. On the basis of sextant biopsy, 8-core, 10-core and 12-core prostate biopsy were also widely proposed and employed in the past years [57, 58]. It was reported that 12-core systematic biopsy could maximize the detection rate of prostate cancer as well as improve the accuracy of determining the Gleason score [59]. 12-core systematic biopsy was acknowledged as the standard procedure for all patients before the emergence of mpMRI, amongst whom it must have harboured lesions which could be visualized on mpMRI now.

With the advent of mpMRI, combining conventional T2WI imaging with functional sequences, the likes of DWI and DCE could offset the defect of conventional T2WI imaging of prostate, increasing the detection of prostate cancer, providing more additional information of lesions and avoiding unnecessary prostate biopsy [60-62]. Moreover, the mpMRI imaging is reportedly associated with the pathological results

of postoperative samples acquired from radical prostatectomy, and even could foresee the recurrence of prostate cancer after focal therapy [63, 64]. MRI/TRUS fusion targeted biopsy is the product of prostate biopsy based on mpMRI, which is prevalently used for patients with suspected mpMRI outcomes. This technique allows urologists to target the suspected lesions directly and makes prostate biopsy turn a new page. Nevertheless, most scholars are in favor of combining MRI/TRUS fusion targeted biopsy with systematic biopsy for diagnosis of prostate cancer in patients with suspected mpMRI results. The aim of my study is to identify the role of MRI/TRUS fusion targeted biopsy and systematic biopsy in diagnosis of prostate cancer, respectively and determine the possibility and efficiency using only MRI/TRUS fusion targeted biopsy for those patients.

4.2 Core length and the detection of prostate cancer

To begin with, our results revealed that the length of apex cores was shorter than its corresponding value of the length of middle or base cores when implementing systematic biopsy. It is probably the reason for the low tumor detection rate in apex region using systematic biopsy. As reported, the raised detection rate of prostate cancer was related to a longer length of core [51]. Consequently, low cancer detection rate in apex area is supposed to be the biggest shortcoming of systematic biopsy, in line with some other studies, where additional needle biopsy on apex could increase the cancer detection rate [36, 65, 66].

The results of another comparison did show that the average length of total cores with MRI/TRUS fusion targeted biopsy (TB) followed by 12-core systematic biopsy (SB) was shorter than the one using only 12-core systematic biopsy in my cohort. In addition to the effect of sample size, the length of cores in MRI/TRUS fusion targeted biopsy may be a drag to the overall length of cores in MRI group. This is mainly because lesions in peripheral zone remain easier and more common to be grasped by mpMRI and prostate cancer is apt to occur in the peripheral zone [67], which is hugely close to the rectum. Thus, the length of cores tends to be shorter in MRI/TRUS fusion targeted biopsy. But it is not surprising that the overall cancer detection rate for

patients in MRI group was higher than that in standard group, because targeted biopsy could detect more clinically significant prostate cancers than systematic biopsy due to its high efficiency [68-72]. My study comparing MRI group with standard group concerning the detection rate of clinically significant prostate cancer has also yield the same trends with the detection rate of overall prostate cancer. Hence, MRI-based biopsy is an effective approach to detect csPCa. However, MRI/TRUS fusion targeted biopsy was performed with a concurrent systematic biopsy for patients in MRI group.

4.3 The role of targeted biopsy and systematic biopsy

After identifying the relative contribution of MRI/TRUS fusion targeted biopsy and systematic biopsy in our cohorts (MRI group) and comparing TB plus SB approach with SB approach, we found it to be challenging to select the most suitable approach. Though no significantly statistical difference was demonstrated between TB plus SB approach and TB alone approach regarding the detection rate of clinically significant prostate cancer for patients with positive mpMRI results, the detection rate of csPCa for all lesions in TB combined with SB approach seems to have potential superiority over TB alone approach. We speculate that it actually showed the same trends and results because TB plus SB approach still showed that it had higher efficiency to detect csPCa than TB alone approach among 139 patients in MRI group. The difference is just that there was no statistical significance. However, the detection rate of clinically insignificant prostate cancer in TB plus SB approach was also remarkably higher than that in TB alone approach, both in the analysis for patients and lesions. This implies that elevated detection rate of clinically significant prostate cancer is almost in equal proportion with the increased detection rate of clinically insignificant prostate cancer when comparing TB plus SB approach with TB alone approach, no matter in the analysis for patients (6.5% versus 7.9%) or lesions (12.7% versus 11.3%). Thus, it does not seem to be worth performing combined approach, in the case of TB alone approach having possessed such high efficiency in detecting clinically significant prostate cancer, which at least accounted for approximately 80 percent of total prostate cancer in patients with positive mpMRI results in our study.

But the corresponding fractions of clinically significant prostate cancers would be missed as well if only performing TB alone approach. Moreover, there are some studies, reporting that TB alone approach is not predominant in the detection of clinically significant prostate cancer over SB approach [73], even for the detection of overall prostate cancer [74]. They suggest that additional systematic biopsy would also be needed in MRI-based biopsy strategy, and targeted biopsy cannot completely replace the role of systematic biopsy [75-77].

4.4 MRI parameters and the detection of prostate cancer

In order to shed light on this dilemma, a correlation analysis between mpMRI parameters and the detection rate of clinically significant prostate cancer for TB+SB approach and TB alone approach were performed in this study, respectively. The diameters of lesions on mpMRI for predicting the detection of csPCa was comparable between these two approaches, though lesion diameter was reportedly linked to the risk of prostate cancer and diameter ≥ 15cm was reported to be the best threshold to distinguish the PI-RADS 4 and 5 lesions [78, 79]. The number of ROIs as a predictive factor of clinically significant prostate cancer detected by TB+SB approach was also not different from it identified by TB alone approach, in keeping with previous studies that the number of ROI as variable was not included in the nomogram of MRI-based targeted biopsy strategy for the detection of clinically significant prostate cancer [80, 81].

Moreover, TB alone approach has been demonstrated to have awesome results for yielding clinically significant prostate cancer in PI-RADS 3 lesions or PI-RADS 5 lesions without increasing additional detection of clinically insignificant prostate cancer. Nevertheless, TB+SB approach could provide higher detection rate of clinically significant prostate cancer for PI-RADS 4 lesions. It might be that clinically significant prostate cancer is highly likely to present in PI-RADS 5 lesions, and additional systematic biopsy could not be more supportive, but only raise the detection rate of clinically insignificant prostate cancer. PI-RADS 3 lesions on mpMRI itself featuring equivocality, but with least chance being malignant in all

lesions on mpMRI, the detection rate for prostate cancer detected by targeted biopsy approach or systematic approach was quite low, let alone for clinically significant prostate cancer. But PI-RADS 4 lesions as an intermediate level need contribution of detection from both targeted biopsy and systematic biopsy. Additionally, as Hakozaki showed, targeted biopsy could upgrade Gleason score of PI-RADS 4 lesions compared with systematic biopsy, combination of TB and SB could perform the highest detection rate of clinically significant prostate cancer [82].

Lastly, TB alone approach was observed to yield paralleled detection rate of clinically significant prostate cancer for lesions in peripheral area over TB+SB approach. My data are consistent with the previous study, documenting that targeted biopsy alone approach is able to detect 100% of clinically significant prostate cancer for PI-RADS 5 lesions in peripheral zone and 88% of that in patients with PIRADS 4 lesions in peripheral zone, respectively [83]. To sum up, targeted biopsy alone could be considered in specific cases.

4.5 Risk factors for the detection of clinically significant prostate cancer

Multivariate logistic regression analysis indicated that age at biopsy, PSAD, prior negative biopsy, PI-RADS score, and the location of lesion were common risk factors in TB+SB approach and TB alone approach for the detection of clinically significant prostate cancer. PSAD and PI-RADS score were the two most important predictors for clinically significant prostate cancer in TB+SB approach as well as TB alone approach. Besides, PSAD and PI-RADS score were found to be not only the predictive factors for naive patients [84, 85], but also two highly strong risk factors for patients undergone repeated prostate biopsy [86]. The difference was that family history of prostate cancer was the independent risk factor for TB alone approach, whereas suspect findings in digital rectal examination increased the likelihood of detecting clinically significant prostate cancer in TB+SB approach, not family history of prostate cancer. Bjurlin, et al [87] also reported that abnormal digital rectal examination could independently predict the risk of clinically significant prostate cancer using TB+SB approach for repeated biopsy cases. On the other hand, digital

rectal examination was the decisive factor associated with clinically significant prostate cancer in systematic biopsy [88, 89]. Hence, we infer that the digital rectal examination would be contained in multivariate logistic regression model when performing the combined approach. Moreover, family history of prostate cancer is a risk factor for the detection of clinically significant prostate cancer in systematic biopsy [90]. However, clinically significant prostate cancer in TB alone approach will rather be associated with mpMRI parameters, such as PI-RADS score, not be highlighted with the risk factors which play a crucial role on systematic biopsy.

As discussed in 4.2, 4.3 and 4.4 parts, my findings coincide with others that TB+SB approach have higher detection rate of clinically significant prostate cancer compared with TB alone approach, but identifying more clinically insignificant prostate cancer in the meantime [91, 92]. Targeted biopsy alone approach will miss a few clinically significant prostate cancers, which is also similar with the point of view of Delongchamps [93], who showed that 4% of clinically significant prostate cancers would be missed in patients with positive mpMRI results if only using targeted biopsy. Hence, we believe that well-selected patients could be the candidates for undergoing targeted biopsy alone approach. It should be noted that MRI-based biopsy strategy has been confirmed as a cost-effective protocol, offering good oncological outcomes [94], but it would also rely on the experience of clinician, no matter the use of rigid or elastic registration for MRI-based targeted biopsy [95].

4.6 Limitations of the study

Obviously, retrospective study design is the main flaw in my study. All the patients who underwent the prostate biopsy were treated in a single institution, Diakonie Klinikum Stuttgart, which may lead to sample selection bias. In addition, we just attempted to calculate the relative detection contribution by MRI/TRUS fusion targeted biopsy alone approach and 12-core systematic biopsy alone approach in the same session, then simulatedly to compare the oncological efficacy between MRI/TRUS fusion targeted biopsy and MRI/TRUS fusion targeted biopsy followed by a 12-core systematic biopsy. Here I did not conduct real comparisons in practice

between the MRI/TRUS fusion targeted biopsy alone approach and the combined approach for patients with positive mpMRI outcomes. Furthermore, the small series of patients in my study were not sufficient for a convincing and influential research, which could weaken the statistical efficiency. Larger sample size should be used in further analysis. Moreover, the whole samples were not biopsied by the same clinician and digital rectal examination were mostly performed by different urologists, which could be affected by subjective feelings. Additionally, another bias is that eight patients were measured by 1.5T MRI scan in spite of most patients tested by 3.0T MRI scan, which may result in the possibility of missing some small underlying tumors. Undetected tumors could contribute to the alternations of MRI parameters of lesions in the cohorts, for instance, the numer of region of interest, the composition of the PI-RADS and the diameter of lesions. Lastly, those who underwent transperineal MRI-targeted biopsy from January 2017 to March 2018 in our centre were not included in my analysis and only those who underwent tranrectal biopsy approach were recruited in the study. As for some patients strongly doubted with apex tumor, it is transperineal MRI-targeted biopsy that may be superior, not transrectal biopsy strategy.

4.7 General conclusions and outlook

In general, MRI/TRUS fusion targeted biopsy together with systematic biopsy could detect more clinically significant prostate cancers than MRI/TRUS fusion targeted biopsy alone approach, but it could also cause equal chance of more clinically insignificant prostate cancers to be detected. However, MRI/TRUS fusion targeted biopsy alone approach has been proved to be a sophisticated method, especially for lesions located in peripheral zone and lesions with PI-RADS score of 3 and 5. For those with specific lesions above who have an urge to undergo biopsy with fewer needle cores taken from prostate, MRI/TRUS fusion targeted biopsy without systematic biopsy might be an effective method to achieve comparable oncological outcomes over combined approach, but the risk of missing clinically significant prostate cancer also needs to be communicated to those patients before the biopsy.

Naturally, patients with positive mpMRI results who have a great psychological burden of missing clinically significant prostate cancer are still the preferred candidates for MRI/TRUS fusion targeted biopsy followed systematic biopsy. Besides, software registration for MRI/TRUS fusion targeted biopsy requires additional fusion equipment as well as trained clinicians. It is still a challenge to select MRI/TRUS fusion targeted biopsy for those in less developed areas of medical care, in which systematic biopsy would still be the only option. There is no absolutely perfect biopsy strategy for patients with positive mpMRI results so far. Every patient should be individually assessed and discussed in the clinical decision making. Prospective, multicentric and randomised trials are valued and required to confirm my conclusions in the future. We also look forward to discovering some new molecular biomarkers such as PCA3 [96, 97], which has been approved by FDA in order to carry out a risk assessment at the molecular level before the prostate biopsy. Even integrating the data of transcriptomics [98], metabonomics [99] and proteomics [100, 101] of prostate cancer, points out the possibility of detecting clinically significant prostate cancer as well as clinically insignificant prostate cancer for each patient, comprehensively determining the biopsy strategy for patients with positive mpMRI results and avoiding overdiagnosis and overtreatment of prostate cancer.

5 Summary

To date randomised systematic biopsy guided by transrectal ultrasound is still the standard care for diagnosis of prostate cancer, as prostate cancer is characterised by multifocal growth, high heterogeneity and lack of typical symptoms. Nevertheless, in the wake of the development of new molecular imaging on diagnosis of disease, multiparametric magnetic resonance imaging (mpMRI) has been progressively used in urology in recent years. There is growing evidence that magnetic resonance imaging/transrectal ultrasound (MRI/TRUS) fusion targeted biopsy with merits of detecting more clinically significant prostate cancers (csPCa) and fewer needle cores taken from the prostate is becoming a promising method in prostate biopsy, especially for patients with positive mpMRI results. More thrillingly, at the beginning of this year a multicentric trial, PRECISON, has suggested that MRI/TRUS fusion targeted biopsy could be performed solely in these patients and it could achieve utterly satisfactory outcomes. However, it is highly debated that whether it is still necessary to add a 12-core systematic biopsy after MRI/TRUS fusion targeted biopsy to these patients, which is backed by the point of view that MRI/TRUS fusion targeted biopsy is also likely to miss some cases with csPCa. Currently, majority of centres still conservatively adopt MRI/TRUS fusion targeted biopsy followed by a 12-core systematic biopsy in patients who have suspicious lesions on mpMRI. This work aims to evaluate the possibility and accuracy of only carrying out MRI/TRUS fusion targeted biopsy without 12-core systematic biopsy in patients with positive mpMRI results. The exploratory findings demonstrated that MRI/TRUS fusion targeted biopsy combined with systematic biopsy could obviously detect more prostate cancers, to a certain extent, more clinically significant prostate cancers compared with MRI/TRUS fusion targeted biopsy alone approach, but it also led to more risk of clinically insignificant prostate cancer to be detected. Further analysis illustrated that MRI/TRUS fusion targeted biopsy alone approach was superior to the combined approach without detecting additional clinically insignificant prostate cancers in lesions with PI-RADS score of 3 and 5 as well as for lesions situated in peripheral

zone when we considered the correlation between mpMRI parameters of lesions and the detection rate of csPCa. Moreover, the number of region of interest (ROI) as well as the diameter of lesions were found perhaps not the deciding factors between MRI/TRUS fusion targeted biopsy alone approach and the combined approach. Multivariate logistic regression analysis showed that in addition to several common risk factors such as age at biopsy, PSAD, prior negative biopsy, PI-RADS score, and the location of lesion, family history of prostate cancer was an independent predictor for csPCa in MRI/TRUS fusion targeted biopsy alone approach, while digital rectal examination required to be more highlighted using combined approach. Hence, MRI/TRUS fusion targeted biopsy approach could achieve as great the oncological efficacy as combined approach and may be warranted in selective cases with positive mpMRI results. Further well-designed, prospective, multicentric and randomised trials are awaited to validate this conclusion and better define the role of MRI/TRUS fusion targeted biopsy.

6 Zusammenfassung

Bis heute ist die randomisierte systematische ultraschallgesteuerte transrektale Prostatastanzbiopsie Standard zur Diagnose des Prostatakarzinoms, da dieses sich durch multifokales Wachstum, hohe Heterogenität und das Fehlen typischer Symptome kennzeichnet. Im Zuge der Entwicklung neuer molekularer Bildgebungsverfahren zur Diagnose der Erkrankung, hat die multi-parametrische Magnetresonanztomographie (mpMRI) in den letzten Jahren zunehmend Einzug in der Urologie gehalten. Es gibt immer mehr Belege dafür, dass die MRT-Ultraschall-Fusionsbiopsie mit einem besseren Nachweis von klinisch signifikantem Prostatakrebs (csPCa) bei geringerer Anzahl entnommener Stanzen aus der Prostata zu einer vielversprechenden Biopsie-Methode, besonders bei Patienten mit positiven MRT-Befunden, wird. Spannend ist, dass zu Beginn dieses Jahres in einer multizentrische Studie, PRECISON, vorgeschlagen wurde, dass eine MRT/TRUS Fusionsbiopsie speziell bei diesen Patienten durchgeführt werden kann und zu völlig zufriedenstellenden Ergebnissen führt. Die Notwenigkeit einer zusätzlich systematischen 12-Kern-Stanzbiopsie im Anschluss an eine MRT-Ultraschall-Fusionsbiopsie, steht weiterhin zu Debatte. Dies wird durch den Standpunkt einiger Studien unterlegt, dass eine alleinge zielgerichtete Biopsie mittels MRI / TRUS-Fusion einige Fälle mit csPCa uebersieht. Gegenwärtig findet die alleinige Fusionsbiopsie in der Mehrzahl der Zentren bei Patienten mit verdächtigen Läsionen im mpMRI eher zurückhaltend Anwendung. Diese Arbeit zielt darauf ab, die Möglichkeit und Genauigkeit der alleinigen Durchführung einer MRT-Ultraschall-Fusionsbiopsie ohne systematische 12-Kern-Stanzbiopsie bei Patienten mit positiven MRT-Ergebnisse zu bewerten. Die explorativen Ergebnisse zeigten, dass eine MRT-Ultraschall-Fusionsbiopsie in Kombination mit einer systematischen Biopsie offensichtlich mehr Prostatakarzinome, bis zu einem gewissen Grad ebenfalls mehr klinisch signifikante Prostatakarzinome im Vergleich zur alleinigen Fusionsbiopsie detektieren konnte. Jedoch führte dies auch zur Detektion klinisch unbedeutender Prostatakarzinome. Der weitere Vergleich zeigte, dass ein

alleiniger MRT/TRUS-Fusionsbiopsie-Ansatz der Kombination beider Stanzverfahren überlegen war, ohne zusätzliche klinisch unbedeutende Karzinome bei Läsionen mit PI-RADS-Score von 3 und 5 oder solchen mit Lokalisation in der peripheren Zone zu detektieren, wenn wir die Relevanz der Korrelation zwischen den MRT-Parametern der Läsionen und der Detektivrate von csPCa separat betrachten. Ferner wird angenommen, dass die Anzahl der „regions of interest“ (ROI) sowie der Durchmesser der Läsionen möglicherweise nicht für den Nachweis von csPCa in sowohl dem MRI / TRUS-Fusionsbiopsie-Ansatz als auch dem kombinierten Ansatz ausschlaggebend sind. Multivariate logistische Regressionsanalysen zeigten, dass die Familienanamnese zusätzlich zu mehreren allgemeinen Risikofaktoren wie Alter bei Biopsie, PSAD, vorheriger negativer Biopsie, PI-RADS-Score und Läsionsort, einen unabhängigen Prädiktor hinsichtlich eines csPCa bei alleiniger MRT-Ultraschall-Fusionsbiopsie darstellte, während die digitale rektale Untersuchung in Verbindung mit einem kombinierten Ansatz stärker hervorgehoben werden sollte. Daher könnte ein alleiniger MRT/TRUS-Fusionsbiopsie-Ansatz eine ebenso große onkologische Effizienz vorweisen wie die Kombination aus Fusionsbiopsie und systematischem Biopsieschema und kann in ausgewählten Fällen mit positiven mpMRT-Ergebnissen gerechtfertigt sein. Weitere gut geplante, multizentrische, prospektive und randomisierte Studien sind weiterhin nötig, um unsere Schlussfolgerungen zu validieren und die Rolle der MRT-Ultraschall-Fusionsbiopsie in der Zukunft besser zu definieren.

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8 List of Figures

9 List of Tables

10 Declaration

I declare that this dissertation was completed by myself, under the supervision of Professor Dr. Christian Schwentner. All the research related to the study was performed by me. Any sources from others were all marked in the text. I carried out data analysis, statistics as well as thesis writing. In addition, a letter as appendix 1 published in European Urology regarding liquid biopsy was also written and revised by me. All the co-authors reviewed this letter. Furthermore, one paper submitted to Journal of Endourology which was titled “Non-whole-gland High-Intensity Focused Ultrasound (HIFU) versus whole-gland HIFU for Management of Localised Prostate Cancer: A One-year Oncological and Functional Outcomes” is now in the status of major revision. I conducted the study and wrote the whole paper and revised it according to other co-authors’ suggestions.

Tuebingen, den 18.07.2018

Ye Lei

11 Acknowledgement

Blink of an eye, my medical doctoral study is about to an end. So many wonderful moments are worth remembering and immense gratitude and appreciation are needed to express, though no words can fully convey my thankfulness to those who always help and support me.

First and foremost, I would like to seize this special opportunity to thank my supervisor Prof. Christian Schwentner, who offers me such a precious chance to study in Tuebingen University and chooses this cutting-edge, clinically significant topic for me as well as instructs throughout my study. I also greatly cherish the ambitious character I have learned from him, which keeps me always on the track of pursuing my life dream.

In addition, I need to especially thank Dr. Jens Mundhenk, who always helps me and takes care of me. Without his persistent guidance, careful revision and scientific discussion, my doctoral dissertation will not be accomplished so smoothly and quickly.

I am also fortunate to get acquainted with some new friends including Dr. Patrick Zanker, Dr. Serdar Yildiz, etc, who give me strength to succeed and bring me massive fun. I am also grateful to all my colleagues in department of Urology helping me in my clinical training and patients data collection.

Last but not the least, a debt of gratitude is owed to my parents for giving me a large amount of supports and encouragements throughout my whole learning stage and dealing with all of my absence in the family get-together with adequate understanding. I hope I can always accompany with them in the future and compensate them what I have not done in the past few years.

12 Appended Paper and Manuscript

Appendix 1:

Lei Y, Mundhenk J, Schwentner C. Re: Sumanta K. Pal, Guru Sonpavde, Neeraj Agarwal, et al. Evolution of Circulating Tumor DNA Profile from First-line to Subsequent Therapy in Metastatic Renal Cell Carcinoma. Eur Urol. 2017 Dec;72(6):e180-e181.

Appendix 2:

Lei Y, Zanker P, Yildiz S, Hancke K, Seidl D, Koch O, Schwentner C, Mundhenk J. Non-whole-gland High-Intensity Focused Ultrasound (HIFU) versus whole-gland HIFU for Management of Localised Prostate Cancer: A One-year Oncological and Functional Outcomes. Journal of Endourology. (**Major Revision**)

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Non-whole-gland High-Intensity Focused Ultrasound (HIFU) versus whole-gland HIFU for Management of Localized Prostate Cancer: A One-year Oncological and Functional Outcomes

Journal:	*Journal of Endourology*
Manuscript ID	END-2018-0468-OR
Manuscript Type:	Original Research
Date Submitted by the Author:	19-Jun-2018
Complete List of Authors:	Lei, Ye; Diakonie-Klinikum Stuttgart Zanker, Patrick; Diakonie-Klinikum Stuttgart Yildiz, Serdar; Diakonie-Klinikum Stuttgart Seidl, Daniel; Diakonie-Klinikum Stuttgart Koch, Orlando; Diakonie-Klinikum Stuttgart Schwentner , Christian; Diakonie-Klinikum Stuttgart Mundhenk, Jens; Diakonie-Klinikum Stuttgart
Keyword:	Focal Therapy, Prostate Cancer
Manuscript Keywords (Search Terms):	HIFU, Non-whole-gland HIFU, Whole-gland HIFU, Prostate Cancer, IPSS, IIEF-5
Abstract:	Objective: To compare the oncological and functional outcomes in localised prostate cancer patients who received non-whole-gland High-intensity focused ultrasound (HIFU) with patients who received whole-gland HIFU therapy. Patients and Methods: 86 patients from September 2012 to January 2017 in our center were retrospectively analysed. Oncological outcomes included histological absence of prostate cancer, biochemical disease-free survival (BDFS) as well as the absence of lesions suspected for harboring prostate cancer in mpMRI. Regarding functional outcomes, we determined International prostate symptom score (IPSS), pad-free rate, pad-free and leakage-free rates as well as International index of erectile function-5 (IIEF-5). Results: Out of the 86 patients, 25 patients who underwent non-whole-gland HIFU and 61 patients who underwent whole-gland HIFU were enrolled in our one-year follow-up study. There were no significant differences in histological absence of prostate cancer (p=0.655), BDFS (p=0.820), PSA nadir (p=0.453) and absence of suspicious lesions in mpMRI (p=0.633) between non-whole-gland HIFU group and whole-gland HIFU group. However, compared with the whole-gland HIFU, the non-whole-gland HIFU group had fewer IPSS at 1 month (8.64±3.63 versus 10.85±6.10), a longer time to PSA nadir (5.04±2.07 versus 3.83±1.65), less temporary urine retention rate (20.0% versus 44.3%), less complication rate especially urinary tract strictures (4% versus 26.2%),

	whereas pad-free rate, pad-free and leakage-free rates and IIEF scores were comparable. Conclusion : Non-whole-gland HIFU is a promising type of treatment for localized prostate cancer with satisfactory oncological results with less impairment of functional outcomes and complications compared to whole-gland HIFU, but it requires longer follow-up and larger samples of randomized control trials.

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Abbreviations

Abbreviation	Full name
HIFU	High-Intensity Focused Ultrasound
BDFS	Biochemical Disease-free Survival
IPSS	International Prostate Symptom Score
IIEF-5	International index of erectile function-5
EAU	European Association of Urology
PSA	Prostate-specific Antigen

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Non-whole-gland High-Intensity Focused Ultrasound (HIFU) versus whole-gland HIFU for Management of Localised Prostate Cancer: A One-year Oncological and Functional Outcomes

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Key words: HIFU; Non-whole-gland HIFU; Whole-gland HIFU; Prostate Cancer; IPSS; IIEF-5

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ABSTRACT

Objective: To compare the oncological and functional outcomes in localised prostate cancer patients who received non-whole-gland High-intensity focused ultrasound (HIFU) with patients who received whole-gland HIFU therapy.

Patients and Methods: 86 patients from September 2012 to January 2017 in our center were retrospectively analysed. Oncological outcomes included histological absence of prostate cancer, biochemical disease-free survival (BDFS) as well as the absence of lesions suspected for harboring prostate cancer in mpMRI. Regarding functional outcomes, we determined International prostate symptom score (IPSS), pad-free rate, pad-free and leakage-free rates as well as International index of erectile function-5 (IIEF-5).

Results: Out of the 86 patients, 25 patients who underwent non-whole-gland HIFU and 61 patients who underwent whole-gland HIFU were enrolled in our one-year follow-up study. There were no significant differences in histological absence of prostate cancer (p=0.655), BDFS (p=0.820), PSA nadir (p=0.453) and absence of suspicious lesions in mpMRI (p=0.633) between non-whole-gland HIFU group and whole-gland HIFU group. However, compared with the whole-gland HIFU, the non-whole-gland HIFU group had fewer IPSS at 1 month (8.64±3.63 versus 10.85±6.10), a longer time to PSA nadir (5.04±2.07 versus 3.83±1.65), less temporary urine retention rate (20.0% versus 44.3%), less complication rate especially urinary tract strictures (4% versus 26.2%), whereas pad-free rate, pad-free and leakage-free

rates and IIEF scores were comparable.

Conclusion: Non-whole-gland HIFU is a promising type of treatment for localized prostate cancer with satisfactory oncological results with less impairment of functional outcomes and complications compared to whole-gland HIFU, but it requires longer follow-up and larger samples of randomized control trials.

INTRODUCTION

There is a great debate about the treatment options for prostate cancer, with disagreement on whether patients with localized tumor ought to undergo deferred treatment or radical interventions, and on the most suitable type of management. Immediate radical interventions burden patients with more risks of treatment-related side-effects, especially urinary incontinence, and to some extent are more likely to constitute overtreatment compared to active surveillance [1]. Nevertheless, those who choose active surveillance face uncertainty of tumor control and anxieties about subsequent series of psychological problems like emotional distress [2]. On the other hand, the latest European Association of Urology (EAU) guidelines have further specified that active surveillance can be considered not only for patients with low-risk tumor, but can also be expanded to selected patients with favorable intermediate-risk localized prostate cancer (Gleason score 3+4), despite carrying increased risk of metastases [3]. Hence, we are more puzzled how to balance morbidity of treatment and quality of life and, at the same time, avoid overtreatment for low- and intermediate-risk localized cases. There is need to explore new concepts of treatment

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to help both urologists and oncologists make better clinical decisions.

Transrectal high-intensity focused ultrasound (HIFU) therapy, as an alternative therapy, is increasingly used as primary treatment of localised prostate cancer for which radical prostatectomy and definitive radiotherapy, have been considered as constituting gold standard management for a long time. Moreover, HIFU is also now used as salvage therapy for recurrent disease [4]. There is already evidence that the chances for overall-survival (OS) and metastasis-free survival (MFS) up to five years are the same for both patients who have undergone whole-gland HIFU treatment and radical prostatectomy [5]. However, with the emergence of radiographic technologies such as multiparametric magnetic resonance imaging (mpMRI) helping to distinguish clinically significant from clinically insignificant prostate cancer, and the concept of precision medicine on the other hand, there are already some cohort studies that have focused on the use of hemiablation as the non-whole-gland HIFU for prostate cancer treatment[6, 7, 8]. Ahmed et. al., [9,10] have advanced the theory of index lesion and carried out a study of focal ablation targeting the index lesion in multifocal localised prostate cancer, which may corroborate the thesis that metastatic phenotype have only monoclonal origins and that secondary lesions are not attributed to PSA biochemical failure [11,12]. However, it is unclear and scarcely reported whether the oncological and functional outcomes of non-whole-gland HIFU and whole-gland HIFU are distinct.

The aim of our study is to primarily compare the one-year oncological and functional outcomes between non-whole-gland HIFU and whole-gland HIFU for the primary

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treatment of localized prostate cancer, in order to establish how HIFU may be integrated into our clinical practice best.

PATIENTS AND METHODS

Patient Preparation

86 localized prostate cancer patients without metastases verified via bone scan, pelvic CT or MRI scan from September 2012 to January 2017 were enlisted in our retrospective study. Of these patients, twenty-five underwent the primary non-whole-gland HIFU therapy, including 13 hemiablations and 12 zonal ablations. All other patients were treated with a whole-gland HIFU. Patients were informed of all possible treatment options and were counseled about possible risks. Prostate cancer was detected by systematically transrectal ultrasound-guided, random biopsy of 12 cores in all patients. When the MRI scan showed suspicious areas within the prostate, additional targeted fusion-biopsies were performed either through a transperineal or transrectal approach to increase detection rate. Seven patients in our study received androgen deprivation therapy, which had no statistical significance in non-whole-gland and whole-gland group.

Transrectal High-Intensity Focused Ultrasound Procedure

Under general anesthesia, all patients received a single-shot antibiotic prophylaxis. After sterile placement of transurethral Foley catheter patients are positioned in a lateral posture. Before insertion of the transducer, the prostate and rectum is examined and the anal sphincter is gradually and carefully stretched. Non-resistant movement is

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indispensable for procedure. In our scheme, to ensure accuracy and reduce bias, the prostate is divided into 24 zones, as shown in Figure 1. In the past we mostly used the whole-gland HIFU therapy in our clinic. We also applied three types of non-whole-gland HIFU ablations – Hemiablation, zonal ablation and target ablation – based on patient-specific treatment plans (Figure 2). It must be pointed out that in this series only salvage cases were treated by targeted ablation. This was planned on the basis of preoperative mpMRI and real-time transrectal ultrasonography images during HIFU and confirmed by fusion biopsies. Taking the safty distance between the rectum, nerve bundle, sphincter and apex of prostate into account, therapeutic range is contoured precisely through real-time three-dimensional ultrasonic planning at the console. As a landmark alleviating treatment planning we used an indwelling catheter. In a whole-gland Hifu ablation it was left in-situ during the treatment of the left lobe and removed during the treatment of the right lobe and the urethral area of the prostate.

Follow-up procedure

As a follow-up procedure, patients who underwent the HIFU therapy were subjected to serum prostate specific antigen (PSA) level tests quarterly during the first year. Biochemical disease-free survival (BDFS) at 12 months was defined using the Phoenix criteria (PSA nadir + 2 ng/ml). Scheduled mpMRI comprising T2-weighted, diffusion-weighted and dynamic contrast-enhanced sequences was used to identify the tumor location and possible local invasion after HIFU procedure at 6 months and 12 months, and a final score determined using the Prostate Imaging Reporting and Data

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System (PI-RADS) developed by the European Society of Urological Radiology (ESUR). Our primary oncological outcome was histological absence of prostate cancer at 12 months. However, in our research, systematic postoperative prostate biopsy at 12 months was not a routine procedure because most patients refused repeated biopsies except PSA or mpMRI showed clinical evidence of further recurrence. Thus, we only performed control prostate biopsies, when there was biochemical or imaging signs of recurrence. Functional assessments were mainly carried out according to the following parameters: an international prostate symptom score (IPSS) questionnaire was used to estimate the lower urinary tract symptom (LUTs) preoperatively and postoperatively; Continence status was defined as 'pad-free' or 'pad-free and leakage free'; the International index of Erectile function-5 (IIEF-5) score was used to assess sexual function including erectile confidence, ability for penetration, maintaining and completing intercourse as well as achieving sexual satisfaction.

Statistical analyses

Statistical description and analysis of quantitative data were performed using the mean ± standard deviation and t-test, respectively. Statistical analysis of enumeration data analysis was applied by χ^2-test. All statistical analyses were carried out using the Statistical Package for Social Science (SPSS version 21.0) software. $p<0.05$ was set to be statistically significant.

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RESULTS

Baseline demographics

Of the 86 patients included in this analysis, a group of 25 patients were subjected to non-whole-gland HIFU treatment, out of which 13 underwent hemiablation and 12 were treated by zonal ablation. All basic characteristics of the 86 patients are listed in Table 1. Although we have indicated the results from both hemiablation and zonal ablation in the non-whole-gland HIFU group, all statistical results were derived from the comparison carried out between the entire non-whole-gland HIFU and the whole-gland HIFU group. There were no significant differences concerning the parameters of age (p=0.058), PSA (p=0.290), Gleason score (p=0.308), risk classification (p=0.099) and clinical T stage (p=0.255) before treatment between the two groups. Nonetheless, the prostate volumes before treatment in non-whole-gland group were greater than in the whole-gland group (p=0.000). This is in accordance with the preoperative prostate volume reduction rate (p=0.000), as 36 percent of the patients underwent the transurethral resection of prostate (TURP) or thulium laser enucleation of prostate in the non-whole-gland HIFU group, which was less than 83.6 percent of whole-gland HIFU group.

Oncological outcomes

Among the 25 patients subjected to the non-whole-gland HIFU, preoperative and postoperative PSA at 3 months, 6 months, and 12 months were 8.39±6.84, 2.08±1.70, 1.44±1.06, 2.13±1.37 (ng/ml) In the whole-gland HIFU group PSA were 6.70±5.97,

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1.18±1.50, 1.46±1.89, and 1.79±1.85, respectively (Figure 3A and B). PSA kinetics indicated that the PSA decreasing rates by 3 months and 6 months from baseline were comparable between these two groups, whilst a significant difference of PSA levels could be found at 3 months (p=0.026). No difference was observed in terms of PSA nadir (p=0.453), whereas PSA-Nadir was reached markedly earlier in the whole-gland HIFU group compared to patients in the non-whole-gland HIFU group (3.83±1.65 versus 5.04±2.07 months; p=0.006). Histological absence of prostate cancer at 12 months was 20 of 25 patients (80.0%) in non-whole-gland HIFU group, which was comparable to 52 of 61 patients (85.2%) in whole-gland HIFU group (p=0.655). There was no remarkable difference observed in non-whole-gland and whole-gland HIFU group according to the BDFS (96.0% versus 91.8%; p=0.820). No mpMRI measurable prostate cancer occurred in 20 (80%) patients of non-whole-gland HIFU group, which was also comparable to 53 (86.8%) patients of whole-gland HIFU group (p=0.633). Nine patients from the whole-gland HIFU group and five patients from the non-whole-gland HIFU group who had a PSA relapse at 12 months after primary HIFU treatment were treated by a salvage HIFU with an according energy adjustment. All the results regarding oncological efficacy are summarized in Table 3.

Functional outcomes

As presented in Table 4, IPSS at 0 month, 1 month, 3 months, and 12 months in the non-whole-gland HIFU group were 4.88±2.83, 8.64±3.63, 5.44±3.06, and 4.56±2.16, respectively and 5.20±4.33, 10.85±6.10, 6.21±5.07, and 5.36±4.36 in the whole-gland HIFU group, respectively. IPSS of patients who received non-whole-gland HIFU

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therapy at 1 month were less than those of patients treated to whole-gland HIFU (p=0.042). Notably, IPSS scores at 1 month were significantly higher than IPSS baseline scores for patients of both the non-whole-gland HIFU group and the whole-gland HIFU group. There were no differences noted at 3 months and 12 months within each group (Figure 3C and D). Postoperative temporary urine retention was found more frequently in the whole-gland HIFU group than in the non-whole-gland HIFU group (44.3% versus 20%; p=0.035). However, the incidence of urinary tract infection in the non-whole-gland HIFU group was the same as in the whole-gland HIFU group (p=0.297). When comparing erectile dysfunction of both groups, no significant difference in IIEF scores could be detected (IIEF score of the non-whole-gland group: 19.36±3.56 at 0 month, 13.00±4.90 at 3 months, 15.64±4.91 at 12 months versus 18.48±3.65 at 0 month, 12.07±4.48 at 3 months, 15.15±4.57 at 12 months in the whole-gland group; Figure 3E and F). Likewise, continence was also evaluated at 0 month, 3 months, and 12 months. Our findings showed that the proportion of the pad-free rates, as well as the pad-free and leakage free rates of the whole-gland HIFU group was not different from the patients in the non-whole-gland HIFU. With regards to postoperative complications, 16 patients in the whole-gland HIFU group displayed urinary strictures compared to only one patient in the non-whole-gland HIFU group (p=0.040). Moreover, two patients from the whole-gland HIFU group suffered a vesico-rectal fistula and one suffered an intra-abdominal abscess. Both, vesico-rectal fistula and intra-abdominal abscess were not identified in the non-whole-gland HIFU group.

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DISCUSSION

Focal therapy in patients with low- and intermediate-risk localized prostate cancer is regarded as posing a challenge to the conventional notion that prostate cancer is a heterogeneity-abounded malignancy in every sense, including the clinical, spatial, morphological and genetic diversity [13, 14]. Good local tumor control is essential for the prognosis of prostate cancer patients[15, 16]. How to achieve a good local control is an intractable problem, usually experienced in focal therapy. In our study, we have compared the local tumor control and functional results between non-whole-gland HIFU and whole-gland HIFU treatment, to establish the advantages and disadvantages of non-whole-gland treatment as a focal therapy.

Based on data analysis conducted in this study, the PSA at 3 months and time to PSA nadir for whole-gland HIFU are higher than those for non-whole-gland HIFU. However, there are no differences of PSA at 6 months and at 12 months, as well as the PSA nadir. These results confirm the widely held belief that benign prostate tissue can also contribute to PSA level, thus hindering PSA level to PSA nadir [17]. Even a tiny tumor lesion which cannot be detected by the current image techniques contributes to a slight difference. The recovery of PSA to the same level at 12 months and BDFS at 12 months indicate that in spite of undergoing a non-whole-gland HIFU procedure, the tumor is not in progression, at least at the biochemical level. It can also be confirmed by imaging and repeated biopsies that the absence of prostate cancer in the non-whole-gland HIFU group at 12 months were comparable to that in the whole-gland HIFU group. Moreover, all the relapsed patients after the primary HIFU

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treatment could be successfully treated using salvage HIFU. Non-whole-gland HIFU would not have increased the difficulties and decrease possibilities of salvage treatment, which were also identified by other reports [18,19].

No significant changes were observed in IPSS scores for urinary function at 12 months compared with the baselines in both groups. However, a sharp increase in IPSS at 1 month was found within both groups, similar to other studies [20, 21]. It is noteworthy that IPSS at 1 month was also higher in the whole-gland HIFU group than in the non-whole-gland HIFU group. Similarly, the incidence of urinary retention was higher in the whole-gland HIFU group. We speculate that it might be caused by longer operation time, greater energy transfer to the gland causing more edema and swelling. Erectile functions recovered to pre-operative levels, though in the non-whole-gland HIFU group no negative impact on erectile functions could be observed. Yap and colleagues [22] have pointed out that the only determinants of erectile function after HIFU therapy is the preoperative erectile function status. Furthermore, even though the incontinence rates are the same for both groups, severe complications such as urinary tract stricture and fistula formation were not observed in the non-whole-gland HIFU group. This observation suggests the non-whole gland concept might show a more favourable profile of adverse events.

Non-whole-gland HIFU may be regarded as a in-between concept in the range of active surveillance and radical treatment, e.g. radical prostatectomy or external beam radiation therapy. It offers acceptable oncological control, causing less frequent adverse effects compared to the whole-gland HIFU regime. However, no significant

differences have been discovered in the functional outcomes of the two types of management at 12 months. Meanwhile HIFU therapy as such, may markedly reduce patients' psychological burden with low- and intermediate-risk prostate cancer. Therefore HIFU therapy may be the optimal concept for those patients, who are unfit for major surgical interventions or are reluctant to undergo active surveillance. Considering worries about side effects, especially the use of a non-whole-gland treatment strategy might meet concerns best.

Retrospective design constitutes the predominant limitation in our study. Whole-gland HIFU was basically used in our center before 2014 wherever the lesion was located and no matter how many lesions were present. In addition, HIFU device may also be considered as a heterogeneity factor in our study, as FocalOne HIFU was introduced to our center in 2016. FocalOne HIFU might be different from the device used before 2016 at our clinic. Furthermore, only eight patients without the PSA biochemical recurrence and postoperative measurable mpMRI signs consented to have a re-biopsy during the follow-up process and we consider the patients who didn't undergo the re-biopsy without PSA recovery and suspicious lesions in MRI after HIFU treatment as histological absence of prostate cancer. This is a factor that could influence the oncological outcome in both groups. Hence, there is need for further prospective, randomised, multicenter and comparative studies featuring active surveillance, non-whole-gland HIFU and whole-gland HIFU, and even the radical prostatectomy and radiation, in order to reach more consensuses on patients selection criteria, as well as a standardised follow-up scheme after focal ablation therapy.

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CONFLICTS OF INTEREST

There are no conflicts of interest to this work.

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ACKNOWLEDGEMENT

Thank Ms. Uta Roland, Ms. Sarah Gerner, Ms. Christiane Uder, Ms. Eva Maria Klotz, and Dr. Carola Wotzka for helping us with patients' data collection.

FIGURE LENGENDS

Figure 1. Diagrammatic depiction of zones of prostate in HIFU treatment from the transverse base, middle, and apex plane, respectively.

Figure 2. Diagram of four different HIFU treatments for prostate cancer in our centre.

(A) Diagram of whole-gland HIFU treatment. Blue solid edge: prostate; green circle: urethra; red pentagram: lesion; vertical lines: therapeutic range. (B) Diagram of Hemiablation treatment. (C) Diagram of zonal ablation treatment. (D) Diagram of targeted HIFU treatment. Blue dotted edge: incised prostate; blue pentagram: recurrent lesion.

Figure 3. PSA kinetics and functional outcomes of prostate cancer patients under

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non-whole-gland HIFU and Whole-gland HIFU.

(A) PSA kinetics of non-whole-gland HIFU at preoperative 0 month, postoperative 3, 6, and 12 months. (B) PSA kinetics of whole-gland HIFU at preoperative 0 month, postoperative 3, 6, and 12 months. (C) IPSS is affected at 1, 3, and 12 months after non-whole-gland HIFU treatment, in contrast with preoperation (*$p<0.05$). (D) IPSS is affected at 1, 3, and 12 months after whole-gland HIFU treatment, in contrast with preoperation (*$p<0.05$). (E) Effect on erectile function of non-whole-gland HIFU treatment using IIEF-5 questionnaire at preoperative 0 month, postoperative 3 and 12 months. (F) Effect on erectile function of whole-gland HIFU treatment using IIEF-5 questionnaire at preoperative 0 month, postoperative 3 and 12 months.

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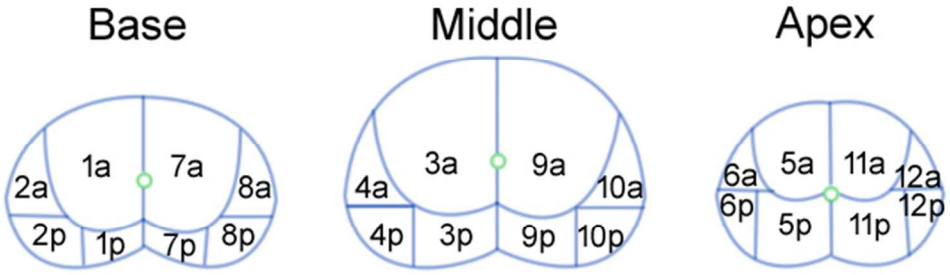

Diagrammatic depiction of zones of prostate in HIFU treatment from the transverse base, middle, and apex plane, respectively.

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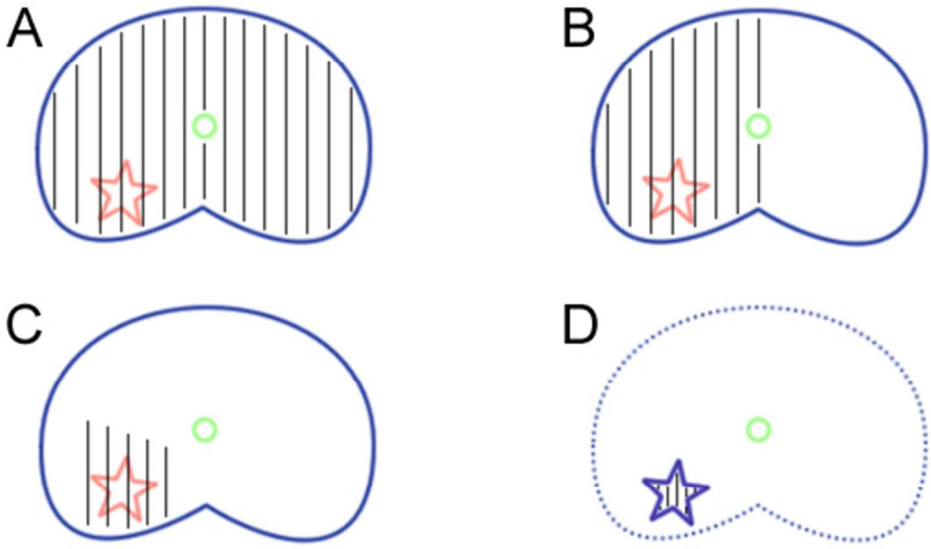

Figure 2. Diagram of four different HIFU treatments for prostate cancer in our centre.

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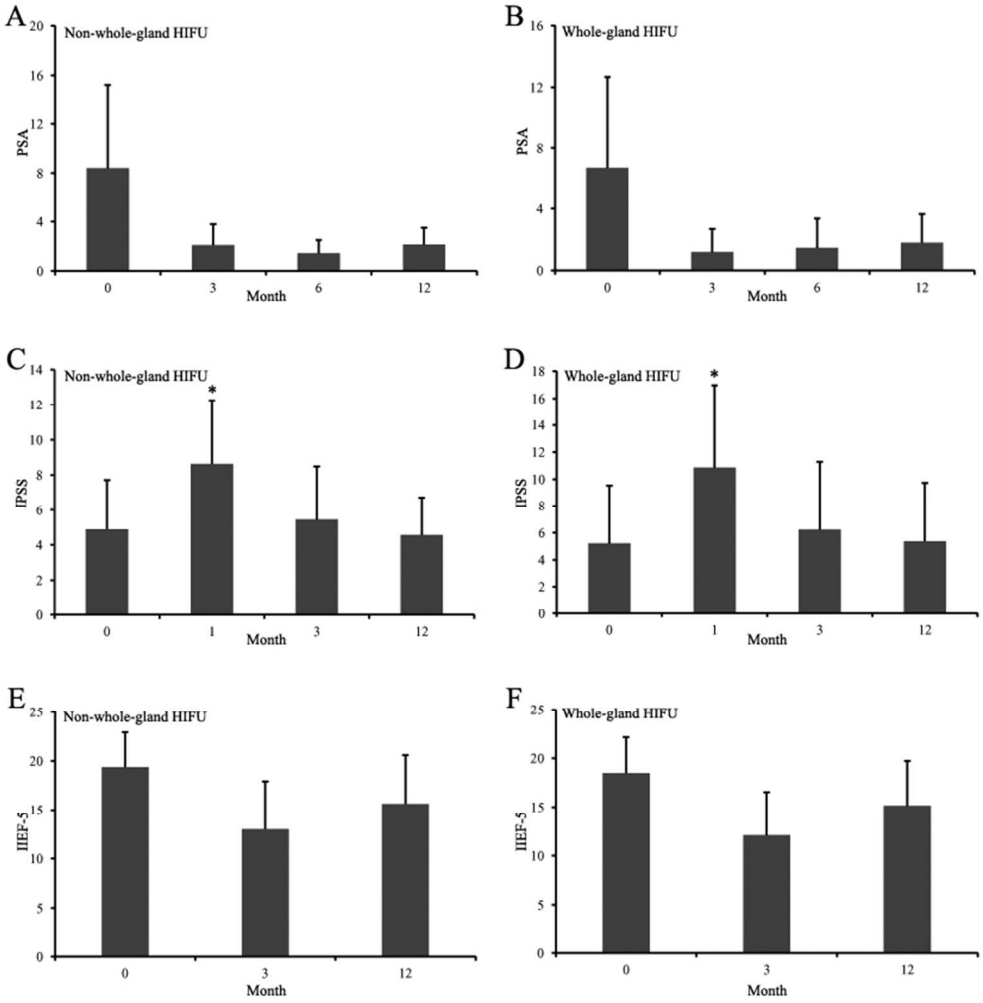

Figure 3. PSA kinetics and functional outcomes of prostate cancer patients under non-whole-gland HIFU and Whole-gland HIFU.

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Tables

Table 1. Clinical baseline characteristics of prostate cancer patients with Non whole-gland HIFU and Whole-gland HIFU.

Variables	Non-whole-gland HIFU		Whole-gland HIFU	*p* Value
	Hemiablation	Zonal ablation		
Number	13	12	61	
Age (year)	70.54±8.38	68.67±6.93	73.16±7.65	0.058
Pre-PSA (ng/ml)	8.54±8.43	8.23±4.96	6.70±5.97	0.290
Prostate volume (ml)	37.30±8.86	40.25±10.86	30.32±9.40	**0.000**
Pre-PVR (%)	7 (53.8)	2 (16.7)	51 (83.6)	**0.000**
ADT	1 (7.7)	0 (0.0)	6 (9.8)	0.642
Clinical T stage				0.255
T1c (%)	8 (61.5)	11 (91.7)	36 (59.0)	
T2a (%)	4 (30.8)	0 (0.0)	12 (19.7)	
T2c (%)	1 (7.7)	1 (8.3)	13 (21.3)	
Gleason score				0.308
≤6 (%)	3 (23.1)	4 (33.3)	23 (37.7)	
7a (%)	5 (38.4)	6 (50.0)	15 (24.6)	
7b (%)	3 (23.1)	2 (16.7)	13 (21.3)	
≥8 (%)	2 (15.4)	0 (0.0)	10 (16.4)	
Risk group (D'Amico)				0.099
Low (%)	2 (15.4)	2 (16.7)	15 (24.6)	
Intermediate (%)	8 (61.5)	10 (83.3)	34 (55.7)	

High (%)	3 (23.1)	0 (0.0)	12 (19.7)

Pre-PSA: Preoperative prostate-specific antigen; Pre-PVR: Preoperative prostate volume reduction; ADT: Androgen deprivation therapy

Table 2. The PSA kinetics of prostate cancer patients with Non Whole-gland HIFU and Whole-gland HIFU.

PSA (ng/ml)	Non-whole-gland HIFU		Whole-gland HIFU	*p* value
	Hemiablation	Zonal ablation		
At 0 months	8.54±8.43	8.23±4.96	6.70±5.97	0.290
At 3 months	1.85±1.65	2.34±1.80	1.18±1.50	**0.026**
At 6 months	1.14±1.03	1.75±1.04	1.46±1.89	0.934
At 12 months	1.86±1.23	2.42±1.49	1.79±1.85	0.358

Table 3. Elementary tumor control outcomes of prostate cancer patients with Non Whole-gland HIFU and Whole-gland HIFU.

Variables	Non-whole-gland HIFU		Whole-gland HIFU	*p* value
	Hemiablation	Zonal ablation		
PSA nadir (ng/ml)	1.06±1.06	1.58±1.15	1.06±1.52	0.453
Time to PSA nadir (month)	4.62±1.56	5.50±2.50	3.84±1.66	**0.006**
PSA decreasing rate at 3 months	75.4%±16.9%	71.2%±19.6%	79.0%±23.7%	0.285
PSA decreasing rate at 6 months	83.4%±15.3%	70.4%±36.6%	74.9%±29.2%	0.743
Histological absence of	11 (84.6%)	9 (75.0%)	52 (85.2%)	0.655

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prostate cancer (%)				
BDFS (%)	12 (92.3%)	12 (100.0%)	56 (91.8%)	0.820
No mpMRI measurable prostate cancer (%)	11 (84.6%)	9 (75.0%)	53 (86.8%)	0.633

BDFS: Biochemical disease-free survival (%); mpMRI: Mutltiparametric magnetic resonance imaging

Table 4. Elementary functional outcomes and adverse events of prostate cancer patients with Non Whole-gland HIFU and Whole-gland HIFU.

	Non-whole-gland HIFU		Whole-gland HIFU	*p* value
	Hemiablation	Zonal ablation		
IPSS				
At 0 month	4.69±2.29	5.08±3.42	5.20±4.33	0.691
At 1 month	8.62±2.87	8.67±4.44	10.85±6.10	**0.042**
At 3 months	5.38±3.45	5.50±2.71	6.21±5.07	0.389
At 12 months	4.92±2.22	4.17±2.12	5.36±4.36	0.268
Temporary Urinary retention (%)	2 (15.4)	3 (25.0)	27 (44.3)	**0.035**
Urinary tract infection (%)	1 (7.7)	0 (0.0)	9 (14.8)	0.297
Pad-free (%)				
At 0 month	13 (100.0)	12 (100.0)	60 (98.4)	1.000
At 3 months	12 (92.3)	11 (91.7)	53 (86.9)	0.763
At 12 months	12 (92.3)	11 (91.7)	59 (96.7)	0.704
Pad-free and leakage-free (%)				

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At 0 month	13 (100.0)	11 (91.7)	54 (88.5)	0.500
At 3 months	10 (76.9)	11 (91.7)	48 (78.7)	0.792
At 12 months	12 (92.3)	11 (91.7)	55 (90.2)	1.000
IIEF-5				
At 0 month	18.92±4.15	19.83±2.89	18.47±3.65	0.307
At 3 months	12.92±4.75	13.08±5.26	12.06±4.47	0.395
At 12 months	15.53±4.96	15.75±5.08	15.15±4.57	0.663
Urinary stricture (%)	1 (7.7)	0 (0.0)	16 (26.2)	**0.040**
Fistula (%)	0 (0.0)	0 (0.0)	2 (3.3)	0.898
Intra-abdominal abscess	0 (0.0)	0 (0.0)	1 (1.6)	1.000

IPSS: International prostate symptom score; IEFF-5: International index of erectile function-5;

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Letter to the Editor

Re: Sumanta K. Pal, Guru Sonpavde, Neeraj Agarwal, et al. Evolution of Circulating Tumor DNA Profile from First-line to Subsequent Therapy in Metastatic Renal Cell Carcinoma. Eur Urol 2017;72:557–64

Pal and coworkers [1] identified changes in the circulating tumor DNA (ctDNA) profile in patients with metastatic renal cell carcinoma (mRCC) and ctDNA fluctuations during first-line and post first-line targeted therapy using a HiSeq2500 sequencing system. To little surprise, a high yield of genomic mutations (79%) was observed in this heterogeneous enrichment malignancy, with gene mutations of *TP53* (35%), *VHL* (23%), *EGFR* (17%), *NF1* (16%), and *ARID1A* (12%). The results indicate a significant increase in mutation frequency in mRCC patients receiving targeted therapy for subsequent therapeutic lines when compared to first-line treatment, especially for *TP53* (49% vs 24%), *VHL* (29% vs 18%), *NF1* (20% vs 8%), *EGFR* (15% vs 8%), and *PIK3CA* (17% vs 8%). This largest study to date on ctDNA in mRCC revealed that liquid biopsy has promise for guiding targeted therapy. However, we feel that these results deserve to be reconsidered with a view to revealing hidden information behind this methodologically well-conducted study.

Initially, the authors concluded that the frequency of ctDNA mutations was higher in the post–first-line than in the first-line setting. From basic principles, it is known that the level of ctDNA mutations in the bloodstream is determined by both release from tumor cells undergoing necrosis, apoptosis, and active secretion, and engulfment of scavenger cells such as macrophages [2]. However, a subtle fact is that VEGF inhibitors could induce apoptosis of renal cancer cells [3]. Hence, there is a great possibility that the increase in mutation frequency partly results from an increase in release caused by the inhibitor itself rather than real changes in the tumor, and this probably accounts for a considerable portion because of the large tumor burden in mRCC. Moreover, mTOR inhibitors, another major class, are responsible for induction of macrophage inhibition, and even selective macrophage death [4]. This apparently indicates that a decrease in phagocytosis, as another confounding factor, may also affect the mutation frequency. Therefore, the increase in mutation frequency could possibly be an "illusion" and might not totally reflect real levels of ctDNA, which seems to be ignored by the authors, and new mutations may be relatively more instructive.

In addition, a recent study suggested that the liver and kidney are also involved in clearance of ctDNA [5]. Thus, we recommend that the authors reanalyze their data and consider intrinsic clearance and the glomerular filtration rate, which were not taken into account in their study, to obtain more comprehensive findings.

Furthermore, mutations for three significant genes, *PBRM1*, *BAP1*, and *KDM5C*, are potentially associated with outcomes for crossover of targeted therapy according to a previous study [6], but these are not included in the Guardant360 testing system. This disparity may introduce bias when urologists use the Guardant360 platform to test for ctDNA in mRCC.

In general, despite the merits of ctDNA in overcoming heterogeneity via a scalpel-free method with real-time analysis, many impact factors need to be taken into consideration for use in clinical practice, especially for guiding targeted therapy in mRCC patients.

Conflicts of interest: The authors have nothing to disclose.

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DOI of original article: http://dx.doi.org/10.1016/j.eururo.2017.03.046.
http://dx.doi.org/10.1016/j.eururo.2017.07.009
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