Endorectal power Doppler/grayscale ultrasound-guided biopsies vs. multiparametric MRI/ultrasound fusion-guided biopsies in males with high risk of prostate cancer: A prospective cohort study

ZHIZHONG HE1, ZHIFAN YUAN1, LIMEI LIANG1, XINX IN XIE2, JIANJUN YUAN1, WENXU HE1, JUNJUN CHEN1 and YONGPEI KUANG1

1Department of Ultrasound, Dongguan People’s Hospital Affiliated to Southern Medical University, Dongguan, Guangdong 523000; 2Department of Ultrasound, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, P.R. China

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Abstract. Multiparametric MRI fusion with transrectal ultrasound (mpMRI/TRUS)-guided biopsy has the sensitivity of mpMRI with the practicality of TRUS, but males with no cancerous lesion(s) detected on mpMRI have a considerable remaining risk of cancer. Endorectal power Doppler ultrasound improves the sensitivity of grayscale ultrasound-guided biopsies. The objective of the present study was to evaluate the beneficial effect of endorectal power Doppler/grayscale ultrasound-guided biopsy over that of mpMRI/TRUS-guided biopsy for decision-making regarding prostatectomy in males with a high risk of prostate cancer. Data regarding endorectal power Doppler/grayscale ultrasound-guided biopsies and mpMRI/TRUS-guided biopsies of 1,094 males with elevated specific prostate antigen, were included. Radical prostatectomy was performed in males aged <70 years with Gleason scores ≥3+4 in any one of the biopsy reports. The histopathological data of the surgical specimen of 776 males were included in the analysis. Compared to the histopathology of the surgical specimen, endorectal power Doppler/grayscale ultrasound-guided biopsies had a lower sensitivity (0.930 vs. 1.000; P<0.0001) but mpMRI/TRUS-guided biopsies had the same sensitivity (0.990 vs. 1.000; P=0.02). The accuracy of mpMRI/TRUS-guided biopsies was higher than that of endorectal power Doppler/grayscale ultrasound-guided biopsies (0.944 vs. 0.783). On mpMRI, lesions of 105 subjects (10%) with a Likert scale score of <3 were identified. Among them, 14 subjects (2%) had Gleason scores of ≥3+4 as determined by endorectal power Doppler/grayscale ultrasound-guided biopsies. In addition, 20 (2%) false-positive lesions compared to the histopathological analysis of the surgical specimen were identified from mpMRI/TRUS-guided biopsies. In conclusion, mpMRI/TRUS-guided biopsy was indicated to have a moderate performance and endorectal power Doppler/grayscale ultrasound-guided biopsy had a scant performance for decision-making regarding prostatectomy.

Introduction

In Europe and in the US, prostate cancer is the most common cancer type in males (1). The occurrence of prostate cancer varies among different ethnicities (2). In Chinese males, prostate cancer has an incidence of 121 in 1,000,000 males (2) and it is the fifth leading cause of cancer-associated mortality in males (3). Mortality due to prostate cancer may be reduced by proper diagnosis (4). Radiological images have a crucial role in the diagnosis of prostate cancer (5). Additionally, serum prostate-specific antigen testing is frequently performed following biopsy due to the high frequency in the elevation of prostate-specific antigen expression in patients with prostate cancer (6).

Prostate-specific antigen is produced by the prostate but is not a prostate cancer biomarker. It may also be altered during inflammation or infection, as well as in benign prostatic hyperplasia (6). In Chinese males, it is also associated with obesity (7). Urologists in China have put rigorous effort in improving the quality of screening and treatment of cancer of the prostate gland with radiological methods, e.g. MRI, CT, transrectal ultrasound (TRUS), and positron emission tomography (8). Among the radiological methods, TRUS provides more appropriate details than MRI and CT (5). Multiparametric MRI (mpMRI) has value in the diagnosis of prostate cancer (8) but it is only able to diagnose localized prostate cancer with a volume of ≥0.2 ml (9). A prostate biopsy
is performed in order to discover a prostate cancer in the case of persistent altered prostate-specific antigen level and/or in the case of suspicion warranting digital rectal examination (10). mpMRI fused with TRUS (mpMRI/TRUS)-guided biopsy has the sensitivity of mpMRI (11) with the practicality of TRUS (12) and is a promising method (13) for prostate cancer diagnosis (14). However, to overcome inaccuracies associated with the biopsy technique, mpMRI/TRUS fusion biopsies require a high volume of samples (14). Subjects with undetected cancerous lesion(s) on mpMRI still have a certain probability of having prostate cancer (15) but mpMRI/TRUS is not performed for those.

The utility of power Doppler with grayscale ultrasound is used in the detection of prostate cancer (5). Endorectal power Doppler ultrasound may detect capsular extension, visualize tumor vascularity and improve the sensitivity of grayscale ultrasound-guided biopsies (16). All of these pre-operative data should be utilized by the surgeon to perform the best radical prostatectomy technique in order to obtain the best achievable functional result (17,18).

The objective of the present prospective study was to evaluate the beneficial score of endorectal power Doppler combined with grayscale ultrasound-guided biopsy over that of mpMRI/TRUS-guided biopsy for decision making regarding prostatectomy in Chinese males with a high risk of prostate cancer.

Materials and methods

Materials. Levofloxacin (Loxof) was purchased from Ranbaxy Pharmaceuticals Pvt. Ltd (Sun Pharmaceutical Industries, Ltd.). Lidocaine jelly (Xylocaine gel) was purchased from AstraZeneca Pharmaceuticals Co. Ltd. Diclofenac (50 mg) with paracetamol (500 mg) tablet (Lederflam Forte) was purchased from Wyeth, Inc. The loose enema was purchased from Torrent Pharmaceuticals, Ltd.

Inclusion criteria. Between January 2013 and February 2019, a total of 1,215 males aged ≥40 years with complaints including weak flow during urination, difficulties to start urinating, weak flow of urine and a sensation of improper urinary bladder emptying were available at an outpatient setting of Dongguan People’s Hospital Affiliated to Southern Medical University (Dongguan, China) and the First Affiliated Hospital of Anhui Medical University (Anhui, China) were included in the present study (19). Males with elevated prostate-specific antigen (normal range, ≤3.0 ng/ml for subjects <50 years, ≤3.5 ng/ml for 50-59 years, ≤4.5 ng/ml for 60-69 years and ≤5.5 ng/ml for ≥70 years) (20) or abnormal structure of the prostate on palpitation on rectal examination (hard, lumpy or enlarged prostate) under digital rectal examination (19) were included in the study.

Exclusion criteria. Males with confirmed prostate cancer, negative biopsies for prostate cancer in the past 6 months, normal prostate-specific antigen levels, normal rectal examinations, men with normal prostate-specific antigen levels and abnormal prostate palpitations (considered inflammation of the prostate and not prostate cancer), a Gleason score of 3+3 and age of <40 years were excluded from the study. Although patients with age ≥70 years were not recommended for prostatectomy, they were also subjected to biopsies.

mpMRI. Males were examined with an MRI 3.0 Tesla (AIRIS Vento O5 0.3T; Hitachi Aloka, Medical, Ltd.) using phased-array torso coils (16 elements, Hitachi Aloka Medical, Ltd.) and with an endorectal coil. Dynamic contrast-enhanced imaging, diffusion-weighted imaging with b-values of >1,500, apparent diffusion coefficient value imaging and multiplanar T2-weighted imaging (T2WI) scans were performed for all patients (21). MR images were analyzed with the Prostate Imaging Reporting and Data System version 1 (22). Based on the overall impression of the prostate in MR images, each lesion was assigned a Likert scale score (five-point scale method: Unlikely benign, 1; most probably benign, 2; equivocal prostate cancer, 3; probably malignant, 4; and highly suspicious of malignancy, 5 (23). Males with lesions with a Likert scale score of ≥3 were subjected to mpMRI/TRUS-guided biopsies (according to the institutional guidelines for prostate cancer examinations) (23). Five radiologists (with a minimum of 3 years of experience) of the institute(s) performed mpMRI and assigned the Likert scale score to each of the lesions. All enrolled patients were subjected to both types of biopsies, which were performed sequentially.

Endorectal power Doppler/grayscale ultrasound-guided biopsy. The patients were instructed to lie down in the left lateral decubitus position with flexed knees and hips. Rectal lidocaine jelly was applied to the rectal probe and the latex cuff. The prostate gland was examined with a Color Doppler System (F31; Hitachi Aloka Medical Ltd.) and 7.5-MHz endorectal probes (Hitachi Aloka Medical Ltd.) in the axial and sagittal sections. Ultrasound equipment was set at the level of background noise. In total, seven sonographers (blinded regarding the mpMRI results; minimum 3 years of experience) of the institute(s) performed endorectal power Doppler with grayscale ultrasound examinations. After the endorectal power Doppler/grayscale ultrasound examinations, a 18 G biopsy needle (BD Surgical, Inc.) was inserted in the location where the most intensive signal had been detected and two cores from the transitional zone, six cores from the peripheral zone, two cores from the hypoechoic region (darker area in the grayscale ultrasound image) and two cores from vascular clustering area (increased number of vessels in power Doppler ultrasound image) (Fig. 1) were collected (5). A total of 15 physicians (blinded regarding the mpMRI results, minimum of three years of experience) of the institute(s) performed the biopsies. Endorectal power Doppler/grayscale ultrasound-guided biopsies adhered to the Standards for Reporting of Diagnostic accuracy studies guidelines (24). To overcome the deformation of ultrasound images obtained by transrectal ultrasound, the ultrasound probe was held against the skin without pressure.
lateral parts) and each side of the transition zone of the prostate. In addition, two cores were collected from solid and hypoechoic areas (denser mass than usual on the grayscale ultrasound image; Fig. 2) (21). A total of 15 physicians (minimum three years of experience, blinded regarding endorectal power Doppler/grayscale ultrasound-guided biopsies) performed the biopsies. The mpMRI/TRUS guided biopsies adhered to the guidelines of the Standards for Reporting for MRI-Targeted biopsy studies consortium (25).

For prophylactic purposes, all patients had been prescribed levofloxacin 500 mg twice a day for three days prior to the biopsies and all patients had received a cleansing enema prior to the examinations (26). To control pain, a rectal lidocaine jelly was applied 30 min prior to the biopsies and afterwards, oral 50 mg diclofenac with 500 mg paracetamol was prescribed twice a day for two days (5). Anticholinergic drugs (oxybutynin, 5 mg orally 2-3 times a day) were given to the patients prior to the biopsies to overcome difficulties in diagnosis due to reactions including pelvic muscle pressure and pelvic muscle contraction.

Pathological analysis. The biopsy lesions were preserved in 10% formalin and sent to a laboratory for histopathology purposes. All samples were paraffin-embedded and slides were prepared. The slides were stained with hematoxylin and eosin. Each slide was examined under a light microscope (Olympus) by urologic pathologists. A total of 13 pathologists (minimum three years of experience) of the institute(s) performed the histopathological examination. Each histopathological specimen was assigned primary and secondary Gleason scores (Fig. 3), numbers of cores positive for cancer and the percentage of cores with cancer (21,27). Samples with Gleason scores ≥3+4 (defined as most of the tumor being of grade 3 and the second-largest section of the tumor being grade 4) were considered as prostate cancer (21,28).

Figure 1. Region of interest for endorectal power Doppler fusion grayscale ultrasound-guided biopsy. (A) Pictorial presentation of the hypoechoic area. (B) Grayscale ultrasound image of the hypoechoic area. (C) Pictorial presentation of vascular clustering. (D) Power Doppler ultrasound image of vascular clustering. A total of 15 physicians (blinded regarding the multiparametric MRI results) performed the biopsies. All had a minimum of 3 years of experience. The biopsies adhered to the Standards for Reporting of Diagnostic accuracy studies guidelines. L1, left side.

Figure 2. Region of interest for multiparametric MRI fusion with transrectal ultrasound-guided biopsy. (A) Pictorial presentation of the solid and hypoechoic area. (B) Grayscale ultrasound image of a solid and hypoechogenic area. The biopsies were performed by 15 physicians blinded regarding endorectal power Doppler/grayscale ultrasound-guided biopsies. All had a minimum of 3 years of experience. Biopsies had adhered to the Standards for Reporting of Diagnostic accuracy studies guidelines.

Robotic-assisted laparoscopic radical prostatectomy. After obtaining histopathological results of the two types of biopsies, the urologists performed robotic-assisted laparoscopic radical prostatectomy in males aged <70 years with Gleason scores of ≥3+4 in any one of the biopsy reports (29). During the surgical procedure, the prostate and surrounding tissues were removed (9). A total of 17 urologists (minimum three years of experience) of the institute(s) performed the prostatectomy. A single-surgeon approach was used. Details on prostatectomy were reported in line with the Strengthening the Reporting of Cohort Studies in Surgery criteria (30).
Histopathology. Sampling of the resected prostate was performed using the Stanford technique. Transverse (4-5 mm) and sagittal (6-7 mm) sections from apex to base were taken and subjected to pathological examination (9). Gleason scores were recorded (21,27). Specimens with Gleason scores of $\geq 3+4$ were considered as prostate cancer.
cancer (21,28). A total of 10 pathologists (minimum three years of experience; blinded regarding radiological examinations) of the institute(s) examined the histopathological results.

**Prostatectomy decision analysis.** Decision curve analysis was performed to evaluate the prostatectomy decision in the subjects enrolled as per Eq. i (31):

\[
\text{Lesions with accurate Gleason cores} \geq 3+4 \text{ present}\quad \times \quad \text{Lesions with false Gleason cores} \geq 3+4 \text{ present}
\]

\[
\text{Men included in the pathology}\quad \times \quad \text{Men included in the pathology}
\]

\[
\text{Level of diagnostic confidence above which Gleason cores} \geq 3+4 \text{ present}
\]

\[
1=\text{Level of diagnostic confidence above which Gleason cores} \geq 3+4 \text{ present}
\]

\[
0 \quad \text{(men included in the pathology)}
\]

Statistical analysis. InStat Software for Windows (version 3.0; GraphPad Inc.) was used for statistical analysis. Differences between groups in discrete variables were analyzed using Fisher's exact test (21). Continuous data are presented as the mean ± standard deviation. Linear weighted k coefficients were determined to evaluate interobserver agreement (poor agreement, k ≤0.40; moderate agreement, 0.4> k ≤0.60; and substantial agreement, k >0.60) (22). All results were considered significant at a confidence level of 99%.

**Results**

**Patients.** Among included patients, 52 patients had an age of <40 years, 18 had confirmed prostate cancer, 26 had negative biopsy reports in the past 6 months, 11 had normal prostate-specific antigen values and 14 had normal rectal examinations, and were therefore excluded from the analysis. Finally, the data of 1,094 subjects were included in the study. The flow diagram of the study is presented in Fig. 4.

**Medical history and demographics.** The demographic parameters of the cohort are provided in Table I. Among the patients (age range, 41-91 years; mean age: 69.45±8.47 years) enrolled, 90% were Han Chinese, 9% were Mongolians and 1% were Tibetans. Furthermore, 48% of the subjects had a body mass index of <25 kg/m², 33% of 25-30 kg/m² and 19% of >30 kg/m². A total of 293 patients were obese (definition, waist circumference >490 cm). In addition, 32% of the subjects had diabetes and 18% had hypertension.

**Pathological analysis.** By using endorectal power Doppler/grayscale ultrasound-guided biopsies following pathological analysis, Gleason scores of ≥3+4 were determined in 589 patients. On mpMRI, lesions were identified in 105 subjects with a Likert scale score of <3. Therefore, the other 989 patients were subjected to mpMRI/TRUS-guided biopsies. mpMRI/TRUS-guided biopsies followed by pathological analysis revealed Gleason scores of ≥3+4 in 808 patients. Among those subjects with a Likert scale score of <3 (n=105) who were not subjected to mpMRI/TRUS-guided biopsy, 14 had reported Gleason scores of ≥3+4 determined from endorectal power Doppler/grayscale ultrasound-guided biopsies. Therefore, a total of 822 patients had Gleason scores of ≥3+4 in either of the biopsy reports. Among them, 43 patients had an age of ≥70 years (as per institutional guidelines for surgery). Therefore, the urologists did not offer them any prostatectomy and 3 further patients refused to undergo surgery. Finally, a total of 776 subjects underwent prostatectomy and all resected prostates were subjected to pathological analysis (Fig. 5).

**Diagnostic parameters.** Endorectal power Doppler/grayscale ultrasound-guided biopsy had a lower sensitivity than histopathology of the surgical specimen (0.93 vs. 1.00, P<0.0001) but mpMRI/TRUS-guided biopsy had the same sensitivity as that of the histopathology of the surgical specimen (0.99 vs. 1.00, P=0.02) and negligible inconclusive results (8 vs. 0, P=0.024). Accuracy was in the order of histopathology of the surgical specimen (1.00)>mpMRI/TRUS-guided biopsy (0.944)>endorectal power Doppler/grayscale ultrasound-guided biopsy (0.783). However, compared with

| Characteristic | Value |
|---------------|-------|
| Age (years) | 41-91 |
| Mean ± SD | 69.45±8.47 |
| Ethnicity | |
| Han Chinese | 983 (90) |
| Mongolian | 102 (9) |
| Tibetan | 9 (1) |
| Serum prostate-specific antigen (ng/ml) | |
| ≤40 years | 7.12±1.01 |
| 40-49 years | 9.01±1.22 |
| 50-59 years | 10.22±1.55 |
| 60-69 years | 11.19±1.89 |
| ≥70 years | |
| Body mass index (kg/m²) | |
| ≤25 | 523 (48) |
| 25-30 | 359 (33) |
| >30 | 212 (19) |
| Diabetes | 347 (32) |
| Hypertension | 201 (18) |
| Manual rectal examination | |
| Hardness | 414 (38) |
| Lumps | 343 (31) |
| Enlarged prostate | 337 (31) |
| Central obesity | |
| No | 801 (73) |
| Yes | 293 (27) |
| Alcohol abuse | 45 (4) |
| Chronic urinary tract infection | 12 (1) |

| Table I. Demographical characteristics of the male patients enrolled (n=1,094). |
|------------------|-------|
| Characteristic | Value |
| Age (years) | 41-91 |
| Mean ± SD | 69.45±8.47 |
| Ethnicity | |
| Han Chinese | 983 (90) |
| Mongolian | 102 (9) |
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| ≤40 years | 7.12±1.01 |
| 40-49 years | 9.01±1.22 |
| 50-59 years | 10.22±1.55 |
| 60-69 years | 11.19±1.89 |
| ≥70 years | |
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| Diabetes | 347 (32) |
| Hypertension | 201 (18) |
| Manual rectal examination | |
| Hardness | 414 (38) |
| Lumps | 343 (31) |
| Enlarged prostate | 337 (31) |
| Central obesity | |
| No | 801 (73) |
| Yes | 293 (27) |
| Alcohol abuse | 45 (4) |
| Chronic urinary tract infection | 12 (1) |

| Random blood glucose ≥140 mg/dl. | Blood pressure >90/130 mmHg. |
| Central obesity was defined as a waist circumference ≥490 cm, while a waist circumference of ≤90 cm was defined as no central obesity. Constant variables are presented as n (%) and continuous data are presented as the mean ± SD unless otherwise specified. SD, standard deviation. Normal value of body mass index for Chinese men is 25±2 kg/m². |
the histopathological examination of the surgical specimen, the combined results of the two biopsies exhibited insignificant false-negative results (P=0.012), inconclusive results (P=0.024) and sensitivity (P=0.024) but higher accuracy (Table II).

**Interobserver agreement.** Compared with final results adopted, all evaluations had a moderate linear-weighted agreement (0.4> k ≤0.60; Table III).

**Prostatectomy decision analysis.** The working area that detects at least one lesion with Gleason scores ≥3+4 for endorectal power Doppler/grayscale ultrasound-guided biopsies, mpMRI/TRUS-guided biopsies, and combinations of endorectal power Doppler/grayscale ultrasound-guided biopsies and mpMRI/TRUS-guided biopsies was 0.330-0.920, 0.180-0.935 and 0.170-0.965, respectively. Above 0.920, 0.935 and 0.965, endorectal power Doppler/grayscale ultrasound-guided biopsies, mpMRI/TRUS-guided biopsies and combinations of endorectal power Doppler/grayscale ultrasound-guided biopsies and mpMRI/TRUS-guided biopsies had the risk of overdiagnosis (Fig. 6).

**Discussion**

The present study indicated that mpMRI/TRUS-guided biopsies had a higher working area that detects Gleason scores ≥3+4 at least one time in the collected lesion. In addition, the same sensitivity, negligible inconclusive results and high accuracy to those of the histopathology analysis of the surgical specimen were obtained. The results of the study were in line with those of previous studies (8,9,11-13,15,19,21,23). mpMRI/TRUS-guided biopsy promises the detection of clinically significant prostate cancer(s).
The negative predictive value of mpMRI/TRUS-guided biopsy was then assessed. During the study, 105 (10%) of the patients had a Likert scale score of <3 determined by mpMRI and mpMRI/TRUS-guided biopsies identified lesions with Gleason scores <3+4 in 173 (16%) of patients but they had abnormal rectal examinations and elevated prostate-specific antigen. In addition, among the patients with a Likert scale score of <3, 14 had Gleason scores of ≥3+4 determined by endorectal power Doppler/grayscale ultrasound-guided biopsies. Furthermore, analysis of the mpMRI/TRUS-guided biopsies of the lesions of 20 patients gave a false-positive result, as no prostate cancer was detected by histopathological analysis of the surgical specimen. Seminal vesicle invasion may be more precisely detected by histopathology compared with mpMRI (32). Low-grade tumors are isointense and not detected on T2WI. In addition, tumors in the transition zone are more difficult to detect than those in the peripheral zone (33). Post-irradiation tissue damage, scars, atrophy and prostatitis may also be assumed to be prostate cancer on mpMRI (32). The results of the present study indicate a moderate performance of mpMRI/TRUS-guided biopsy in the detection of prostate cancer.

Compared to histopathology of the surgical specimen, endorectal power Doppler/grayscale ultrasound-guided biopsies had a moderate working area that detects Gleason scores ≥3+4 at least one time in the collected lesions, lower sensitivity and accuracy, and a higher number of inconclusive results (78; 7%) and false-negative results (145; 13%). The results of the present study were in line with those of previous studies (5,16,34,35). Power Doppler US is not able to differentiate cancerous vascular clustering lesions from hypervascular inflammation (5). Endorectal power Doppler/grayscale ultrasound-guided biopsy appears to have a barely sufficient diagnostic performance in the detection of prostate cancer.

Table III. Interobserver agreement for the different evaluation methods.

| Parameter | Endorectal power doppler/grayscale ultrasound-guided biopsies | mpMRI | mpMRI/TRUS-guided biopsies | Pathological analysis |
|-----------|--------------------------------------------------|-------|--------------------------|---------------------|
|           | STARD                                             | START |                          | Stanford technique  |
| Evaluators (n) | 15                                           | 15                             | 13                      |                     |
| k value   | 0.51                                              | 0.53                           | 0.56                    | 0.49                |

Poor agreement, k ≤0.40; moderate agreement, 0.4> k ≤0.60; substantial agreement, k >0.60. STARD, Standards for Reporting of Diagnostic accuracy studies; START, Standards of Reporting for MRI-Targeted biopsy studies; mpMRI/TRUS, multiparametric MRI fusion with transrectal ultrasound.
According to the present results, combination of the two biopsies provided a sensitivity of 0.99, accuracy of 0.964, the highest working area that detects at least one lesion with Gleason scores $\geq 3+4$, as well as insignificant false-negative lesions and inconclusive results compared with the results of the histopathology of the surgical specimen. However, the Chinese Guidelines on Urologic Diseases in the newest 2014 version do not recommend this combination of these two biopsies for detection of prostate cancer (36). The next version of the Chinese Guidelines on Urologic Diseases requires to be updated.

Of note, the present study has several limitations. For instance, survival data during the follow-up were not reported. Furthermore, there was a lack of randomization. In addition, the treatment strategies for 46 patients, to whom the urologists had not offered any prostatectomy (n=43), those who refused to undergo surgery (n=3), and those with a low and intermediate risk, were not included. Two types of biopsies were performed, which was not recommended in a clinical setting. In addition, the results of Chinese populations may not be comparable to those from other regions of the world.

In conclusion, mpMRI/TRUS-guided biopsy was indicated to have a moderate performance and endorectal power Doppler/grayscale ultrasound-guided biopsy had a scant performance for decision-making regarding prostatectomy. It is recommended that the health department of the P.R. China releases a new algorithm for the detection of prostate cancer in Chinese males in its new Guidelines on Urologic Diseases.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors have reviewed and approved the manuscript submitted for publication. ZH was project administrator and contributed to the data curation, literature review and supervision of the study. ZY contributed to the conceptualization, literature review and resources of the study. LL contributed to the conceptualization, validation and literature review included in the study. XX contributed to the resources, data curation, formal analysis, literature review, and editing of the manuscript for intellectual content. JY contributed to the formal analysis, software processing and literature review of the study. WH contributed to the investigation, literature review, software and supervision of the study. JC contributed to the supervision, validation, formal analysis and literature review included in the study. YK contributed to the formal analysis and literature review, as well as drafting reviewing and editing of the manuscript for intellectual content. The authors agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Ethical approval and consent to participate

The protocol of the study (DPH/CL/04/15 dated 12 January 2013) was approved by the review board of Southern Medical University. The study adhered to China, Strengthening the Reporting of Observational studies in Epidemiology statement and the 2008 Helsinki Declaration. An informed consent form had been signed by each of the patients enrolled prior to participation regarding pathology, radiology, biopsies, surgeries (if required), and to undergo additional procedure for research purposes only.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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