Trans rectal ultra sound guided prostate biopsies: a single centre experience in Sri Lanka

M D S Lokuhetty[1], **H D Wijesinghe**[2], **D T Abeysuriya**[3], **U C Samarasinghe**[4] and **N D Perera**[5]

(Index words: carcinoma prostate, prostate biopsy, Sri Lanka, serum PSA)

Abstract

Background Trans rectal ultrasound guided prostate biopsy (TRUS) was introduced to Sri Lanka in 2002.

Objectives 1. To study clinicopathological features of males subjected to TRUS biopsy 2. To compare estimation of tumour burden by two methods in carcinoma prostate (CaP).

Methods 749 symptomatic males subjected to TRUS biopsy over 64 months at a single centre. Information was retrieved from case records. Tumour burden in CaP was calculated as: 1. Calculated tumour burden (CTB) – total percentage tumour in each core/total number of cores 2. Percentage positive biopsy cores (PPBC) – number of positive cores / total number of cores X 100. SPSS 15.0, student's t test and Spearman's rank correlation coefficients were used for statistical analysis.

Results 35.2% had CaP, microacinar in type. 34.88% were poorly differentiated. CaP was frequent among older patients (P<0.00001). The prostate volume in CaP was significantly lower than in the benign group (P<0.05). Prostate specific antigen (PSA) level was significantly higher in CaP (P<0.00001). A 99.6% sensitivity and 4.7% specificity was observed at PSA of 4ng/ml for detecting CaP. Specificity was 98% at 25.5ng/ml, with a sensitivity of 44.4%. CTB and PPBC had similar correlations with biochemical/histological parameters of CaP and were strongly correlated (0.786).

Interpretation Males with CaP were older, had higher PSA levels and smaller prostates. A cut off level of PSA >4ng/ml could be used for directing symptomatic patients for TRUS biopsy to detect CaP, keeping in mind that specificity is 98% only at 25.5ng/ml. Both CTB and PPBC could be used to calculate tumour burden in TRUS with CaP.

Introduction

Carcinoma prostate (CaP) accounted for 4.9% (301 cases) of all cancers affecting Sri Lankan men in 2005 [1]. Trans rectal ultrasound guided core biopsy of the prostate (TRUS biopsy), is considered a safe and accurate diagnostic test for CaP [2]. This study aims to document our experience with 749 TRUS biopsies in symptomatic men, since introduction of the technique to Sri Lanka in September 2002.

[1,2,3]*Department of Pathology, Faculty of Medicine, University of Colombo,* [4]*Nawaloka Hospital, Colombo* and [5]*National Hospital of Sri Lanka.*

Objectives

1. To study clinicopathological features of symptomatic men subjected to TRUS biopsy of prostate, with a view to formulate future diagnostic strategies for CaP.

2. To compare estimation of tumour burden by calculated tumor burden (CTB) and percentage positive biopsy core (PPBC) methods in diagnosed CaP.

Materials and methods

749 TRUS biopsies performed over a period of 64 months at a single tertiary care hospital in the private sector were included in the study. All these men presented with lower urinary tract symptoms with or without abnormal digital rectal examination (DRE) findings. DRE and ultrasound examination of the prostate followed by biopsies, were performed by a single radiologist using an 18 G needle. A minimum of 6 tissue cores were obtained from right and left sides of the base, middle and the apical regions of the prostate. Additional cores were obtained from nodules, if present.

The age and serum PSA (obtained prior to DRE and ultrasonography) were retrieved from case records. The prostate volume was obtained from documented ultrasonography findings. Prostate specific antigen density (PSAD) was calculated by dividing the serum PSA in ng/ml by the volume of prostate in milliliters. Hematoxylin and eosin stained slides were examined by a single pathologist and categorised as follows 1. Benign with/without inflammation 2. CaP (acinar/ductal) and atypical glands suspicious, but not diagnostic of carcinoma. CaP were graded and scored based on the Gleason scoring system [3].

The tumour burden was calculated as:

$$\text{Calculated tumor burden (CTB)} = \frac{\text{Total of percentage tumor in each core}}{\text{Total number of tissue cores}}$$

$$\text{Percentage positive biopsy cores (PPBC)} = \frac{\text{Number of positive tissue cores} \times 100}{\text{Total number of tissue cores}}$$

Presence of high-grade prostatic intra epithelial neoplasia (PIN) and perineural invasion were documented. SPSS 15.0 software was used for analysis. Student's t test was used to compare means and Spearman's rank correlation coefficients were used to assess correlations.

Results

264 (35.2%) were diagnosed to have CaP on TRUS biopsy. 454 (60.6%) were diagnosed as benign. Small acini

that were suspicious but not diagnostic of carcinoma were seen in 31 cases (4.2%). The age of the study population ranged from 33-90 years with a mean age of 69.3 years (SD=8.2 years). The mean age of men with CaP was 71.3 years (SD=7.8 years). The mean age of those diagnosed as benign was 68.1 years (SD=8.2 years). Older men had malignant disease more often than younger men (P<0.00001) (Figure 1).
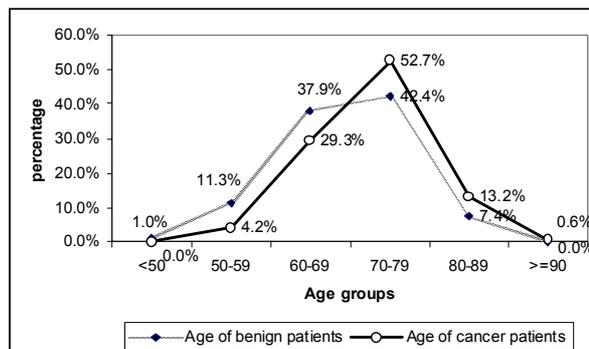

Figure 1. **Distribution of patients with benign and malignant diagnosis according to age**

Serum PSA was measured in 716 men (Table 1). The mean serum PSA was 51.2 ng/ml (SD=80.0 ng/ml) in men with diagnosed CaP. It was 20.1 ng/ml (SD=31.1 ng/ml) in the benign group (Table 2). This difference was statistically significant (P< 0.00001). When the receiver operating curve (ROC curve) was applied, a sensitivity of 99.6% and a specificity of 4.7% were seen at a serum PSA level of 4 ng/ml in detecting CaP. A specificity of 98% was observed only at serum PSA of 25.5 ng/ml, however with a low sensitivity (44.4%). Application of recommended age specific PSA cut off values [4] showed no change in sensitivity and no significant increase in specificity as compared to a cut off serum PSA of 4 ng/ml. The mean Serum PSA Density (PSAD) for the CaP and the benign groups were 1.3 ng/ml^2 (SD=1.8 ng/ml^2) and 0.56 ng/ml^2 (SD=2.1 ng/ml^2) respectively. This difference was not statistically significant (p>0.05). The mean prostate volume was 41.6ml (SD=26.8 ml) in the CaP group. The non-cancer group had a mean prostate volume of 52.3 ml (SD=32.8 ml). This difference was statistically significant (P<0.001).

CaP was small acinar in type in 99.2% (262/264). An additional large duct component was present in two. The combined Gleason score of CaP group is shown in table 3. Majority (60/172-34.88%) had poorly differentiated carcinomas with a Gleason score of 8 to 10. There was a trend for increasing levels of serum PSA and PSAD with higher Gleason scores (Table 3). High grade prostatic intraepithelial neoplasia (PIN) was seen in a man, associated with a moderately to poorly differentiated adenocarcinoma of small acinar type. Perineural invasion was present in 19 (7.1% - 19/264) men with CaP. There was

no association between perineural invasion and the Gleason's score (P>0.05).

Spearman's rank correlation coefficients for associations of PPBC and CTB with the biochemical and histological parameters are shown in Table 4. None of the differences of correlations between CTB and PPBC were statistically significant (Table 4). However, a strong correlation of 0.780 was noted between PPBC and CTB.

Table 1. **Serum PSA levels in relation to histological diagnosis**

	<4 ng/ml	4.1-10 ng/ml	>10.1 ng/ml	Total number
Benign	21	137	275	433
Malignant	1	55	196	252
Benign with suspicious foci	1	12	18	31
Total	**23**	**204**	**489**	**716**

Table 2. **Means of PSA, PSAD and prostate volume in relation to histological diagnosis**

	Mean serum PSA (ng/ml)	Mean (ng/ml^2)	PSAD prostate volume (ml)
Benign	20.17 (SD=31.15)	0.56 (SD=2.12)	52.36 (SD=32.87)
Malignant	51.22 (SD=80.01)	1.31 (SD=1.87)	44.54 (SD=55.97)
Benign with suspicious foci	27.75 (SD=64.28)	0.5 (SD=1.02)	56.04 (SD=29.98)

Table 3. **Distribution of the combined Gleason's score in patients with CaP and its association with serum PSA and PSAD**

Combined Gleason's Score	Differentiation	Number of patients	Percentage %	Mean PSA	Mean PSAD
2-5	Well	2	1.16	24.17	1.06
6	Moderately	58	33.72	24.58	0.76
7	Moderately to poorly	52	30.23	55.99	1.29
8-10	Poorly	60	34.88	88.99	2.14
Total		**172**	**100.00**		

Table 4. **Spearman's rank correlation coefficients for association of PPBC and CTB with biochemical and histological parameters of CaP**

	PPBC	Calculated tumor burden (CTB)	Difference between the two correlations
PSA level	0.398 (p<0.01)	0.245 (p<0.01)	Not significant
PSA density	0.435 (p<0.01)	0.329 (p<0.01)	Not significant
Combined Gleason's score	0.400 (p<0.01)	0.295 (p<0.01)	Not significant
Perineural invasion	-0.176 (p<0.01)	-0.175 (p<0.05)	Not significant

Discussion

The prevalence of CaP in this TRUS guided biopsy series is 35.2%. Brawer *et al* reported a prevalence of 30.5% for CaP in 187 TRUS biopsies of men who had PSA levels greater than 4.0 ng/ml [5]. The prevalence observed in this study is slightly higher.

Mean PSA level of men with CaP was significantly higher than those with benign disease. The mean prostate volume in patients with CaP was significantly lower than in the benign group; however the difference between the mean PSAD values of the two groups was not statistically significant. These observations can be explained by current knowledge that malignant prostate epithelial cells are capable of producing more PSA per gram of tissue than normal or hyperplastic cells [6]. It also confirms that PSAD is not reliable for exclusion of a man with high PSA from biopsy.

A sensitivity of 99.6% for CaP detection was obtained at a cut off serum PSA level of 4 ng/ml. Therefore it is desirable that all symptomatic men with serum PSA levels above 4 ng/ml are directed towards further investigations including TRUS biopsy. However, it should be borne in mind that the specificity for CaP is only 4.7% at this level of serum PSA. As the specificity for CaP increases with rising serum PSA (36.8% at PSA 10.05 ng/ml and 98% at PSA of 25.5 ng/ml) a raised level of PSA especially above 25.5 ng/ml makes a symptomatic man more likely to have CaP. It is documented that most men with slightly elevated PSA levels (4-10 ng/ml) do not have carcinoma [7]. Our observations were similar.

The pathology of CaP in Sri Lanka is hitherto not documented. 99.2% of the CaP in this series was of small acinar type. The majority were poorly differentiated with a combined Gleason score of 8-10. High grade PIN was detected in one case in association with CaP. None had high grade PIN in the absence of carcinoma. Documented incidence for high grade PIN in TRUS is 4.6% [8]. However, in these countries serum PSA is used as a screening tool for CaP in asymptomatic men [9]. Therefore it is likely that men with pre-invasive stage of disease (high grade PIN) are detected more often than in our setting.

Recent studies show that both the number of cores positive for cancer and the total percentage of core length involved by cancer independently predict extra capsular extension and positive surgical margins [10]. This information obtained by TRUS biopsies play a critical role in patient management. Having calculated the burden of tumour in the study sample by two different methods, PPBC showed a higher correlation with the PSA level, PSA density and combined Gleason's score when compared with CTB. The difference in correlations by the two methods however were not significant. In view of the strong correlation observed between them, it is possible to use both PPBC and CTB to calculate tumour burden in TRUS biopsies. However, calculation of CTB is time consuming and laborious, where as PPBC is more user-friendly. PPBC was shown to be related to the preoperative serum PSA level, Gleason score, clinical stage, extra-prostatic disease, seminal vesicle involvement and to have a relationship with biological outcome after radical prostatectomy [11]. Similarly PPBC was related to the serum PSA level and the Gleason score in this study. Although radical prosta-tectomy is still not widely performed in Sri Lanka, it is offered more often in therapeutic protocols of localized CaP. Therefore, the results of this study on tumour burden on TRUS biopsies will be useful when CaP diagnosed on TRUS biopsy are directed to curative surgery.

Acknowledgements

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