

Outcomes of standard 12-core transrectal ultrasound-guided prostate biopsy in biopsy naive Indian men -single center experience

Abhishek Laddha*, Appu Thomas, Deepak Chandran Nair, Greeshma C Ravindran¹,
Ginil Kumar Pooleri

Departments of Urology and ¹Biostatistics, Amrita Institute of Medical Sciences, Kochi, Kerala, India

*E-mail: drabhishekladdha@gmail.com

ABSTRACT

Introduction: Prostate cancer is now the second-most common cancer in many parts of India. Despite being the second-largest population in the world, data regarding outcomes of biopsy in Indian men are limited. We report the correlation of biopsy finding with prostate-specific antigen (PSA) level in Indian men undergoing biopsy for either elevated PSA and/or abnormal digital rectal examination (DRE) findings.

Materials and Methods: We retrospectively analyzed data of 853 men who underwent TRUS-guided prostate biopsy in a single institution from January 2014 to October 2019. The biopsy was performed when serum PSA was more than 4.00 ng/mL and/or DRE findings were suspicious for malignancy.

Results: Overall cancer detection rate was 38.8%. Patients were classified in five groups based on PSA levels, irrespective of DRE findings (0–3.99 ng/mL, 4.00–9.99 ng/mL, 10.00–19.99 ng/mL, 20.00–39.99 ng/mL, and \geq 40 ng/mL). Overall prostate cancer detection rates at corresponding at PSA levels were 3/23 (13%), 62/282 (21.9%), 86/226 (38.05%), 66/126 (52.3%), and 165/196 (84.18%), respectively. 331 (38.8%) patients of the total 853 had suspicious DRE, the cancer detection rate in corresponding PSA groups, based on DRE alone was 3/23 (13.04%), 23/42 (54.76%), 39/56 (69.64%), 43/52 (82.69%), and 157/160 (98.13%), respectively.

Conclusion: The overall prostate cancer detection rate at our center was 38.8%, which is much higher as compared to other Indian data. Our study also emphasizes the role of DRE in Indian men presenting with elevated PSA.

INTRODUCTION

The incidence of prostate cancer (CaP) is rising in India with more than 25000 cases diagnosed every year.^[1] Globally, too, the incidence of prostate cancer is rising and it is expected that by the year 2030, number of patients with CaP may grow to 1.7 million cases resulting in the death of around 499,000 patients.^[2] CaP is now the second-most common cancer in men worldwide and is the sixth leading cause of cancer deaths. Most patients in India still present with locally advanced disease or metastases even with the widespread availability of

prostate-specific antigen (PSA) screening.^[3] In spite of being the second-largest population in world, data regarding outcomes of transrectal ultrasound-guided biopsy (TRUS biopsy) in Indian men are limited. It has been proposed that Asians have lower incidence of prostate cancer as compared to non-Asians but recently, a change in trend is expected with a rising incidence of CaP in India.^[2,4] A prostate biopsy is indicated in men with PSA $>$ 4.00 ng/mL and/or digital rectal examination (DRE) findings suspicious for malignancy. There is a continuum of risk for CaP based on the level of PSA, higher the PSA more is the risk of

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CaP.^[5] We did a retrospective analysis to study outcomes of standard 12-core transrectal ultrasound-guided prostate biopsy in 853 biopsy naive Indian men presenting to single center with elevated serum total PSA and/or abnormal DRE.

MATERIALS AND METHODS

The objective of our study was to determine the outcome of first TRUS biopsy in an Indian male presenting to the Urology OPD with either elevated PSA and/or abnormal DRE with no previous history of any medications or intervention which might alter PSA levels and or DRE findings.

We retrospectively analyzed data of 853 men who underwent TRUS-guided prostate biopsy in a single institution from January 2014 to October 2019, by review of the electronic database of our hospital. The biopsy was performed when serum PSA was more than 4.00 ng/mL and/or DRE findings suspicious for malignancy. Patients who had a previous negative biopsy, prostatic surgery, history of pelvic radiation, and previous use of 5-alpha reductase inhibitors were excluded from the study. PSA measurement was done using electro-chemiluminescence assay and last available value before the biopsy was used for the final analysis. In case of marginal elevation PSA (4 ng/mL to 10 ng/mL), if there wer no features of urinary infection, no antibiotics were prescribed and PSA was rechecked at 2 weeks intervals). Multiparametric-magnetic resonance imaging (mp-MRI) was done in selected patients with PSA <10 ng/dl and normal DRE, or in patients with persistently elevated PSA PSA derivatives were not done as per department policy [Figure 1]. All biopsies were performed by an experienced consultant urologist under antibiotic cover

(oral ciprofloxacin and tinidazole combination twice a day for 5 days and one dose of injection amikacin 750 mg just before the procedure) using transrectal ultrasound guidance (BK flex focus 800, BK Medical, Mileparkan, Denmark) and 18-G biopsy needle (Biopty, C. R. Bard, Covington, GA, USA). All patients underwent systematic 12-core biopsy with additional target cores as per the discretion of the surgeon taking a biopsy if indicated.

Each patient underwent systemic 6-core biopsy from the right and left side with additional cores if needed based on a suspicious lesion on TRUS or mp-MRI (when done). All biopsies were done in standard fashion, with biopsies from the right lateral base, right lateral midzone, and right lateral apex followed by three medial cores on the same side (base, mid zone, and apex). A similar procedure was repeated on the left side. All cores were labeled and sent in separate containers (pre-labeled as R1 to R6 and L1 to L6, target core is marked as T1, T2, and so on depending on the number of cores taken). The procedure was done as daycare and all patients were discharged from the hospital after 4 h. As per hospital protocol, all patients reported to the surgeon the next morning and followed up after 10–14 days for discussion of biopsy results in person. The requirement of emergency visits and the need for hospital admission was noted by a review of the electronic database of our hospital. Pathological examination was done by a dedicated uropathologist in the same institution.

Statistical analysis was performed using IBM SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). To find out the association between two categorical variables, the Chi-square test was applied. To compare the DRE with biopsy among PSA categories, McNemar’s test was used with validity parameters such as sensitivity, specificity, positive predictive value, and negative predictive value. $P < 0.05$ was considered statistically significant. For collection of this retrospective data ethical committee of Amrita Institute of medical sciences Kochi had given approval via letter number AIMS/EC/2019-01/07 dated 12/01/2019. All procedures adhered to the ethical guidelines of declaration of Helsinki and its amendments. Written permission was taken prior to procedure and for use of clinical details(without disclosing identity) for academic purpose. We confirm availability and access of all original data reported in this study.

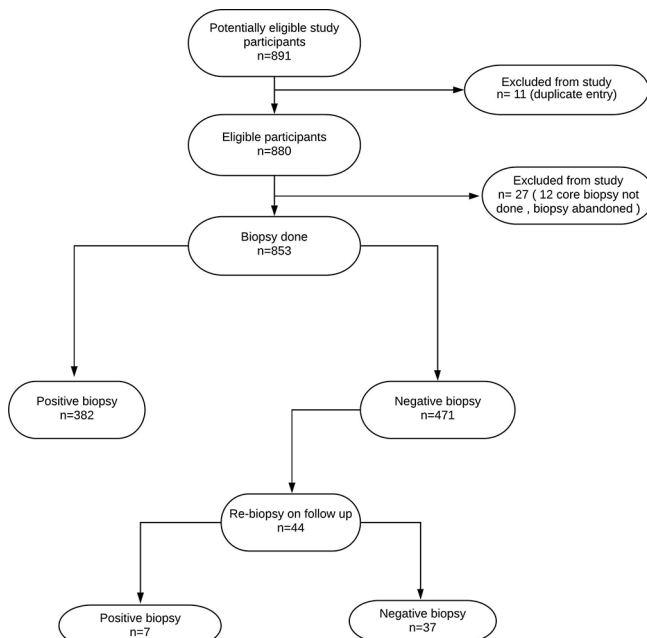


Figure 1: Patient accrual

RESULTS

We reviewed and analyzed the data of 853 men who underwent TRUS biopsy for elevated PSA and/or suspicious DRE and correlated it with the PSA levels. The mean age of patients was 69.5 ± 8.2 years and the median prostate volume was 39 g. Median PSA values were 14 ng/mL (interquartile range [IQR]: 26.6 ng/mL). Three hundred and eighty-two (44.8%) patients had a positive biopsy and 357 had significant cancer (Gleason score 7 or more) on the final assessment.

The mean age of patients with prostate cancer was 71 ± 8.5 versus 68.3 ± 7.7 years with negative biopsy ($P \leq 0.001$). The median overall PSA value was higher in patients with prostate cancer 29.74 ng/mL (IQR: 78.61 ng/mL) versus 9.77 ng/mL (IQR: 9.8 ng/mL) in the group of patients without prostate cancer ($P \leq 0.001$). There was no significant difference in the size of the prostate in either group in our study (38.9 g vs. 40.6 g in patients with negative biopsy). Patients with prostate cancer were more likely to have suspicious DRE (69.4% vs. 14%, $P < 0.001$) [Table 1]. We categorized Serum PSA levels into five main categories: 0–3.99 ng/mL, 4.00–9.99 ng/mL, 10.00–19.99 ng/mL, 20.00–39.99 ng/mL, and ≥ 40 ng/mL. Overall prostate cancer detection rates at corresponding PSA levels were 3/23 (13%), 62/282 (21.9%), 86/226 (38.05%), 66/126 (52.3%), and 165/196 (84.18%), respectively. In patients with PSA, < 4 ng/mL one patient had neuroendocrine differentiation.

We also analyzed the Gleason score in various PSA subgroups. Patients with PSA more than 40 are likely to present with a high Gleason score [Table 1]. Three hundred and thirty-one (38.8%) patients of 853 had suspicious DRE, the cancer detection rate in corresponding PSA groups, based on DRE alone was 3/23 (13.04%), 23/42 (54.76%), 39/56 (69.64%), 43/52 (82.69%), and 157/160 (98.13%), respectively [Table 2]. Table 3 summarizes the sensitivity,

specificity, positive predictive value, and negative predictive value of DRE.

mp-MRI was offered to patients with PSA < 10 ng/dl who had normal DRE on clinical examination, 72 patients underwent mp-MRI before biopsy. 15/72 (20.83%) patients had a positive biopsy. None of the patients with PI-RADS lesion 1–3 had a positive biopsy (49/72) while 15/23 with PI-RADS 4 or 5 lesion had a positive biopsy. Overall cancer detection rate in biopsy naive men with or without MRI was similar if the biopsy is done in all men irrespective of MRI findings based on PSA levels, on the other hand, mp-MRI can significantly improve biopsy detection rates in case of abnormal mp-MRI findings (PI-RADS 4 or 5 lesions).

In 471 patients with negative biopsy, chronic prostatitis was the most common (281, 59.66%) pathology followed by benign prostatic hyperplasia (199, 42.25%), 14 (2.97%) patients had atypical glands, and 6 (1.27%) patients had high-grade prostatic intraepithelial neoplasia on biopsy. Forty-four (9.3%) had atypical glands and high-grade prostatic intraepithelial neoplasia underwent a second repeat biopsy, of which seven men had a positive result for cancer. Three patients underwent a third biopsy of none of which was positive for prostate cancer. The overall complication rate was low, 27 patients (3.16%) reported macroscopic

Table 1: Patient characteristics

Demographics	Total	With cancer	Without cancer	P
Patients, n (%)	853	382 (44.8)	471 (55.2)	NA
Age (year), mean \pm SD	69.56 \pm 8.25	71.09 \pm 8.56	68.31 \pm 7.71	<0.001
Number of cores, median (IQR)	12.0 (12.0)	12.0 (12.0)	12.0 (12.0)	NA
Average number of positive cores, median (IQR)	NA	2.0 (2.0)	NA	NA
Serum PSA (ng/mL), median (IQR)	14 (26.6)	29.74 (78.61)	9.77 (9.8)	<0.001
DRE findings (%)				
Normal	522 (61.2)	117 (36.6)	405 (86)	<0.001
Suspicious	331 (38.8)	265 (69.4)	66 (14)	
Gleason scoring of tumors	Positive biopsy	Gleason score		
		6	7	8-10
PSA levels (ng/mL)				
<4 ng	n=3	0	3	0
4-9.99	n=62	14	26	22
10-19.99	n=86	5	51	30
20-39.9	n=66	2	27	37
≥ 40	n=165	4	35	126

NA=Not available, SD=Standard deviation, PSA=Prostate specific antigen, IQR=Interquartile range, DRE=Digital rectal examination

Table 2: Cancer detection rate based on digital rectal examination and prostate-specific antigen levels

PSA levels (ng/mL)	Patients (n)	Cancer detection rate, n (%)	Cancer detection based on DRE and PSA levels			
			Normal DRE		Abnormal DRE	
			Incidence (n)	Cancer detection, n (%)	Incidence (n)	Cancer detection, n (%)
<4	23	3 (13.0)	0	0 (0)	23	3 (13.04)
4-9.99	282	62 (21.9)	240	39 (16.25)	42	23 (54.76)
10-19.99	226	86 (38.05)	170	47 (27.65)	56	39 (69.64)
20-39.9	126	66 (52.3)	74	23 (31.08)	52	43 (82.69)
≥ 40	196	165 (84.18)	36	8 (22.22)	160	157 (98.13)
Total	853	382 (44.78)	522	117 (33.91)	331	265 (80.06)

PSA=Prostate specific antigen, DRE=Digital rectal examination

hematuria (required no intervention), six patients had rectal bleeding that required no intervention (Clavien-Dindo Grade I), 23 (2.5%) had fever requiring prolonged antibiotic with five requiring admission in the ward without intensive care unit care, 17 patients had acute urinary retention postbiopsy which required temporary catheter placement (Clavien-Dindo Grade II), and one patient with rectal bleeding required electrocoagulation using sigmoidoscope under local anesthesia to stop bleeding (Clavien-Dindo Grade IIIa). None of the patients had Clavien-Dindo Grade IV or V complications.

DISCUSSION

With the widespread availability of PSA testing in the community, the number of patients presenting to Urology OPD with elevated PSA is increasing. Counseling plays a vital role in the management of such patients as increased PSA is associated with a lot of mental stress and anxiety regarding the disease, the biopsy, and its complications. Our retrospective analysis focused on outcomes of a systematic 12-core biopsy in biopsy naive Indian men based on PSA levels and DRE findings at a single center in Southern India.

In 2005, Gupta *et al.* published a series of 142 patients who underwent biopsy for elevated PSA between 4 and 10 ng/mL and normal DRE, with overall cancer detection rates of 24% (34/142) after a sextant biopsy. Of 107 patients, 48 underwent 13-core biopsy after 3 months, who had either stable or rising PSA levels after an antibiotic course. Five patients of 48 (10.4%) were found to have a positive biopsy.^[6] In 2009, Chavan *et al.* published a series of 440 patients who underwent biopsy in Mumbai. The overall cancer detection rate was 8.7% irrespective of PSA levels. They found cancer detection rate 2.3% (4/171), 2.5% (3/118), 34.1% (14/41),

and 54.9% (56/102) in Indian men with PSA values among 4–10 ng/mL, 10–20 ng/mL, 20–50 ng/mL, and >50 ng/mL, respectively.^[7] In 2011 Sinha *et al.* published a series of 119 patients who underwent biopsy at the Hyderabad region and found an overall cancer detection rate of 24.36%. There cancer detection rate was 7% (2/28), 7% (3/24), 52% (24/56) at PSA levels of 4–10 ng/mL, 10–20 ng/mL, and >20 ng/mL, respectively. They also found that at all levels of PSA, DRE remained a significant predictor of malignancy.^[8] Patil *et al.* in 2017 published outcomes of TRUS biopsy in 235 males in the Mumbai region and found an overall cancer detection rate of 25.53% (60/235). The cancer detection rate was 5.95% (PSA range 4–10 ng/dl), 13.16% (PSA range 10–20 ng/mL), 31.81% (PSA range 20–30 ng/mL), 33.33% (PSA range 30–50 ng/mL), and 100% (PSA >50 ng/mL).^[9]

Alvin *et al.* in 2015 published a series of 804 men who underwent 12-core TRUS biopsy in Singaporean males with overall cancer detection rates 35.1%. Cancer detection rate was 9.5% (4/42), 20.9% (87/417), 38.4% (66/172), 72.3% (125/173) for PSA levels of <4 ng/mL, 4–9.99 ng/mL, 10–19.99 ng/mL, and >20 ng/mL, respectively.^[10] Yong *et al.* in 2016 presented outcomes of TRUS biopsy in 1022 northern Han Chinese population with an overall cancer detection rate of 42.8% (438/1022). They found cancer detection rate of 30% (21/70), 22.6% (61/270), 36.0% (123/342), 59.1% (146/247), and 93.5% (87/93) for PSA range <4.0, 4.0–10.0, 10.0–20.0, 20.0–100.0, and ≥100.0 ng/mL, respectively. Similar to our study the significant number of patients had advanced cancer at initial diagnosis.^[11] Our study and study by Gupta *et al.* show a similar cancer detection rate and is comparable with the western and Asian literature^[6] [Table 4].

We observed a much higher incidence of positive biopsy at lower PSA levels when compared with other Indian studies

Table 3: Digital rectal examination characteristic at various prostate-specific antigen levels for overall prostate cancer detection

PSA (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Abnormal DRE and PSA <4	–	–	13	–
Abnormal DRE and PSA 4–9.99	37.1	91.4	54.8	83.8
Abnormal DRE and PSA 10–19.99	45.3	87.9	69.9	72.4
Abnormal DRE and PSA 20–39.9	65.2	85	82.7	68.9
Abnormal DRE and PSA ≥40	95.2	93.2	98.1	77.8

PPV=Positive predictive value, NPV=Negative predictive value, PSA=Prostate specific antigen, DRE=Digital rectal examination

Table 4: Comparative Outcome of transrectal ultrasound biopsy in Asian males and its outcomes as per positive predictive value levels

Study (year)	Region	n	Overall biopsy positive rate	Outcomes of biopsy at various PSA levels (ng/ml)			
				<4	4–9.99	10–19.99	>20
Present study (2020)	Kochi region	853	382/853 (44.8)	3/23 (13)	62/282 (21.9)	86/226 (38.05)	231/322 (71.73)
Patil <i>et al.</i> (2017) ^[9]	Mumbai region	235	60/235 (25.53)	1/10 (10)	5/84 (5.95)	10/76 (13.16)	44/65 (67.69)
Jia <i>et al.</i> (2016) ^[11]	Northern Han Chinese population	1022	438/1022 (42.8)	21/70 (30)	61/270 (22.6)	123/342 (36)	233/340 (68.52)
Lee and Chia (2015) ^[10]	Singapore	804	282/804 (65.1)	4/42 (9.5)	87/417 (20.9)	66/172 (38.4)	125/173 (72.3)
Sinha <i>et al.</i> (2011) ^[8]	Hyderabad region	119	29/119 (24.36)	NA	2/28 (7)	3/24 (7)	24/56 (52)
Chavan <i>et al.</i> (2009) ^[7]	Mumbai region	440	38/440 (8.7)	NA	4/171 (2.3)	3/118 (2.5)	70/143 (48.95)

NA=Not available, PSA=Prostate specific antigen

which may suggest a change in the demographic profile of patients over a period of time and improvement in biopsy practice including pathological analysis by a dedicated uropathologist.

As pointed out by Jain *et al.*^[2] who evaluated the epidemiology of prostate cancer in India via various cancer registries and found out a significant rise in the incidence of various cancers in India. Prostate cancer was reported to be the second-most common cancer in males in large Indian cities such as Delhi, Kolkatta, Pune, and Thiruvananthapuram, and the third-most common cancer in cities such as Bengaluru and Mumbai and is among the top then cancer among the rest of the population-based cancer registries of India. They also recorded the statistically significant rising incidence of prostate cancer over time (annual percentage change of 3.4% at Bengaluru, 4.2% at Chennai, 3.3% at Delhi, 0.9% at Mumbai, and 11.6% in Kamrup Urban District). The rising trend of prostate cancer may be due to increased migration of rural population to urban areas, an adaptation of Western lifestyle increased awareness, and improved access to medical care.^[2]

Our study further emphasizes the role of DRE in Indian males, a finding that is similar to what was concluded by the other Indian studies.^[8] DRE although a subjective test provides valuable information and when done after counseling, should be well-tolerated by most patients. Cancer detection rate is higher in patients with abnormal DRE and should always be done in a willing patient.^[12-14]

As our study is not a population-based study and limited to a single institution, we cannot draw direct conclusions about the changing status of the demography of prostate cancer and the prevalence of cancer in Indian society. The limitations of our study are that it is limited to a single institution and is retrospective in design. Probably, further studies from various regions of India may help in the creation of a regional database of biopsy outcomes in Indian males and will help in guiding Indian urologists and patients and allowing them to make an informed decision about outcomes and complications of biopsy. This is the largest data set on the subject currently available and should help in the creation of specific policies and programs for better cancer control and creating local guidelines for the management of prostate cancer in India.

CONCLUSION

We found the overall prostate cancer detection rate at our center was 38.8%, which is much higher as compared to the contemporary Indian data. The higher incidence of prostate cancer in our series correlates well with outcomes of TRUS biopsy in Asian countries and the rest of the world and

probably represents changing the demography of prostate cancer in a subset of Indian males.

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