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Contemporary outcomes in the detection of prostate cancer using transrectal ultrasound-guided 12-core biopsy in Singaporean men with elevated prostate specific antigen and/or abnormal digital rectal examination

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Abstract *Objective:* Despite being the third commonest cancer in Singaporean men, there is a dearth of basic data on the detection rate of prostate cancer and post-procedure complication rates locally using systematic 12-core biopsy. Our objective is to evaluate prostate cancer detection rates using 12-core prostate biopsy based on serum prostate specific antigen (PSA) levels and digital rectal examination (DRE) findings in Singaporean men presenting to a single tertiary centre. The secondary objective is to evaluate the complication rates of transrectal prostate biopsies.
Methods: We retrospectively examined 804 men who underwent first transrectal-ultrasound (TRUS) guided 12-core prostate biopsies from January 2012 to April 2014. Prostate biopsies were performed on men presenting to a tertiary institution when their PSA levels were ≥4.0 ng/mL and/or when they had suspicious DRE findings.
Results: Overall prostate cancer detection rate was 35.1%. Regardless of DRE findings, patients were divided into four subgroups based on their serum PSA levels: 0–3.99 ng/mL, 4.00–9.99 ng/mL, 10.00–19.99 ng/mL and ≥20.00 ng/mL and their detection rates were 9.5%, 20.9%, 38.4% and 72.3%, respectively. The detection rate of cancer based on suspicious DRE findings alone was 59.2% compared to 36.5% based on serum PSA cut-off of 4.0 ng/mL alone. The post-biopsy admission rate for sepsis was 1.5%.

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Conclusion: In conclusion, using contemporary 12-core biopsy methods, the local prostate cancer detection rate based on serum PSA and DRE findings has increased over the past decade presumably due to multiple genetic and environmental factors. Post-biopsy sepsis remains an important complication worldwide.

1. Introduction

According to the Singapore Cancer Registry, prostate cancer was the third commonest cancer in men during 2009—2013, making up 12.1% of all cancers reported locally [1]. The incidence of prostate cancer has been rapidly increasing in the last decade. Potential reasons for this increase include the advent of better detection methods, an aging population as well as a shift in dietary patterns [2]. However, the incidence of prostate cancer in Singapore is still much lower compared to other Western countries such as the USA [3]. In years to come, prostate cancer will likely become an increasingly important health issue as its diagnosis and management continues to evolve. Hence, it is essential to review and update our current diagnostic pathway based on the latest evidence so as to further improve patient outcomes.

Current established detection methods of prostate cancer include digital rectal examination (DRE), serum prostate specific antigen (PSA) and transrectal ultrasound (TRUS)-guided prostate biopsy using a systematic 12-core method. Serum PSA cut-offs of between 2.5 and 4.0 ng/mL have been used by studies on prostate cancer screening such as the European Randomized Study of Screening of Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO) [4,5].

The median PSA in Singaporeans is lower than that reported in Caucasian men [6]. However, there is a dearth of basic data for the detection rate of prostate cancer according to serum PSA levels and DRE findings. In this retrospective study, we endeavored to examine the detection rate of prostate cancer on contemporary 12-core TRUS-biopsy in men with either PSA $\geq$4.0 ng/mL and/or have suspicious DRE findings and also to analyze the complication rates of biopsy.

2. Materials and methods

In our study, we retrospectively analyzed 804 men who underwent TRUS-guided prostate biopsy in a single institution from January 2012 to April 2014. The indications for prostate biopsy were serum PSA $\geq$4.00 ng/mL and/or DRE findings suspicious for malignancy (including induration, irregularity, nodularity and asymmetry). Subjects who had previous prostate biopsy, prostate surgery, known diagnosis of prostate cancer and previous use of 5-α reductase inhibitors were excluded from the study. All subjects had at least one or more serum PSA levels measured and were subjected to DRE. All PSA measurements were performed using PSA Hybritech Assay and only the latest results taken prior to prostate biopsy were used in our analysis.

For the prostate biopsy, patients were placed in the left lateral position and a TRUS-guided needle biopsy of the prostate was performed. The ultrasound scanner used was Siemens ACUSON X150. The prostate volume was measured using the ellipsoid formula (π/6 $\times$ craniocaudal $\times$ transverse $\times$ anteroposterior length). Patients underwent systematic 12-core or 18-core biopsy depending on the performing clinician's evaluation of the prostate volume and DRE findings. Additional cores were taken at the urologist's discretion such as taking a core from a hypoechoic lesion seen on ultrasound. The core specimens were examined by pathologists in the same institution. Prostate cancers with Gleason sum $\geq$7 were considered clinically significant. For peri-procedure sepsis prophylaxis, men were given 7 days of peri-procedural oral ciprofloxacin tablets (3 days pre- and 4 days post-procedure) and one dose of intra-muscular gentamicin 120 mg just before the procedure. Bisacodyl suppositories were given for rectal preparation on the day of the procedure. The rectum was cleansed using povidone-iodine solution just before needle biopsy.

We further evaluated the post-procedural complications which required inpatient admission such as infection. In men who developed post-procedure fever, they were given intravenous cefepime and a single dose of amikacin as per institution protocol. The antibiotic used would then be rationalised based on culture and sensitivities.

Statistical analysis was performed using IBM SPSS Statistics 20.0. *t*-test, Kruskal—Wallis and Pearson Chi-square tests were used to evaluate any differences in continuous and categorical variables respectively. Ethics approval was obtained from the Domain-Specific Review Board (DSRB) before commencement of data collection (2010/00318).

3. Results

Eight hundred and four men underwent first TRUS-guided prostate biopsy. Seven hundred and thirty-three (91.2%) were Chinese while 71 (8.8%) were from other races such as Malay, Indian and Caucasian. Their mean age was 68.2 $\pm$ 8.9 years, median prostate volume was 45.0 mL and median serum PSA levels were 8.6 ng/mL (Table 1). The systematic 12-core prostate biopsy were performed on 468/522 (89.7%) of men without cancer compared to 236/282 (83.7%) men with cancer ($p < 0.01$).

Two hundred and eighty-two men (35.1%) had a positive biopsy result for prostate cancer, which included 215 men (76.2%) who had clinically significant disease (Gleason

Table 1 Patient characteristics.

Demographics	Total	Men without cancer	Men with cancer	*p*-Value
Patients, *n* (%)	804 (100.0)	522 (64.9)	282 (35.1)	
Age (year, mean ± SD)	68.2 ± 8.9	66.8 ± 8.6	70.7 ± 8.7	<0.001[a]
No. of cores, median (IQR)	12.0 (12.0, 12.0)	12.0 (12.0, 12.0)	12.0 (12.0, 12.0)	<0.001[b]
DRE findings				
Normal, *n* (%)	566 (100.0)	425 (75.1)	141 (24.9)	
Suspicious, *n* (%)	238 (100.0)	97 (40.8)	141 (59.2)	<0.001[c]
PV (mL, median (IQR))	45.0 (30.0, 64.9)	48.2 (33.7, 68.0)	39.0 (28.0, 57.5)	<0.001[b]
Serum PSA (ng/mL, median (IQR))	8.6 (6.0, 16.4)	7.2 (5.4, 10.5)	16.0 (8.0, 82.8)	<0.001[b]
PSA density (ng/mL^2, median (IQR))	0.196 (0.120, 0.382)	0.152 (0.107, 0.237)	0.463 (0.205, 1.845)	<0.001[b]

IQR, inter quartile range; PV, prostate volume; PSA, prostate specific antigen.
[a] *t*-test.
[b] Kruskal–Wallis test.
[c] Chi-square test.

sum ≥7). Men with prostate cancer were older (70.7 *vs.* 66.8 years, $p < 0.001$) and had higher PSA levels (16.0 *vs.* 7.2 ng/mL, $p < 0.001$) despite having smaller prostates (39.0 *vs.* 48.2 mL, $p < 0.001$). They were also more likely to have suspicious DRE findings (59.2% *vs.* 40.8%, $p < 0.001$) (Table 1). Among the 522 men without cancer, 82 (15.7%) men underwent a second repeat biopsy, of which 14 (17.1%) men had a positive result for cancer. Four patients underwent a third biopsy of which one (25%) of them had a positive biopsy.

Out of the 762/804 (94.8%) men with serum PSA ≥ 4.00 ng/mL, 278/762 (36.5%) had a positive biopsy. Serum PSA levels were categorised into four main categories: 0–3.99 ng/mL, 4.00–9.99 ng/mL, 10.00–19.99 ng/mL and ≥20.00 ng/mL. Their corresponding overall prostate cancer detection rates, regardless of DRE findings, were 4/42 (9.5%), 87/417 (20.9%), 66/172 (38.4%) and 125/173 (72.3%), respectively (Table 2).

In total, 238/804 (29.6%) men had suspicious DRE findings. The detection rate of cancer based on DRE alone is 141/238 (59.2%). When a cut-off of PSA ≥4.00 ng/mL was used, the detection rate of cancer in patients with suspicious DRE was increased to 137/196 (69.9%). The corresponding overall cancer detection rates of suspicious DRE findings were 4/42 (9.5%), 21/54 (38.9%), 20/34 (58.8%) and 96/108 (88.9%) when serum PSA levels were 0–3.99 ng/mL, 4.00–9.99 ng/mL, 10.00–19.99 ng/mL and ≥20.00 ng/mL, respectively (Table 2). The corresponding clinically significant cancer detection rates based on suspicious DRE findings were 2/42 (4.8%), 16/54 (29.6%), 17/34 (50.0%) and 95/108 (88.0%), respectively (Table 3). Men with prostate cancer were more likely to have suspicious DRE findings in the 4.00–9.99 ng/mL, 10.00–19.99 ng/mL and ≥20.00 ng/mL serum PSA categories ($p = 0.001$, $p = 0.01$ and $p < 0.001$, respectively). Table 4 summarises the sensitivity, specificity, positive predictive value and negative predictive value of DRE.

Among the 762 men with PSA ≥4.00 ng/mL, 161 (21.1%) had benign prostate hyperplasia while 252 (33.1%) had prostatitis on biopsy. Forty-one (5.4%) had atypical glands while 29 (3.8%) had high grade prostatic intra-epithelial neoplasia on biopsy. One (0.1%) patient had a spindle cell neoplasm. Among the 41 men with atypical glands on biopsy, 23 underwent a second repeat biopsy, of which nine (39.1%) had a positive biopsy for prostate cancer.

Twelve (1.5%) men were admitted for inpatient hospital stay due to post-procedure sepsis, of which three (25.0%) developed severe sepsis. One suffered from cardiorespiratory collapse (pulseless electrical activity) and died. Another patient was sent to the surgical intensive care unit for septic encephalopathy and the last patient had hypotension which was fluid responsive. Seven (58.3%) had a

Table 2 Overall prostate cancer detection rates based on serum PSA levels and DRE findings.

PSA (ng/mL)	Patients (*n*)	Cancer detection rate, *n* (%)	Normal DRE		Abnormal DRE	
			Incidence (*n*)	Cancer detection, *n* (%)	Incidence (*n*)	Cancer detection, *n* (%)
0–3.99	42	4 (9.5)	–	–	42	4 (9.5)
4.00–9.99	417	87 (20.9)	363	66 (18.2)*	54	21 (38.9)*
10.00–19.99	172	66 (38.4)	138	46 (33.3)*	34	20 (58.8)*
≥20.00	173	125 (72.3)	65	29 (44.6)*	108	96 (88.9)*
Total	804	282 (35.1)	566	141 (24.9)*	238	141 (59.2)*
4.00–19.99	589	153 (26.0)	501	112 (22.4)*	88	41 (46.6)*
≥4.00	762	278 (36.5)	566	141 (24.9)*	196	137 (69.9)*
<20.00	631	157 (24.9)	501	112 (22.4)*	130	45 (34.6)*

*$p < 0.05$, Chi-square test.
DRE, digital rectal examination; PSA, prostate specific antigen.

Table 3 Clinically-significant prostate cancer detection rates based on serum PSA levels and DRE findings.

PSA (ng/mL)	Patients (*n*)	High-grade cancer detection rate, *n* (%)	Normal DRE		Abnormal DRE	
			Incidence (*n*)	High-grade cancer detection, *n* (%)	Incidence (*n*)	High-grade cancer detection, *n* (%)
0–3.99	42	2 (4.8)	–	–	42	2 (4.8)
4.00–9.99	417	45 (10.8)	363	29 (8.0)*	54	16 (29.6)*
10.00–19.99	172	48 (27.9)	138	31 (22.5)*	34	17 (50.0)*
≥20.00	173	120 (69.4)	65	25 (38.5)*	108	95 (88.0)*
Total	804	215 (26.7)	566	85 (15.0)*	238	130 (54.6)*
4.00–19.99	589	93 (15.8)	501	60 (12.0)*	88	33 (37.5)*
≥4.00	762	213 (28.0)	566	85 (15.0)*	196	128 (65.3)*
<20.00	631	95 (15.1)	501	60 (12.0)*	130	35 (26.9)*

*$p < 0.05$, Chi-square test.
DRE, digital rectal examination; PSA, prostate specific antigen.

positive blood culture which grew *Escherichia coli*, of which only one of them was positive for extended-spectrum β-lactamase.

4. Discussion

According to the Singapore Cancer Registry, 3456 new cases of prostate cancer were diagnosed during 2009–2013. The age-standardised incidence rate for prostate cancer has risen dramatically over the last 40 years from 5.2/100,000 in 1973–1977 to 28.1/100,000 in 2009–2013. Prostate cancer also has the 5th highest cancer mortality in Singapore. The 5-year age-specific standardised observed survival of prostate cancer was 74.86% from 2009 to 2013 compared to 70.77% from 2004 to 2008 [1]. This is in comparison with an observed survival of 98.9% in the USA from 2004 to 2010 [3] and 81.4% in England from 2005 to 2009 [7].

In this study, we retrospectively analyzed the detection rate of prostate cancer in patients undergoing biopsy from January 2012 to April 2014 in a single tertiary hospital. With increasing use of serum PSA testing in the urology outpatient setting as well as part of individual health-screening packages offered in primary care, there is a need to examine the prostate cancer detection rates based on serum PSA levels and DRE findings using contemporary 12-core prostate biopsy as well as its complication rates. This will help guide urologists and patients in making well-informed decisions regarding the indications for biopsy, together with the discussion of the potential risks.

Table 4 Characteristics of DRE at various PSA categories for overall prostate cancer detection on biopsy.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DRE + PSA < 4.00 ng/mL	–	–	9.5	–
DRE + PSA 4.00–9.99 ng/mL	24.1	90.0	38.9	81.8
DRE + PSA 10.00–19.99 ng/mL	30.3	86.8	58.8	66.7
DRE + PSA ≥ 20.00 ng/mL	76.8	75.0	88.9	55.4
DRE+ any PSA	50.0	81.4	59.2	75.1

DRE, digital rectal examination; PSA, prostate specific antigen; PPV, positive predictive value; NPV, negative predictive value.

For the past 8 years, there has been no update on the detection rate of prostate cancer using 12-core TRUS biopsy in our local population. Our study provides some insight into the diagnostic yield of serum PSA and DRE using contemporary biopsy methods. Our results demonstrated a higher detection rate of prostate cancer compared to previous studies done locally. In men with serum PSA less than 20.00 ng/mL, the detection rate of prostate cancer in our current study is 24.9%, compared to previous data of 19.4% reported by Ng et al. (2002) [8] and 8.9% reported by Tan et al. (1995) [9]. Sextant core biopsy and 10-core biopsy were performed in the study by Tan et al. [9] and Ng et al. [8] respectively, compared to systematic 12-core biopsy in our current study. The indications for prostate biopsy in all three studies were similar. Due to differences in the sample populations, one can only postulate that the current increased detection rate is due to an increase in the number of cores taken on TRUS prostate biopsy, improvement in technique of biopsy as well as increasing incidence of prostate cancer which is likely multifactorial [10].

In patients with serum PSA level of 4.00–9.99 ng/mL, the detection rate of overall prostate cancer, regardless of DRE findings, was 20.9%. This rate is less than the 26.1% detection rate reported by Catalona et al. [11] in American men using only sextant biopsy. Meanwhile, Andriole et al. [4] reported a detection rate of 35.7% (297/832) from the initial screening round of PLCO. Within the same PSA range of 4.00–9.99 ng/mL, Egawa et al. [12] reported a detection rate of 15.8% in Japanese men who underwent a sextant biopsy while Masumoto et al. [13] reported a rate of 19.7% in men who underwent systematic 12-core biopsy. Similarly, Seo et al. [14] reported a 19.6% detection rate in a Korean study population of which only about 50% were subjected to a 12-core biopsy. Various factors may explain the differences in prostate cancer detection rate across various geographical populations. These include differences in sample characteristics (e.g., screened *vs.* unscreened),

biopsy indications and methods, the number of cores taken during biopsy and inherent ethnic differences [10]. In particular, many Asian countries such as Singapore may be losing their protective cultural factors and acquiring high-risk lifestyle, dietary or environmental factors which may account for the decreasing gap in prostate cancer incidence and detection rates amongst Asian and Western populations [2].

DRE remains a relevant and important tool for clinicians in the detection of prostate cancer [15–17]. In our study, the sensitivity and specificity of DRE for prostate cancer detection, regardless of PSA levels, are 50.0% and 81.4% respectively. The detection rate of prostate cancer based on suspicious DRE findings alone (59.2%) is superior than that of using serum PSA levels (at a cut-off of 4.00 ng/mL = 36.5%) alone, with a combined detection rate of 69.9% (if both PSA ≥4.00 ng/mL and suspicious DRE). It has to be noted that DRE is not a sensitive test for prostate cancer in patients with intermediate PSA levels (4.00–9.99 ng/mL) with suspicious DRE findings being only able to detect 24.1% of prostate cancers on initial biopsy. However, DRE is still useful in picking up cancers which are likely to be clinically significant. 92.2% of cancer patients who had suspicious DRE findings had a Gleason sum of 7 and above (analysis not shown) on histopathological analysis. This is concordant with other studies that demonstrated that an abnormal DRE was an independent predictor of cancer, especially clinically significant cancers [18–20].

It is noted that in men with PSA levels between 0 and 3.99 ng/mL, DRE had a low positive predictive value of prostate cancer – about 11 biopsies would be required to diagnose one cancer (9.5% detection rate) and 21 biopsies for one significant cancer (4.8% detection rate). All four men diagnosed with cancer had serum PSA <2.50 ng/mL. There is currently no good evidence to demonstrate any reduction in morbidity and mortality from prostate cancer when it was detected by DRE. Bozeman et al. [21], Carvalhal et al. [22], Fowler et al. [23] and Schröder et al. [24] have all previously reported that the positive predictive value of DRE in men with PSA levels of 0–3.99 ng/mL is general low (10%, 8.8%, 13% and 19%, respectively). In another study in Korea where there is a relatively lower incidence of prostate cancer, Shim et al. [25] found that there were no differences in detection rates of cancer based on DRE findings (abnormal *vs.* normal) in men 45–59 years as well as men with PSA levels 2.50–3.99 ng/mL. Gosselaar et al. [26] studied men with PSA 2.00–3.99 ng/mL and found that PSA as a biopsy indication outperformed DRE in cancer detection at the cost of overdiagnosis of clinically insignificant cancers and was also able to pick up potentially aggressive tumours that were T1c cancers. Vis et al. [27] suggested that DRE as a screening test for prostate cancer at low PSA values may be replaced by screening using PSA testing alone as 289 DREs are required to find one case of clinically significant disease and 96 DREs to diagnose any prostate cancer. Unfortunately, our study lacks data on the cancer detection rate in men with PSA 0–3.99 ng/mL and normal DRE for comparison. With only a small number of men with PSA 0–3.99 ng/mL in our study, caution should be taken in making any firm conclusions regarding the relevance of DRE in men with low PSA levels in our local population.

Infection-related complications remain the greatest concern in patients undergoing prostate biopsy via the transrectal route, especially with the emergence of antibiotic resistant strains [28–31]. Only 1.5% (12/804) of men who underwent TRUS biopsy in our institution suffered infection-related complications which required inpatient admission. Unfortunately, one patient (0.1%) suffered a mortality due to cardio-respiratory collapse from sepsis. The patient who had tested positive for extended spectrum β-lactamase was treated with ertapenem with no serious sequalae. The incidence of infectious complications requiring hospitalization following prostate biopsy via transrectal route ranges from 0.6% to 4.1% [32]. Hence, the post-TRUS biopsy infection rates in our institution are similar to other centres around the world and more importantly, our data can be used in the counselling of men for prostate biopsy locally.

There are currently no official guidelines regarding prostate cancer screening in Singapore. PSA tests are usually offered as part of public health screening packages via general practitioners. In the urology clinic, PSA testing is often part of the work-up in male patients presenting with lower urinary tract symptoms. Both the American Urological Association (AUA) and European Association of Urology (EAU) conclude that mass screening for prostate cancer is likely to be inappropriate and that early detection is a shared decision to be made by a well-informed man [33,34]. Both do not suggest routine PSA testing in men older than 70–75 years as the benefit of reducing prostate cancer specific mortality may not be actualized. Much evidence which form the basis of these guidelines was obtained from Western populations and its generalisability to Asian populations has yet to be proven and will unlikely be available in the near future due to the lack of well-designed trials in the region. While PSA >4.0 ng/mL serves as a traditional cut-off to offer a prostate biopsy, it has to be emphasised that PSA levels reflect a continuum of risk and even men with PSA <4.0 ng/mL may harbour clinically significant cancer. Perhaps, more could be done to help improve the risk stratification process with regard to prostate cancer via more complex, multi-variable prediction models/nomograms, rather than using blunt PSA cut-offs.

In recent years, advancements in magnetic resonance imaging (MRI) have made it an emerging tool in the arena of prostate cancer detection [35–37]. The use of multiparametric MRI followed by selective use of MR-guided biopsy have been shown to reduce the detection of low-risk, likely clinically insignificant cancers as well as the need for biopsy [37]. More importantly, they help improve detection of high-risk disease [37]. However, these modalities lack sufficient established evidence of long-term oncological outcomes to be accepted as standard practice. Locally, the use of mpMRI and targeted biopsies have largely been based on shared decisions between clinicians and patients as well as the availability of the required resources and consideration of financial costs.

Admittedly, there are some limitations which have to be considered before drawing any firm conclusions from our analysis. Firstly, our study cohort was recruited from an unscreened population who were referred to the urology

clinic for raised PSA, suspicious DRE findings or urinary symptoms. Hence selection bias cannot be excluded. Regrettably, there was no data on the indications of individual PSA testing. Several studies have reported increased risk of prostate cancer detection in men with elevated PSA levels and no or mild lower urinary tract symptoms [38,39], and hence the lack of such information exposed our study to possible detection bias. DREs were performed by multiple urologists and urological trainees in a tertiary hospital, inevitably resulting in inter-observer variability. We reduced this variability by having a standardised protocol for our ultrasound and biopsy method. Many studies have attempted to investigate ways to improve the diagnostic ability of serum PSA such as by adjusting for age, prostate volume and body mass index [40—42] and we will be looking into the application of such adjustments and/or nomograms in our local population.

In our current retrospective study, we endeavored to evaluate the detection rates of prostate cancer using serum PSA levels and DRE findings. Our analysis revealed that prostate cancer detection rate based on serum PSA and DRE findings has increased over the last decade. In men with serum PSA level of 4.00—9.99 ng/mL, the detection rate of prostate cancer, regardless of DRE findings, is 20.9%. This rate suggests that local prostate cancer detection rates are lower than that reported in studies involving Caucasian populations, likely reflecting ethnical differences. Post-procedural sepsis remains a pertinent challenge to men undergoing prostate biopsy worldwide.

Conflicts of interest

The authors declare no conflict of interest.

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