RESEARCH ARTICLE

The Detection of Clinically Significant Prostate Cancer in Chinese Biopsy Naïve Men. The Role of Mpmri and Targeted Biopsy and Risk Stratification Using PSA Density

Authors

Kai Zhang[1,2] ※, Zijian Song[3,4] ※, S. Remmers[1], Rui Chen[4,I], Gang Zhu[2,I],

Monique J Roobol[1,I]

Affiliations

[1] Department of Urology, Erasmus University Medical Center Cancer Institute, Rotterdam, the Netherlands
[2] Department of Urology, Beijing United Family Hospital and Clinics, Beijing, China
[3] Department of Urology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[4] Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, Shanghai, China
[I] Co-senior author

※ Authors contributed equally

Corresponding author:

Rui Chen:
Department of Urology, Shanghai Changhai Hospital, Second Military Medical University
Changhai Road 168, Yangpu District, Shanghai 200433, China.
E-mail address: drchenrui@foxmail.com

Gang Zhu:
Department of Urology, Beijing United Family Hospital and Clinics, Beijing, China
Jiangtai road 2, Chaoyang District, Beijing 100015,China
E-mail address: zhugang2000@outlook.com

Abstract

Objective To evaluate the performance of the systematic (SBx) and targeted prostate biopsy (TBx) in detecting prostate cancer (PCa) and significant prostate cancer (csPCa) and including upfront risk stratification with PSA Density (PSAD) in a biopsy naïve cohort of Chinese men.

Methods A total of 348 men from two medical centers were available for analyses. All men underwent a mpMRI scan based on an elevated PSA and/or abnormal digital rectal examination (DRE). A total of 150 men received both SBx and TBx prostate biopsy (PIRADS >= 3). In these men the detection ratio was calculated as the PCa and csPCa prevalence of the TBx strategy divided by the prevalence of PCa and csPCa of the SBx + TBx strategy. For PSAD analyses the percentage missed csPCa were plotted against the clinically relevant thresholds of PSAD (range 0.01 – 0.20).

Results In the men with PIRADS >= 3, a total of 89 PCa cases (59 being csPCa) were detected. The TBx alone strategy detected 74 of all PCa, leading to a detection ratio of 0.83 (95% CI 0.74-0.90). For csPCa these numbers were 48 of the total 59 csPCa cases, i.e a detection ratio of 0.81 (95% CI 0.69-0.90).With the focus on avoiding missing csPCa diagnoses a cut-off of PSA D 0.10 seemed optimal in this cohort, leading to a reduction of 15% of all referrals, missing 6% of all PCa and 2% of csPCa. A similar cut-off of PSAD holds if also men with PIRADS >= 2 were included.

Conclusion In this Chinese cohort of biopsy naïve men a TBx approach can aid in improved detection of csPCa. Omitting SBx would results in missing csPCa cases. An upfront risk stratification step with the use of PSAD is advised although the optimal PSAD cut-off in Asian men most likely differs from the generally advised cut-off of 0.15 ng/ml/ml.

Keywords: Targeted biopsy, MRI, Prostate carcinoma, PSA density，Diagnosis

1. Introduction

The conventional PSA testing and subsequent transrectal ultrasound (TRUS) – guided systematic prostate biopsy approach led to overdiagnosis and often subsequent overtreatment of prostate cancer (PCa) [1,2,3]. Nowadays, multiparametric MRI (mpMRI) has an important role in PCa diagnosis. It is shown that the use of mpMRI incombination with targeted biopsy improves the accuracy of clinically significant PCa (csPCa) detection worldwide [4,5,6,7,8]. In addition to risk stratification using mpMRI imaging, PSA density (PSAD) has proven to be a strong predictor for the presence of PCa and clinically significant PCa (csPCa). Recent studies have suggested that the combination of PSAD and the result of mpMRI on the basis of the Prostate Imaging Reporting and Data System (PI-RADS) may improve selecting those men at high risk of harboring csPCa and as such avoid unnecessary testing and reduce overdiagnosis [9,10,11,12].

Most data on this topic, however, originate from Caucasian men. In this study we analyse data of mpMRI, PSAD and prostate biopsy outcome in a biopsy naïve population of men from two Chinese medical centers.

The aim of the current study is two-fold. First we will investigate the added value of mpMRI based targeted biopsy (TBx) in addition to the systematic biopsy (SBx) approach in detecting PCa and csPCa. In addition, we will assess the potential of the generally recommended PSAD cut-off of < 0.15 ng/ml/ml in risk stratifying men in high and low risk for having csPCa. This will be investigated in both men biopsied with the classical systematic approach and men biopsied with both systematic and MRI targeted prostate biopsy.

2. Materials and methods

2.1 Study population

From September 2013 until December 2017, a total of 255 men in Shanghai Changhai Hospital, Second Military Medical University and 93 men in Beijing United Family Hospital and Clinics were included in this study. All men were biopsy naïve and all men underwent a mpMRI scan because of a clinical suspicion of PCa (no prior PCa diagnosis) based on an elevated PSA and/or abnormal digital rectal examination (DRE).

2.2 mpMRI protocol

In the Changhai Hospital cohort, MRIs were performed on a 3.0T system (Magnetom Skyra, Siemens Medical Solutions, Erlangen, Germany). The prostate MRI protocols included T1WI, triplanar (axial, sagittal and coronal) T2WI, diffusion weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE) by using an 18-channel phased-array coil. A single radiologist (Qingsong Yang) with 10 years of experience in prostate MRI analyzed the images and marked all the lesions according to the PI-RADS version 1.0 or 2.0 (after 2015).

In the Beijing United Family Hospital and Clinics cohort, a 1.5T system (GE Healthcare) was used and the prostate MRI protocols included T1WI, triplanar (axial, sagittal and coronal) T2WI, DWI and DCE by using an 8-channel phased-array coil. All the MRIs were reported by a single radiologist (Nan Luo) with more than 6 years of experience in prostate mpMRI based on PI-RADS version 1.0 or 2.0.

2.3 Systematic biopsy and MRI-targeted biopsy

In the Changhai Hospital cohort, the systematic biopsy was performed with a TRUS-guided approach using a median number of 12 cores (IQR 12-12) due to elevated PSA (≥4ng/ml) and/or abnormal DRE. MRI-targeted biopsy was implemented using cognitive fusion system, in which the biopsy operator used TRUS imaging to aim the suspicious lesions identified at MRI. The median number of MRI-targeted biopsy core was 3 (IQR 2-4).

In the Beijing United Family Hospital and Clinics cohort, a TRUS-guided systematic biopsy was performed with a median number of 13 cores (IQR 12-16) due to elevated PSA (≥4ng/ml) and/or abnormal DRE. Here, if indicated, men underwent MRI-targeted cognitive biopsy. The median number of MRI-targeted biopsy core was 4 (IQR 3-6).

csPCa was defined as Gleason grade ≥ 3+4/ Gleason Grade group ≥ 2.

2.4 Statistical analysis

The detection ratio was calculated as the prevalence of the TBx method divided by the prevalence of the SBx + TBx strategy. Confidence interval were calculated with the bootstrap percentile method with 3000 bootstrap samples. To investigate the current recommendation of 0.15 for PSA D, we plotted the percentage missed csPCa against the clinically relevant thresholds of PSA D (range 0.01 – 0.20).

The statistical analyses were performed using SPSS version 21.0 and R version 3.5.1

3. Results

3.1 Patient characteristics

Within the entire study cohort of 348 men, 138 PCa cases (40%) were detected of which 93 cases where classified as csPCa (27% and 67% of all PCa). Analyses related to the added value of TBx were performed on a sub cohort of men having received systematic and targeted prostate biopsy with their MRI classified as PIRADS ≥ 3 (N= 150). To evaluate the value of PSA-D in risk stratification we added those men with a PIRADS 2 who received systematic biopsy (total N= 219). Patient characteristics of the entire cohort and the two sub cohorts are displayed in Table 1 A-C.

Table 1A-C: patient characteristics of entire cohort (A) , patient characteristics of cohort with a PIRADS >= 3 and having had both TBx and SBx (B) and all men with PIRADS 2 having had SBx and men with PIRADS >= 3 having had TBx and SBx (C).

1A.

	Median (IQR) / n (%)
Age (year)	65 (60-72)
PSA (ng/ml)	8.6 (6.1-13.3)
PV_MRI (cc)	44.8 (32.6-64.7)
PSAD (ng/ml/ml)	0.19 (0.11-0.35)
PI-RADS	
1-2	129 (37%)
3	70 (20%)
4	85 (24%)
5	64 (18%)

PSA = prostate specific antigen; PV_MRI =prostate volume assessed with MRI; PSAD = prostate specific antigen density

1B.

	Median (IQR) / n (%)
Age (year)	67 (61-72)
PSA (ng/ml)	8.5 (6.3-11.8)
PV_MRI (cc)	42.3 (26.3-57.2)
PSAD (ng/ml/ml)	0.22 (0.12-0.39)
PI-RADS	
3	59 (39%)
4	56 (37%)
5	35 (23%)

PSA = prostate specific antigen; PV_MRI =prostate volume assessed with MRI; PSAD = prostate specific antigen density

1C: patient characteristics of cohort of men that received SBx (PIRADS 2, N= 129) and all men that received SBx plus TBx (PIRADS 3 or higher, N= 150).

	Median (IQR) / n (%)
Age (year)	64 (59-71)
PSA (ng/ml)	8.2 (6.1-11.8)
PV_MRI (cc)	45.0 (32.5-67.3)
PSAD (ng/ml/ml)	0.17 (0.11-0.31)
PI-RADS	
1-2	129 (46%)
3	59 (21%)
4	56 (20%)
5	35 (13%)

PSA = prostate specific antigen; PV_MRI =prostate volume assessed with MRI; PSAD = prostate specific antigen density

3.2 PCa and csPCa detection, systematic and targeted prostate biopsy.

To assess the added value of targeted biopsy we used men with PIRADS >= 3 and having had both systematic and targeted biopsy (N= 150), see Table 1B for patient characteristics.

The systematic biopsy approach detected 75 of the total of 89 PCa cases that were detected (84%), implying that the targeted prostate biopsies accounted for the detection of an additional 14 PCa cases. However, the targeted biopsy approach alone detected 74 of all PCa, leading to a detection ratio of 0.83 (95% CI 0.74-0.90) using only targeted biopsies. For csPCa these numbers were 43 of the total 59 csPCa cases (73%) would have been detected with the systematic biopsy approach and the number of additional diagnoses with targeted biopsy was 16. The targeted approach alone detected 48 of all csPCa, leading to a detection ratio of 0.81 (95% CI 0.69-0.90) using only targeted biopsies.

A strategy where we would have omitted the systematic biopsies would have led to missing 15 PCa diagnoses (17%) overall and 11 csPCa diagnoses (19%).

A strategy where we would have omitted the targeted biopsies would have led to missing 14 PCa diagnoses (16%) overall and 16 csPCa diagnoses (27%).

3.2.1 Risk stratification using PSA D in men with PIRADS ≥ 3.

If a strategy would have been applied where men with a PSA D < 0.15 are not referred for further work-up after MRI , a total of 49 (33%) would not have been biopsied , missing a total of 16 (18% of all) cases of PCa and 5 (8% of all) cases of csPCa. Applying a threshold of PSA D < 0.10 would lead to a reduction of 23 (15%) of all referrals, missing only 5 (6%) cases of PCa and 1 (2%) of csPCa. With the focus on avoiding missing csPCa diagnoses a cut-off of PSA D 0.10 seems optimal in this cohort, see Figure 1.

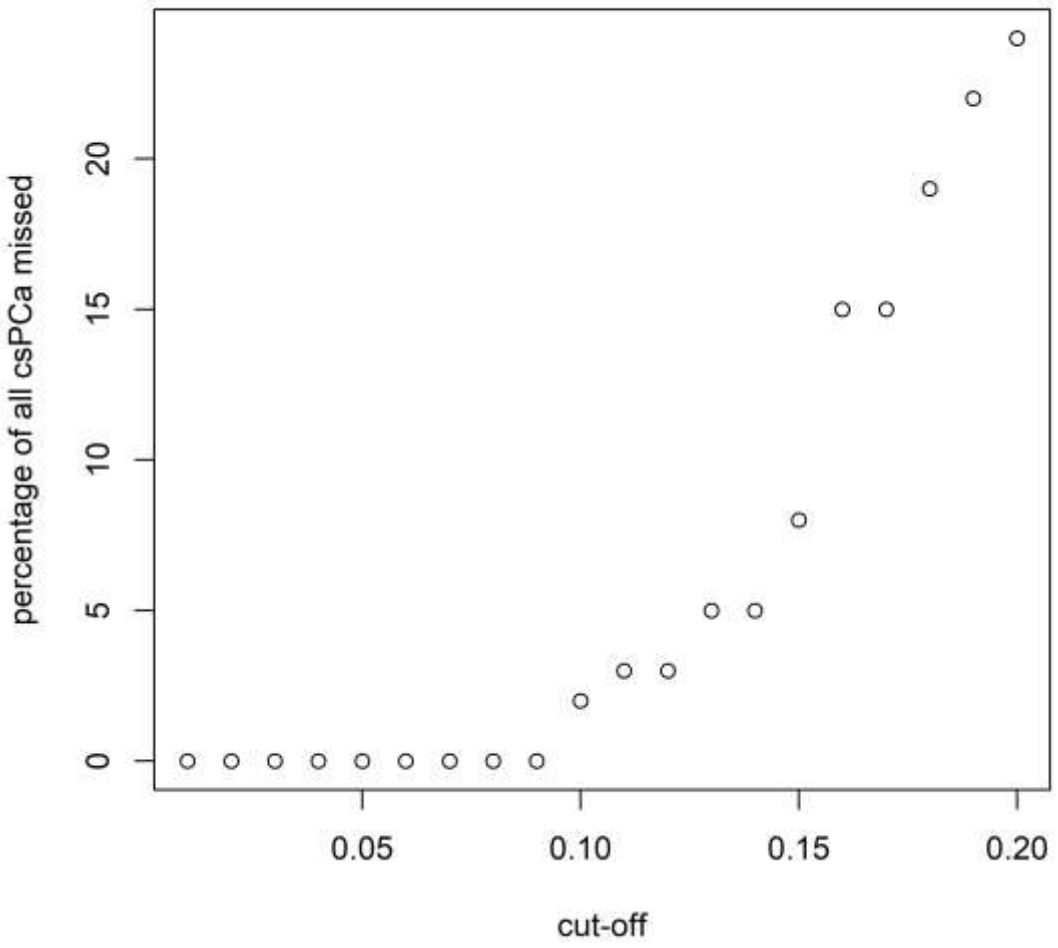

Figure 1: The percentage of csPCa missed per PSAD cut-off (ng/ml/ml) in men with PIRADS >= 3 and having had both systematic and targeted biopsy

3.3 Risk stratification using PSA D in all men referred for MRI

To assess the performance of an upfront (pre-MRI and pre-biopsy) risk stratification step we looked at all men that received systematic biopsy (PIRADS 2, N= 129) and all men that received systematic plus targeted biopsy (PIRADS 3 or higher, N= 150). In this group (N=279) a total of 100 PCa cases were detected (36%) of which 65 (65% and 23% of total cohort) were classified as csPCa, see Table 1C for patient characteristics.

Applying the PSA-D cut-off of < 0.15 within this cohort would have resulted in 118 (42%) men not being biopsied while missing 19 (19% of all) PCa cases detected of which 7 (11%) are considered csPCa. In other words, we would have saved 42.2% MRI investigations and subsequent prostate biopsies (118 of 279 men). Of those 111 (excluding the missed csPCa cases) can be

considered as unnecessary (39.8%). With a threshold for referral of PSA < 0.10, 59 (21%) men did not need referral, missing 7 (7% of all) cases of PCa and 2 (3% of all) cases of csPCa. Also here , when focusing on avoiding missing csPCa diagnoses the cut-off of PSAD < 0.10 seems more appropriate, given the percentages of missed csPCa, see Figure 2

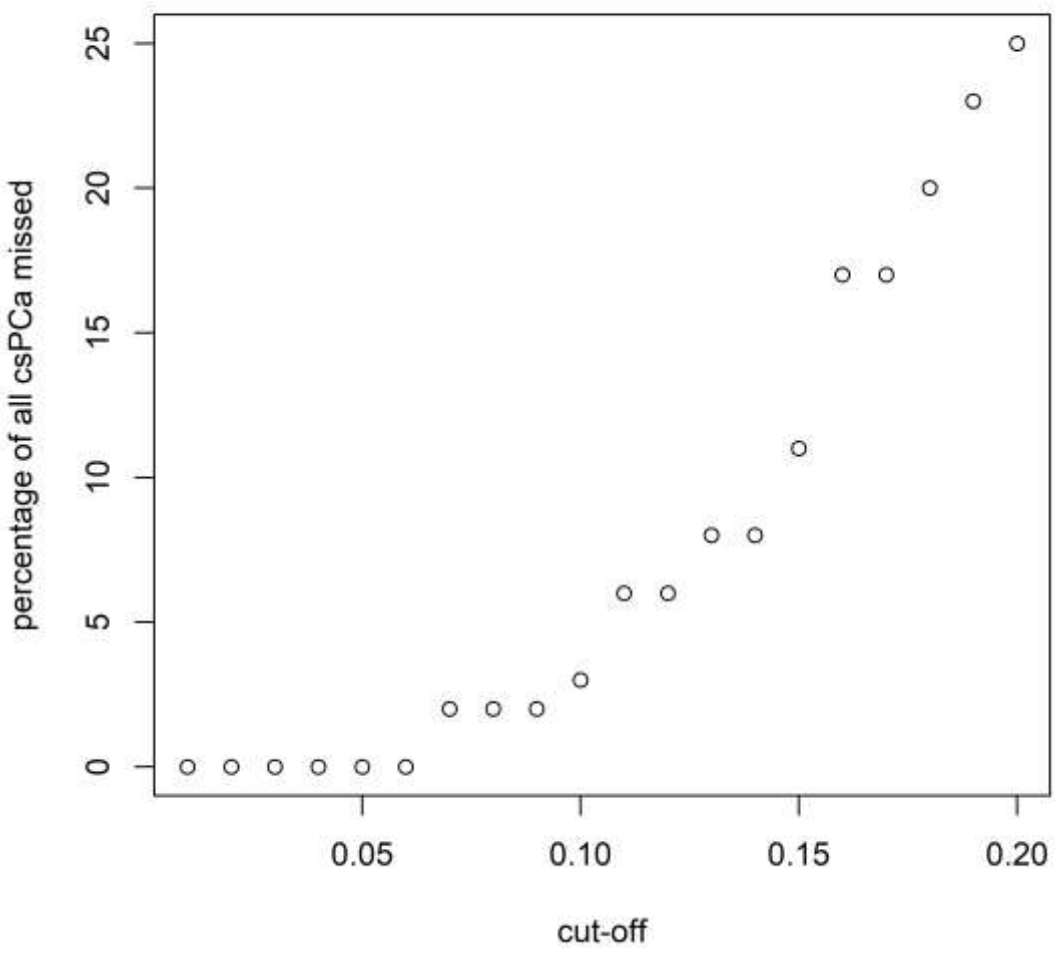

Figure 2: The percentage of csPCa missed per PSAD cut-off (ng/ml/ml) in men with PIRADS >= 2 and having had systematic and targeted biopsy if PIRADS >= 3.

4. Discussion

In this manuscript, based on analyses of data on biopsy outcome in a contemporary, biopsy naive Chinese patient cohort we looked at the PCa and csPCa detection rate using systematic and /or targeted prostate biopsy. The data show an overall PCa detection rate of 40% with 67% of all PCa detected classified as csPCa (Gleason grade ≥ 7 or Grade group ≥2). While the overall cancer detection rate is somewhat lower as compared to western cohorts (55-58%) the

percentage of csPCa among those men diagnosed (61-72%) is comparable [6,13]. In line with currently available data the current results show improved detection of csPCa as compared to the TRUS -guided systematic biopsy [4,14,15,16]. It is however clear from this data that although the targeted biopsy approach increases the detection of csPCa it cannot fully replace the systematic approach. This is in line with previous results based on predominantly Caucasian data. In a cohort of 300 men it was shown that combining systematic and targeted biopsy provided greatest sensitivity for the detection of csPCa and that discordance of tumor locations suggested that the different biopsy approaches detect different tumors [17]. It is important to note that in a recent study it was mentioned that Asian American men have a distinctly different prostate cancer epidemiology than e.g. causcasian men. This is reflected in the different performance of PI-RADS, where in this Asian American population the number of clinically significant PCa cases in men graded as having a PIRADS3 lesion was considerably lower (6% versus 15%).[18] While this observation is not confirmed by our patient cohort it can have implications for the need of additional risk stratification.

It is well known that PSAD is a strong predictor for the presence of PCa at biopsy. The concept of PSAD was first described by Benson et al in 1992 [19]. Many studies after that have recommended the use of this parameter to enhance PSA specificity, especially in the so-called grey area of PSA , i.e. between 3.0-10.0 ng/ml [9,20,21].

Recently, this was confirmed in a study of almost 1000 men who underwent TRUS guided prostate biopsy with PSA levels ≤20.0 ng/ml. The authors concluded that the in general recommended PSAD cut off value of < 0.15 was within the range of PSAD (0.09-0.19) where the detection rate of csPCa was significantly higher as compared to men with PSAD level outside this range [22].

I a recent study of Han et al, using data of 123 men with PSA values between 4-10 ng/ml it was shown that risk stratification using PSAD next to mpMRI increased the capability of selectively detecting significant PCa [23]. In this study men with csPCa , as compared to men with no PCa had statistically significant higher mean PSAD values (0.267 ng/ml/ml versus 0.182 ng/ml/ml res).

In our data it was shown that the generally recommended PSAD cut-off of 0.15 ng/ml/ml was not the optimal choice. When focusing on maintaining the csPCa detection rate as high as possible a PSAD cut-off 0.10 would have been better. Although this lower PSAD cut-off overall results in less avoided MRIs and /or biopsies, the balance between avoided and csPCa diagnoses missed is more favorable.

The observation that cut-off values for biomarkers can differ between Caucasian and Asian men is not new. It has already been shown for e.g. the biomarker PHI (a combination of -2pro PSA, total and free PSA). In a comparative study on the performance of the Prostate Health Index (PHI) the biopsy results of a total of 2488 men from different ethnic groups (1688 Asian and 800 European men from 9 sites) with PSA 2–20 ng/ml and PHI test were evaluated. The conclusion was that PHI was effective in cancer risk stratification for both European and Asian men but that population-specific PHI reference ranges should be used [24].

Combination of PSAD, PI-RADS and other patient characteristics could improve the predictive accuracy PCa and csPCa. The Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculators (ERSPC-RCs) are well validated models which could improve PCa detection and avoid unnecessary biopsy [4,24,25].

The strengths of our study lie in the fact this is a multicenter trial with different experience and biopsy approaches. There were however no significant differences in age, PSA level and PSAD. It must be noted however, although experienced, the MRI images were reviewed by different radiologists and men with a systematic biopsy came from one center while men with both systematic and targeted biopsy came from two centers. In addition, both PI-RADS version1.0 and PI-RADS version 2.0 were used. Here it must be noted that the effect on our results is most likely limited. Studies evaluating the differences between PI-RADS 1.0 and 2.0 demonstrated that the diagnostic accuracy between both versions differs minimally [27,28,29]. Finally, due to the limited sample size our results should be interpreted with caution and warrant further validation.

5. Conclusions

A targeted biopsy approach can aid in improved detection of csPCa. Omitting the systematic biopsy however would results in a loss of csPCa detection. Similar to earlier publications we conclude that in this Chinese cohort a systematic plus targeted biopsy (in indicated by MRI with PIRADS ≥ 3) is the optimal detection strategy. An upfront risk stratification step with the use of PSAD is advised. It must be noted however that the optimal PSAD cut-off in Asian men most is lower than the commonly used, based predominantly on western populations, cut-off of 0.15 ng/ml/ml.

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