

DISCUSSION AT PSA AUDIT MEETING OCTOBER 2003

DISCUSSION AFTER CONSULTANT UROLOGIST'S PRESENTATION

1. Free PSA does not improve specificity. There is no real evidence that complexed PSA or free PSA is better than PSA in a clinical setting. 20 free PSA assays need to be done to benefit 3 patients.
2. Is it better to detect the disease earlier in the natural history of the disease? Patients are more likely to die with prostate cancer than from it. Increasing life expectancy for men will increase the number with the disease.
3. North London Cancer Centre urologists do not use PSA.
4. Some cancers do not produce PSA and acid phosphatase is useful in these patients.

ADDITIONAL NOTES FROM HUGH MITCHELL'S PRESENTATION

PSA was developed as a forensic test for semen.

PSA Stability

Samples should be separated within 3 hours and if stored for longer than 24 hours they should be stored at -20°C in the freezer. Samples for long term storage should be stored at -70°C . Individual manufacturers kit inserts quote varied storage times and temperatures. Assays are now equimolar and measure down to 0.003 ng/ml so the stability studies need repeating. Freezing and thawing of samples is not a problem.

Free PSA

1. Effect of DRE on PSA measurement

DRE releases free PSA which rises and then falls. Not all kit inserts make this clear. Data indicates samples should not be collected until 24 hours after prostate manipulation.

2. Free PSA reference range

< 10 % fPSA = high risk
>20 % fPSA = low risk

3. PSA and free PSA in metastases

PSA has CHO added to it in the Golgi apparatus which stabilises it for extrusion and stops its protease inhibition. Intracellular PSA in metastases has a low % free PSA as it is conjugated more aggressively. If PSA is from normal tissues there will be more free around.

PSA levels post prostatectomy

The median half-life for free PSA is 2 days. The median half-life for complexed PSA is 10 days as it is cleared by the liver.

Method changes

If methods or analysers are changed a comparison of the methods should be done and users informed of the differences they will see.

Reference material

A new set of reference materials is being produced in Baltimore using 10 %, 50 % and 90 % free PSA. This is being sent out by UKNEQAS.

New potential markers

1. TRAP 5 _
2. Tartrate resistant acid phosphatase
3. Kallikreins

They are useful independently of PSA. They are affected by hormones and are a marker of bone metastases.

Standard Setting

There are NICE Guidelines on urological cancers and NHS Prostate Cancer Risk Management Guidelines which should be considered.

1. Standards should be split into lab and clinical guidelines. They need to contain information for primary care.
2. National Guidelines will recommend age related reference ranges. These do prevent inappropriate referrals to urologists.
3. There is little information on PSA levels and race.
4. How do we implement sample collection guidelines?
5. The effects of procedures on PSA levels need to be listed as affected for 24 hours, 48 hours, 1 week and 6 weeks? Need to delay blood collection for 6 weeks after an acute condition resolves. Are the changes seen after procedures small and transient?
6. Need to add if on Finestride PSA result should be doubled for interpretation.
7. These standards will not reduce PSA workload.

PROPOSED RECOMMENDATIONS REGARDING PSA MEASUREMENT

CLINICAL CONSIDERATIONS

1. PSA should **ideally** be performed for suspected prostate cancer if the patient has symptoms suggestive of prostate cancer or if the patient has a strong family history of prostate cancer i.e.: two first-degree relatives.
2. PSA measurement is **not** recommended for the asymptomatic male. However if a concerned well man wishes to have a PSA test then he needs to be given balanced information to assist him in making an informed decision about having the test. There is **no** good evidence to date that screening for prostate cancer using PSA reduces mortality.
3. PSA is likely to be elevated in the following conditions: Acute retention, urinary tract Infection, prostatitis, haematuria"back pain,erectile dysfunction and testicular swelling.
4. It is recommended that blood be taken for PSA **before** any manipulation of the prostate gland and delayed for **48 hours after** ejaculation, **one week after** a digital rectal examination, rigid cystoscopy or ultrasound, and **up to six weeks after** a needle biopsy of the prostate gland ,prostatitis or transurethral resection of the prostate gland Prolonged cycling should be stopped a week **before the test**.
5. PSA alone **cannot** be used to diagnose prostate cancer .It must be used in conjunction with a digital rectal examination. Patients with a raised PSA and a suspicious digital rectal examination should be referred to a urologist.
6. The **main** use for PSA is in the monitoring of those patients in whom a definite diagnosis of prostate cancer has been made., giving an indication of response to treatment and early indication of progression of the cancer. A single PSA measurement should **not** be used as a diagnostic tool for the detection of recurrence.
7. The use of free PSA to calculate a PSA Index is currently controversial and should be used only by Consultants in difficult situations.

LABORATORY CONSIDERATIONS

1. PSA should only be assayed in a laboratory which participates in a CPA recognised External Quality Assessment Scheme.
2. The between run imprecision of the assay at a level equivalent to the cut off value should be less than 8%
3. The assay for PSA should be calibrated against the Stanford Reference Standard IRP 96/270(90% PSA-ACT and 10% free PSA). The methods should use a combination of antibodies that ensure equimolar recognition of both free and complexed PSA forms.
4. Serum for PSA should be centrifuged and refrigerated within 3 hours of phlebotomy. Serum, once separated may be stored for up to 24 hours at 4°C. Samples not analysed within 24 hours of collection should be stored at -20°C.
5. It is recommended that the report issued by the laboratory should state the reference range used. The use of age- and race- specific reference ranges for PSA is controversial but is recommended by the Prostate Cancer Risk Management programme. At present there is limited data available for race-related reference ranges.

REFERENCES

Catalona WJ et al Measurement of prostate specific antigen in serum as a screening test for prostate cancer New Engl J Med 1991 324 1156-1161

Duffy MJ PSA as a marker for prostate cancer: a critical review Ann Clin Biochem 1996 33 511-519

Semjonow A et al Tumour markers in prostate cancer:EGTM recommendations Anticancer Res 1999 19 2799-2801

Brawer MK Prostate specific antigen: current status CA Cncer J Clin 1999 49 264-281

Catalona WJ et al Use of the percentage of free prostate specific antigen to enhance differentiation of prostate cancer from benign prostatic disease:A prospective multicentre clinical trial JAMA 1998 279 1542-1547

Price CP et al Pre- and post-analytical factors that may influence the use of serum prostate specific antigen and its isoforms in a screening programme for prostate cancer Ann Clin Biochem 2001 38 188-216

Fleischer et al Practice guidelines and recommendations for the use of tumour markers in the clinic: Published in National Academy of Clinical Biochemistry 2002 15 20-25

Watson E et al Prostate Cancer Risk Management Programme-an information pack for primary care Published by Cancer Research UK Primary Care Education Research Group 2002