Frequency of detection of carcinoma of prostate by TRUS guided core biopsy in patients with PSA level of 4 to 10 ng/ml: A comparison of eight verses fourteen core biopsies.

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ABSTRACT… Objective: To compare the frequency of detection of prostatic carcinoma in patients with prostatic specific antigen level of 4 to 10ng/ml by TRUS guided eight versus fourteen core biopsies in a tertiary care hospital. Study Design: Interventional Comparative study (Randomized Control Trial). Setting: Department of Urology, Jinnah Hospital, Lahore. Period: January, 2014 to February, 2019. Material & Methods: 340 patients included in the study, according to inclusion criteria, were divided in two groups of 170 patients each. Eight core biopsies were taken in one group and 14 core biopsies were taken in other group by single radiologist to diagnose carcinoma of prostate. Prostatic carcinoma was labeled when pathologist find atypical cells or anaplasia in the biopsy tissues under microscope. Results: Carcinoma of prostate was detected in 123 (36%) patients while rest 217 (64%) showed negative result on histopathology examination. Age of patients in both groups ranged from 40 to 62 years with mean 49.32+5.464 years. The CoP was detected in 55 out of 179 patients younger than 50 years and 68 out of 161 patients older than 50 years. Amongst the 123 patients having been detected CoP, 82 (67%) patients has PSA values ranging 6 to 10 ng/ml while just 41 (33%) has value of 4 to 5 ng/ml. The frequency of detection of CoP among patients having PSA values ranging from 4 to 10ng/ml. by TRUS guided eight core biopsy and fourteen core biopsy group is 17.35% and 18.82% respectively. Conclusion: There is no difference in the frequency of detection of CoP by TRUS guided fourteen core biopsy and eight core biopsy techniques.

Key words: Carcinoma of Prostate (CoP), Prostatic Specific Antigen (PSA), Trans Rectal Ultrasonography (TRUS) Guided Core Biopsy.

INTRODUCTION

Carcinoma of Prostate (CoP) has been recognized as one of major ailments faced by male population. The annual incidence of CoP in Europe is 214 cases per 1000 men and is most common solid tumor affecting men there.[1] Prevalence of CoP varies broadly across the world, but it is more prevalent in developed countries. CoP is the second leading cause of cancer-related death in men in the United States and globally rated as the sixth most common cause of cancer-related deaths.[2,3]

CoP is usually slow growing carcinoma, but some tumors are aggressive in nature. The patients may remain asymptomatic or may present with symptoms usually representing advance stage of the disease. The detection of disease at early or localized stage is very essential for complete cure. The early recognition of disease can be made by using various screening methods including digital rectal examination (DRE), assay of prostate specific antigen (PSA) and other novel tumor markers measurements but prostate biopsy remains the only diagnostic test for the confirmation of diagnosis of disease to date.

In 1989, after landmark study of Hodge and colleagues[4], TRUS-guided biopsies with 6 core scheme has become the accepted standard. However in last decade, many studies has confirmed that the diagnostic power of biopsy increases with greater numbers of biopsies so more than 6 cores schemes has been approved

in different countries.[5,6,7] However, far from a standardized practice, prostate biopsy is still evolving. Indeed. The ideal technique or the so-called "gold standard" of biopsy is yet to be defined fully.[8,9]

On account of scientific advancements, availability of sophisticated imaging modalities, development of tumor markers assays and clear explanation of pathogenesis of CoP, the diagnostic methods and manners for detection of this disease has observed a paradigm shift over the last 30 years. According to the American Cancer Society, approximately 161,360 new cases of prostate cancer were diagnosed and vast majority of such cases about 95% would be localized diseased clinically. The 31,620 men died of this disease in 2019 in USA despite the 5 years relative survival rate of CoP was highest (98%) as compared to other cancers.[10] The use of Trans Rectal Ultrasonography (TRUS) for obtaining core biopsy of prostate tissue has become a popular choice owing to convenience and accuracy. The TRUS guided core biopsy of prostate is the current gold standard for prostate cancer diagnosis.[8]

The chance of prostate cancer detection by biopsy is largely influenced by the amount of tissue collected in specimen leading to a progressive increase in the number of cores of biopsy. For example, in the USA biopsy specimens from 10 to 12 sites are taken while in other countries 8 to 14 cores are taken.[11] The overall CoP detection rate by different methods was 33.3% with the use of different techniques. Prostatic eight cores biopsy and fourteen core biopsy techniques had detection rate of 25.8% and 40% respectively in patients with mean age group of 65 years.[12,13] Although the optimal number of cores for prostate biopsy still remains ambiguous but extended cores protocol is superior to 12-core protocols for detecting CoP.[14] Eighteen core biopsy for detecting CoP among Asian patients with serum PSA levels from 4.0 to 20.0 ng/mL was found to be superior as compared to Twelve core biopsy.[15]

Conversely, Jones et al demonstrated that prostate cancer detection rate did not increase by using saturation technique (24 cores) as an initial strategy. The cancer detection rate was 44.6% by using saturation biopsy and 51.7% with 10-core biopsy ($p = 0.9$). They also suggested that biopsies with greater than 10 to 12 cores are not apposite as an initial biopsy strategy.[16] In a recent systematic review, Eichler et al have observed that taking more than 12 cores has no added benefit and 18 or more cores biopsies have more side-effects.[17]

Currently, there is no universally accepted uniform method to determine the number of core biopsies sufficient to detect CoP more accurately.

The rationale of this study is to observe that amount of tissue collected for biopsy has any influence in detecting of Ca Prostate or not. This study is helpful for procedural guideline to determine the sufficient number of core biopsies to be taken from each patient for purposeful diagnosis of CoP.

MATERIAL & METHODS
An interventional comparative study (Randomized Control Trial) was conducted at the Department of Urology, Jinnah Hospital, Lahore from January, 2014 to February, 2019. The calculated sample size was 340 cases divided in two groups with 170 in each. The Purposive, non-probability sampling was done for each group. Only male aged above 40 years with PSA values (4-10 ng/ml) included in this study. All patients with previous diagnosis of prostatic carcinoma determined by history, having history of bleeding diathesis or Urinary tract infection determined by leukocyturia (>10 cell/hpf) on urine analysis were excluded form study. Informed consent was taken from each patient. Patients were investigated with CBC PT&APTT before performing biopsy to minimize the risk of post operative complications. By using balloting method, patients were randomly divided into two groups i.e. with 8 sites core biopsies scheme and other with 14 site scheme under direct visualization by ultrasound probe. The biopsy scheme were separately labeled and reviewed by one pathologist to determine presence of prostatic carcinoma in both groups. Questionnaire containing background

information i.e. age, sex, scheme used. Volume of prostate and prostate size and outcomewere used as research instrument and data was recorded. A uniform protocol of biopsy was observed. All patients were treated according to department protocols under local anesthesia and patients were given prophylactic antibiotics i.e. Tab. Ciprofloxacin 500mg before procedureand continue three days after biopsy. Data collected was entered and analyzed in the SPSS version 25. Result were projected using descriptive statistics e.g. mean with variables like presence of prostatic carcinoma. Chi square test were used to detect the difference. A p-value $\leq$0.05 was taken as significant.

RESULTS
In our study the age of the patients ranged from 40 to 60 years and mean was 49.32 +5.464 years (Table-I) and 179 (57%) individuals were less than 50 years of age while 161(43%) were above 50 years.(Table-II). The PSA levels of patients ranged from 4 to 10ng/ml with mean of 6.39+2.635 (Table-I). The volume of Prostate ranged from 40 to 80grams with mean of 53.78+11.122ml (Table-I).

In our sampled population (n=340) only 123(36%) individuals were detected with CoP while rest 217 (66%) individuals showed negative results (Table-II). Among the positive patients, 55 (45%) were less than 50 years of age while 68 (55%) were above 50 years.

64 (54%) out of 123 positively detected patients were diagnosed carcinoma of Prostate by using fourteen core biopsy technique and remaining 59 (48%) were detected positive for carcinoma with the use of eight core biopsy method. 106 (49%) patients tested negative by fourteen core biopsy method and 111 (51%) by using eight core biopsy out of all 217 negative cases. (Table-III) The difference was insignificant when we applied chi square test.

On stratification, it was revealed that more cases 210 (62%) have PSA values ranging 6 to 10ng/ml while just 130(38%) have PSA values ranging from 4 to 5 ng/ml (Table-IV). The higher PSA values (6 to 10ng/ml) were associated with higher no of 82 (67%) positive cases while 41 (33%) positive cases have lower PSA values ranging 4 to 5 ng/ml. The difference was statistically insignificant (p value = 0.1616).

The vast majority of the sample population (51%) has prostate size ranging 40-50gms. The prostate specific volume range 40-50gmsis also associated with large no of CoP cases i.e. 66(55%), 51-60gms with 32(25%), 61-70 gms with 13(10%) and 71-80gms with 12 (10%) cases of CoP. (Table-V). So, most of the cancerous tissues of prostate has size of 40-50gms. But the difference was statistically insignificant (p value = 0.6187).

The mean age of the patients was 49.32±5.46 years, the mean prostate specific antigen level of the patients was 6.39±2.64 ng/ml and the mean prostate volume of the patients was 53.78±11.12 gms.

In our study in patients having age <50 years the positive carcinoma was found in 55(45%) patients, similarly in patients having age >50 years the positive carcinoma was found in 68(55%) patients.

According to this study in 14 core biopsy patients 64(52%) patients had prostate carcinoma and in 8 core biopsy patients the prostate carcinoma was found in 59(48%) patients. This difference was statistically insignificant. i.e. p-value=0.5725.

Among patients having 4-5 ng/ml prostatic specific antigens the presence of prostate carcinoma was found in 41(31.53%) patients and in patients having 6-10 ng/ml prostatic specific antigens the presence of prostate carcinoma was found in 82(39.04%) patients. This difference was statistically insignificant. i.e. p-value=0.1616.

n	340
Mean Age In Years	49.32±5.46
Mean Prostate specific antigen level (ng/ml)	6.39±2.64
Prostate Volume (gms)	53.78±11.12

Table-I. Clinical, pathological and demographic characteristics of patients.

Age (years)	Frequency	Percentage	Carcinoma Negative	Percentage	Carcinoma Positive	Percentage
<50	179	57%	124	57%	55	45%
>50	161	43%	93	43%	68	55%
Total	340	100 %	217	100%	123	100%

Table-II. Distribution of sampled population by age groups

Core Biopsies	Prostatic Carcinoma				Total
	No	Percentage	Yes	Percentage	
14 Core biopsy	106	49%	64	52%	170
8 Core biopsy	111	51%	59	48%	170
Total	217	100%	123	100%	340

Table-III. Cross table between number of core biopsies and detection of prostatic carcinoma (n=340)
Using chi square test, p value= 0.5725(Insignificant)

Prostatic Specific Antigen Category	Presence of Prostate Carcinoma				Total Cases	Percentage
	Yes	Percentage	No	Percentage		
4-5ng/ml	41	31.53%	89	68.46%	130	100%
6-10ng/ml	82	39.04%	128	60.95%	210	100%
Total	123	36.17%	217	63.82%	340	100%

Table-IV. Stratification with respect of PSA level (n=340)
Using chi square test, p-value=0.1616 (Insignificant)

Volume of Prostate	Percentage of Detection of Prostate Carcinoma					
	Yes	%	No	%	Total	%
40-50gm	66	55%	106	49%	172	51%
51-60gm	32	25%	53	25%	85	25%
61-70gm	13	10%	29	13%	42	12%
71-80gm	12	10%	29	13%	41	12%
Total	123	100%	217	100%	340	100%

Table-V. Stratification with respect to prostatic volume
Using chi square test, P-value = 0.6187 (Insignificant)

DISCUSSION

The results proved that there is no difference in possibility of detection of CoP in high risk patients with PSA values ranging 4 to 10ng/ml among eight core biopsies group and fourteen core biopsy group as former has detected CoP in 59 patients out of 170 and the later has 64 detections out of 170. The difference was statistically non-significant (P=0.486) when we applied chi square test. Based on this, we can conclude that 8 core biopsies are as effective as 14 core biopsies in terms of detection rate of CoP among patients.

In the present study, 123 (36%) patients being detected with CoP in our total sample population

had mean PSA levels ranging 6.22 $\pm$2.763ng/ml. We may conclude that intermediate range PSA level i.e. between 4 to 10ng/ml is a warning sign of underlying malignancy and patients must undergo biopsy.

The diagnostic accuracy of prostate biopsy has significantly increased after the advent of transrectal ultrasonography which has revolutionized the techniques of biopsy. Prostate specific antigen (PSA) is a protein of kallikrein family present in low concentrations in human serum. It is largely secreted in seminal fluid, where it perform functions of liquefaction of the ejaculate. PSA within serum is circulated in both

bound and unbound forms. By obtaining the cancerous tissues or cores from prostate gland through imaging assisted biopsy, the diagnosis of prostate cancer can be made more accurately.

The Pathologist establishes the final diagnosis of CoP vide histo-pathological examination. The sextant biopsy was first described by Hodge and colleagues in 1989. The 20% to 30% clinically important CoP were missed in the sextant biopsy (bilateral specimen from apex, mid-gland, and base on the sagital plane).[18] In order to increase the accuracy of detection of prostate cancers,various biopsy methods involving taking additional biopsies particularly from peripheral zone of the prostate has been developed.[19] Now a days, vast majority of most researchers preferred to obtain samples or cores from lateral zones to enhance cancer detection rate[20,21] Extended prostate biopsy approach comprising of 8 to 13 cores is adopted by many clinics. This strategy did not associated with an increase in score of clinically insignificant CoP and morbidity.[22,23]

This patient cohort had overall cancer detection rate as 24.41% that commensurate with published data.[23] The patients older in age ,had higher values of PSA and were at advanced stage of disease usually had proportionally increased cancer detection rates. The necessity of eight and fourteen core biopsy protocols to diagnose CoP in men with PSA levels below 10ng.ml has been elucidated.[24]

The 14 cores biopsy protocol to include the peripheral, para-sagittal, basal and apical biopsies is only needed to diagnose prostate cancer in patients with PSA levels up to 4ng/ml. While a protocol of eight cores to include the right and left peripheral basal, apical and para-sagittal apical biopsies would give a 100% detection rate of prostate cancer in patient with PSA level of 10ng/ml.

Norberg et al[25] performed prospective study of 512 patients and observed that eight-core biopsy i.e. sextant biopsy with two additional lateral biopsies has more detection rate of cancer as compared to conventional sextant biopsy technique. Borssner et al[26] found additional 29% cancer detection with 12-core biopsy as compared to traditional sextant biopsyin a retrospective study. More recently, it has been shown by Eskicorapci et al[27] that additional four biopsies from the lateral peripheral zone together with sextant technique enhanced the detection of cancer by approximately 10%. In an exciting study from Asian subcontinent, where prostate cancer has low prevalence, it has been shown that cancer detection rate doubled by increasing biopsies number i.e. 8-14 cores.[27]

However, many studies are available which depicts that rate of cancer detection is not affected by increasing the core number. In one particular study, a 12-core extended biopsy strategy was not superior to traditional sextant biopsy.[28] Ung and others concluded that as the prostate volume increased, the detection rate declined from 40% to 27% but detection rate was same despite increase in number of cores.[29] However, in this study the detection rate is 35% with eight core biopsies and 38% with fourteen core biopsies which are in consonance with the aforesaid studies.

CONCLUSION

There is no difference in frequency of detection of prostatic carcinoma by TRUS guided fourteen core biopsy as compared to TRUS guided eight core biopsy. There is proportionally increase in cancer detection rate among patients having old age and higher PSA levels. In view of foregoing we recommend that eight core biopsy techniques must be employed as initial biopsy strategy among patients undergoing biopsy for detection of CoP, on account of convenient and safe to perform and comparable results with extended biopsy schemes.
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CORRECTION

The amendment of the Professional Vol: 27, No.12 (Prof-3888) on page 2755 & 2762 (Name of 3rd Author) is as under;

INCORRECT

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CORRECT

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Umar Farooq	Data collection, Proof reading, Data analysis.	
3	Akhtar Mahboob	Proof reading, Manuscript writing.	
4	Naveed Iqbal	Proof reading, supervision.	
5	Atiqa Javaid	Data collection, assistance & proof reading.	
6	Sehar Fatima	Data collection, Analysis & Interpretation.	