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Research Article

# Post-Biopsy Rise in Serum PSA

## A Potential Tool for the Dynamic Evaluation of Prostate Cancer/Prostatic Intraepithelial Neoplasia (PIN)

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### KEY WORDS

Adenocarcinoma, Biopsies, Cancer, Dynamic evaluation, PIN, Prostate, PSA, PSA leak, Transrectal ultrasound

## ABSTRACT

**Objectives.** The biochemical response of prostatic cells to needle core biopsies is known to manifest as a rise in serum PSA. The aim of this study is to evaluate the PSA response to mechanical trauma in prostate cancer patients, when compared to benign controls.

**Materials and Methods.** 50 consecutive patients undergoing transrectal ultrasound guided prostatic needle biopsies had their total serum PSA measured thirty minutes after the procedure. Change from the baseline PSA was estimated and correlated to histology.

**Results.** Data was analysed in 48 patients (mean age 68 years; range 55-87 years). Histology showed benign, cancer and PIN results in 24, 19 and 5 patients respectively. The highest rise in post biopsy PSA was observed in the PIN group. A significant difference in the rise in serum PSA was noted between controls and the cancer group.

**Conclusion.** Post biopsy PSA response differs significantly between benign and malignant prostatic tissue. PIN causes an excessive rise in PSA values on mechanical stimulation. This small study indicates that the biopsy model may help us to assess the dynamics of prostate cancer.



## INTRODUCTION AND HYPOTHESIS

Transrectal ultrasound guided prostatic biopsies are routinely performed to detect and diagnose adenocarcinoma of the prostate in patients with abnormal PSA and/or abnormal digital rectal examination. The biochemical response of prostatic tissue to needle biopsies has been well documented in literature.[1,2] Even though a rise in PSA was the common observation, evidence of a difference in the PSA rise between benign and cancer groups has been lacking. It is our hypothesis that an 18-gauge biopsy needle on a spring-loaded gun would produce a more a more or less standard mechanical disruption to the prostate. The response to this mechanical trauma to the prostate would be manifested in the serum PSA soon after the biopsy procedure. It was decided to use the patients with benign histology as controls to assess the PSA response to trauma to the prostate by the biopsy procedure in cancer patients.

Majority of the clinical and laboratory tests available to diagnose and assess prostate cancer behaviour viz. serum PSA, Gleason grade are static tests which give us cross sectional information of a tumour at a point of time either in vitro or on vivo. Based on this information, we form an opinion on the cancer behaviour in an individual patient as being significant or not. In this small study, we indirectly observed the dynamic response of prostatic cells, cancerous and non-cancerous, to mechanical stimulation by documenting the change in total serum PSA. A significant difference in PSA rise between the benign and cancer groups could introduce a model to pick up more tumours in the false negative category.

## MATERIALS AND METHODS

50 consecutive symptomatic patients who attended urology outpatients department were recruited into the study. None of the patients were part of a screening programme. Inclusion criteria were an abnormal DRE and/or elevated total serum PSA. Patients with bleeding diathesis were excluded from the study. Participation in the study was entirely voluntary.

All patients received antibiotic prophylaxis. A triple antibiotic regime in accordance with guidelines from the Institute of Urology, University College, London—parenteral aminoglycoside (Gentamicin 80–120mg stat); per rectal Metronidazole suppository 1 gram stat; oral aminoquinolone ( Norfloxacin 400mg bid for 5 days)—was used. Transrectal ultrasound was performed

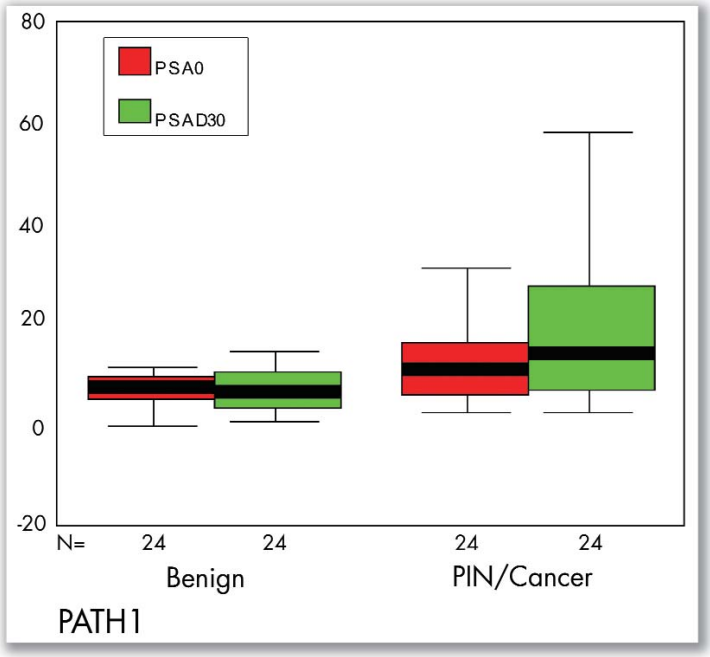


Figure 1. Box Plot of Baseline (red) and Change in PSA (green) in 48 patientsPSA0 = Baseline Serum PSA, PSAD = Change in Serum PSA following Biopsies.

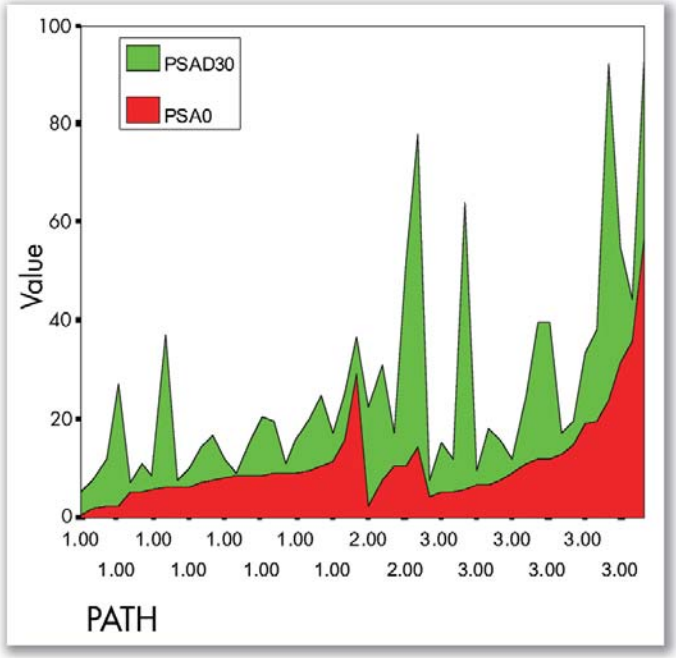


Figure 2. Pattern of Change in PSA(PSAD30) in relation to baseline PSA (PSA0) and pathology (1 Benign, 2 PIN, 3 Cancer), Cases are sorted ascending according to PSA0 in the three groups.

using a Combison-Kretz 311 ultrasound machine with a 7.5 MHz biplanar transrectal probe. With the patient in left lateral decubitus position, routine sextant, octant or more biopsies were obtained with a Biopty gun and 18 gauge Trucut needle depending on the size of the prostate and ultrasound findings.

Thirty minutes following the biopsy procedure blood samples were withdrawn for total serum PSA. Change from baseline PSA was estimated and correlated to histology. PSA assay was carried out using the Bayer PSA measuring kit. PSA data were found to be skewed and non-parametric tests were used for statistical analysis.

## RESULTS

There was a rise of serum PSA in all but one patient which has been excluded from statistical analysis. Twenty-four patients were reported to have a benign histology and 5 patients had prostatic intra epithelial neoplasia. In 19 patients adenocarcinoma of the prostate was detected on histology examination. In one patient with a presenting PSA of 150 ng/ml multiple cysts were visualised on transrectal ultrasound. Because of the nature of pathology very little tissue was obtained for histological examination. The histological diagnosis was indeterminate and this patient was excluded from this study.

The results in 48 patients in this study are as follows:

- the mean age of patients was 68 years (range 55–87);
- sizes of the prostates varied from 16.5 ml to 169 ml (mean 52.4ml);
- 34 patients had routine sextant biopsies;
- 14 patients had sextant and directed biopsies; and
- the mean serum PSA before prostatic biopsies was 11.2 ng/ml (range 0.2–56.20);

There was a rise in serum PSA in all these 48 patients which is shown in Figure 1. The mean rise in serum PSA was as shown in the Table 1 and Figure 2.

There appeared to be the highest rise in PSA in the PIN group and the mean PSA changed from 9 to 40 ng/ml. For further analysis the patients were divided into two groups BENIGN, PIN and CANCERS of 24 each. There was a significant difference in the rise of serum PSA in these two groups (Fig. 2) this was noted to be statistically highly significant (P = 0.000) (see Table 2). In the benign group no relationship was noted between the rise in serum PSA and baseline PSA, prostatic volume, PSA density and the number of biopsy cores.

In the PIN and Cancer group, the change in serum PSA was weakly correlated to the number of positive biopsy cores but it was not related to the Gleason grade or the baseline PSA (see Table 3).

## DISCUSSION

The biochemical response of prostatic tissue to needle biopsies has been well documented in literature. Stamey et al. in 1987[1] first reported rise in serum PSA after prostatic biopsies. Yuan et al. in 1992[2] reported upto 52 fold increase (mean 5.91 fold) in serum PSA post biopsy. Both these papers recommended postponing PSA test for 2 to 4 weeks after biopsy. But the immediate rise in serum PSA was not subjected to analysis in these two studies. In another study on post biopsy PSA, no significant difference was found in rise in serum PSA in patients with benign and cancerous histology.[3] However the histological diagnosis of PIN was not referred to in this study.

In our small study, the greatest rise in post biopsy PSA was observed in the PIN group. When PIN was included in the cancer

Table1 **CHANGE IN PSA HISTOLOGY GROUPS**

| | | Mean | Median |
|---|---|---|---|
| **Benign** | PSA0 | 8.02 | 7.80 |
| | 30m | 16.33 | 14.80 |
| | d30 | 8.30 | 6.75 |
| **PIN** | PSA0 | 9.10 | 10.30 |
| | 30m | 40.30 | 31.10 |
| | d30 | 31.20 | 23.20 |
| **Cancer** | PSA0 | 15.73 | 11.60 |
| | 30m | 34.17 | 24.60 |
| | d30 | 18.45 | 11.30 |

Table 2 **CORRELATIONS OF PSA VALUES AND HISTOLOGY**

| Correlations | | PSA0 | PSA30M | PSAD30 | Histology |
|---|---|---|---|---|---|
| Spearman's rho | PSA0 Correlation Coefficient | 1.000 | .672 | .340 | .331 |
| | Sig. (2-tailed) | – | .000 | .018 | .022 |
| | N | 48 | 48 | 48 | 48 |
| | PSA30M Correlation Coefficient | .672 | 1.000 | .891 | .451 |
| | Sig. (2-tailed) | .000 | – | .000 | .001 |
| | N | 48 | 48 | 48 | 48 |
| | PSAD30 Correlation Coefficient | .340 | .891 | 1.000 | .380 |
| | Sig. (2-tailed) | .018 | .000 | . | .008 |
| | N | 48 | 48 | 48 | 48 |
| | PATH1 Correlation Coefficient | .331 | .451 | .380 | 1.000 |
| | Sig. (2-tailed) | .022 | .001 | .008 | – |
| | N | 48 | 48 | 48 | 48 |

** Correlation is significant at the .01 level (2-tailed).; * Correlation is significant at the .05 level (2-tailed). PSA0 = Baseline serum PSA, PSA30M = Serum PSA 30 min following Biopsies; PSAD30= change in serum PSA at 30 min.

group, there appeared to be a significant difference in rise in PSA between the benign controls and the study group. Thus, the change in serum PSA has been found to relate to the diagnosis of cancer of the prostate. Our hypothesis therefore appears to be tenable in this study. However, when we reanalyzed our results after including PIN in the benign group, our results appear to match previous reports.[3] Despite confounding factors like unsatisfactory imaging of the cancerous lesion by transrectal ultrasound technique, the heterogenous morphology of the prostate and operator factors, the correlation between change in serum PSA and the final histology appears to be better and significantly different than the correlation between serum PSA at baseline and the histological result.

This may indicate that the rise in serum PSA may signify properties of a cancerous lesion other than the properties, which allow prostatic tumours to manifest with raised serum PSA.

**Mechanism of PSA Leak Post-Biopsy.** The mechanism of PSA leak following prostatic needle biopsy has not been looked into and requires investigation. Theoretically two groups of factors may be involved in the phenomenon of PSA leak after prostatic trauma.

**Mechanical Factors.** The degree of prostatic trauma in the biopsy model will be determined by the mechanical energy imparted to the prostate by the spring loaded gun. This mechanical energy may vary between different needle fires depending on the bend in the needle at the time of firing. The spring loaded gun as a result of its design will impart a fixed amount of mechanical energy to prostate. The number of needle fires will obviously determine the total trauma caused to the prostate. There is a weak correlation in our study between number of positive biopsy cores and and the rise in serum PSA.

**Prostatic Factors.** The mechanical properties of the prostate will influence the depth of penetration of the biopsy needle. Mechanical properties of prostate in routine clinical practice are assessed in subjective terms such as size, shape, symmetry, consistency and elasticity. Transrectal ultrasound examination allows the size, shape and symmetry of prostate to be measured. But properties such as elasticity, consistency cannot be measured by the present generation of ultasound machines. But it appears the technology for measuring these properties is evolving at present.[4-8] With the availability of reproducible technology it may become possible to assess the effect of mechanical properties of prostate in context with the phenomenon of PSA leak.

In addition to mechanical properties the morphology of prostate and the location of cancerous lesion within the prostate will affect the phenomenon of PSA leak. The wide variation of serum PSA indicates the heterogeneous morphology of prostate. Transrectal ultrasound has the limitation that the actual cancerous lesion cannot be imaged and localized with current techniques. In addition, factors such as micro vessel density and cell adhesion factors like E- Cadherin, cathepsins and Galactins may influence the phenomenon of post biopsy PSA leak. The host factors like immune status, both humoral and cellular, serum proteins, total body mass may also require further investgation as the determinants of PSA leak.

**Is the Behaviour of Prostate Cancer as Judged by the Rise in PSA After Mechanical Injury of Any Clinical Significance?** It is well known that the tumours in the prostate vary in their significance. To differentiate the significant from the insignificant, three main tools are used in clinical practice. These include serum PSA, the Gleason grade and the clinical stage of the tumour. In addition, a plethora of markers have been introduced in a research setting to predict the behaviour of a tumour in the prostate. These markers have been classified as intra cellular, cellular and molecular. These clinical and laboratory markers give us a cross section of a tumour at a point of time either in vitro or in vivo. Based on this cross sectional static information we form an opinion on the dynamics of cancerous behaviour in an individual patient as being significant or not. The model we are presenting here allows us to make a dynamic assessment of prostate cancer. The behaviour of a prostate cancer as judged by post biopsy PSA leak may or may not be related to its biological and clinical behaviour. We expect this study to stimulate further research into the in vitro dynamics of prostate cancer behaviour. We suggest using static and dynamic terms while referring to tests of cancer assessment. Thus, the answer to the above question will come from large-scale studies incorporating known tumour and host characteristics (including response to treatment and long term survivals of patients) to the post biopsy PSA response.

## THE FUTURE

It should be possible to evolve more refined models on this line using total PSA, free and complexed PSA, RT-PCR analysis of sera at intervals and MRI spectroscopy. RT-PCR (reverse transcriptase-polymerase chain reaction) and MRI spectroscopy are two techniques which hold a special promise for the future of cancer assessment. Reverse transcriptase-polymerase chain reaction is a very powerful tool which allows us to measure very minute quantities of messenger RNA for a specific marker. This technique is highly electronic processing dependent. MRI spectroscopy in combination with 3D MRI has been shown in recent studies to have a sensitivity and specificity of the order of 90% in imaging prostatic cancer.[9] The applications of combined MR imaging and MR spectroscopic imaging of prostate cancer have expanded significantly over the past 10 years and have reached the point of clinical trial results to test robustness and clinical significance. MR spectroscopic imaging extends the diagnostic evaluation of prostate cancer beyond the

morphologic information provided by MR imaging through the detection of cellular metabolites. The combined metabolic and anatomic information provided by MR imaging and MR spectroscopic imaging has allowed a more accurate assessment of the presence, location, extent, and aggressiveness of prostate cancer.[9] MRI spectroscopy has also been used for assessment of MVD of some cancers.[10] In a nutshell MRI spectroscopy allows both a morphological as well as behavioural assessment of a cancer. With the remarkable growth in electronic processing power in the past few years and the prediction of the further growth in the near future, it can be expected that the power and usefulness of these two techniques will increase tremendously in future. These technological advances are likely to bring major shifts in the way we assess and treat patients with prostate cancer.

The majority of the tests, which we use in prostate cancer assessment both in clinical and laboratory setting, are static tests of prostate cancer assessment. With the promise of evolution of dynamic tests we will see a dichotomy of cancer assessment in the form of static and dynamic tests of prostate cancer behaviour. A clear abstraction of this dichotomy from a subliminal level to a conceptual level, will open doors to the realms of cancer research which have not been witnessed before. These concepts will be applicable not only to prostate cancer but to cancer biology in general. It will require a paradigm shift from the highest to the lowest level in personnel engaged in assessment and treatment of cancers in general. This new paradigm will allow us to look at the cancers within our patients, not as objects or single threaded processes but as dynamic entities or systematized groups of processes, in ways not known at present. In the not too distant future we will have a library of information, both static and dynamic for every cancer which will help us in the decision making process necessary for the treatment of each patient on an individual basis.

## CONCLUSION

This is a small study of post biopsy PSA in an unselected group of patients. The results we have obtained in this study will require to be viewed with a degree of caution. In particular the rather excessive rise in PSA in patients with PIN to our knowledge has not been reported before. This observation requires to be reproduced by other investigators. The mechanism of such rise in PSA is open to speculation.

In summary, we have introduced a crude biopsy model for dynamic assessment of prostate cancer behaviour which needs further testing and validation. Our model has allowed us to hypothesize several possibilities for exploring the tumour biology of prostate cancer and cancers in general.

Table 3 **PSA (Pre- and Post-Biopsy) and Histology Details of Individual Patients**

| ID | PSA0 | PSA30M | HISTO | GRADE | CORES |
|---|---|---|---|---|---|
| Patient 1 | 8.30 | 8.90 | Benign | | 7 |
| Patient 2 | 6.00 | 7.50 | Benign | | 6 |
| Patient 3 | 9.30 | 11.00 | Benign | Prostatitis | 6 |
| Patient 4 | 5.00 | 7.10 | Benign | | 6 |
| Patient 5 | 5.70 | 8.50 | Benign | | 6 |
| Patient 6 | 8.10 | 11.90 | Benign | | 6 |
| Patient 7 | 6.10 | 10.00 | Benign | | 6 |
| Patient 8 | 0.20 | 5.30 | Benign | | 6 |
| Patient 9 | 1.80 | 7.50 | Benign | | 6 |
| Patient 10 | 5.20 | 11.00 | Benign | | 8 |
| Patient 11 | 11.10 | 17.00 | Benign | | 10 |
| Patient 12 | 9.30 | 15.80 | Benign | | 6 |
| Patient 13 | 7.10 | 14.10 | Benign | | 11 |
| Patient 14 | 8.40 | 15.50 | Benign | | 9 |
| Patient 15 | 28.80 | 36.90 | Benign | | 6 |
| Patient 16 | 7.50 | 16.70 | Benign | | 9 |
| Patient 17 | 16.00 | 25.30 | Benign | | 7 |
| Patient 18 | 2.30 | 12.00 | Benign | | 8 |
| Patient 19 | 9.40 | 19.90 | Benign | | 6 |
| Patient 20 | 9.20 | 19.80 | Benign | | 6 |
| Patient 21 | 8.50 | 20.50 | Benign | | 6 |
| Patient 22 | 10.70 | 25.10 | Benign | | 6 |
| Patient 23 | 2.60 | 27.20 | Benign | | 6 |
| Patient 24 | 5.90 | 37.30 | Benign | | 8 |
| Patient 25 | 10.30 | 17.30 | Benign | low gr PIN | 1 in 6 |
| Patient 26 | 2.50 | 22.70 | Benign | low gr PIN | 5 in 6 |
| Patient 27 | 7.90 | 31.10 | Benign | low gr PIN | 7 in 7 |
| Patient 28 | 10.70 | 52.20 | Benign | low gr PIN | 1 in 6 |
| Patient 29 | 14.10 | 78.20 | Benign | low gr PIN | 8 in 8 |
| Patient 30 | 9.00 | 11.50 | Ca Prostate | Gl 7 | 6 in 6 |
| Patient 31 | 4.40 | 7.50 | Ca Prostate | Gl 6+PIN | 1 in 7 |
| Patient 32 | 6.20 | 9.40 | Ca Prostate | Gl6 | 2 in 6 |
| Patient 33 | 13.20 | 17.30 | Ca Prostate | Gl5+hi PIN | 1 in 6 |
| Patient 34 | 14.90 | 19.40 | Ca Prostate | Gl 4 | 1 in 6 |
| Patient 35 | 5.40 | 11.80 | Ca Prostate | Gl 7 | 3 in 8 |
| Patient 36 | 12.40 | 39.40 | Ca Prostate | Gl 4 | 2 in 6 |
| Patient 37 | 36.00 | 44.40 | Ca Prostate | Gl 7 | 6 in 6 |
| Patient 38 | 5.30 | 15.20 | Ca Prostate | Gl 4 | 1 in 6 |
| Patient 39 | 6.70 | 18.00 | Ca Prostate | Gl 2 | 1 in 6 |
| Patient 41 | 19.00 | 33.30 | Ca Prostate | Gl 8 | 6 in 6 |
| Patient 42 | 19.50 | 38.40 | Ca Prostate | Gl 7 | 2 in 6 |
| Patient 43 | 31.50 | 54.90 | Ca Prostate | Gl 7 | 1 in 6 |
| Patient 44 | 7.60 | 15.60 | Ca Prostate | Gl 7 | 1 in 6 |
| Patient 45 | 11.60 | 39.40 | Ca Prostate | Gl 2 | 2 in 6 |
| Patient 46 | 56.20 | 93.00 | Ca Prostate | Gl 7 | 6 in 6 |
| Patient 47 | 5.70 | 64.10 | Ca Prostate | Gl 6 | 3 in 6 |
| Patient 48 | 24.00 | 92.10 | Ca Prostate | Gl 7 | 6 in 6 |

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