Prostate specific antigen - brief update on its clinical use

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Abstract

Prostate specific antigen (PSA) testing of asymptomatic men enables the diagnosis of localised prostate cancer which is potentially curable, but it also poses certain risks. Doctors run the risk of litigation for failure to diagnose cancer at a curable stage, while patients run the risk of being diagnosed with non-significant cancer, incurring costs and possible complications without any survival benefit.

PSA reflects a 'range of risk' for prostate cancer: the higher the PSA, the greater the risk. There is no 'normal' PSA, because even with a PSA below 4 ng/ml cancer can be detected on biopsy in up to 20% of men. However, the prevalence of high-grade (life-threatening) cancer is relatively low at low PSA values.

The following recommendations appear reasonable:

- PSA testing should be offered to all men aged 50 years or more (45 years in those with a family history of prostate cancer and – possibly – African men);
- Alternatively, PSA testing should be done at 40, 45 and 50 years and then every two to four years (the lower the baseline value, the lower the risk of ever developing prostate cancer);
- PSA testing should be repeated annually if it is more than 2 ng/ml and every two years if less than 2 ng/ml;
- Stop PSA testing in asymptomatic men over 75 years or with less than 10 years' life expectancy, and in those aged over 65 years with PSA less than 0.5 to 1 ng/ml.

The free-to-total PSA ratio and PSA density (PSA divided by prostate volume) can be used to decide which patients need prostatic biopsy. PSA velocity (increase of PSA per year) can predict which men are likely to develop prostate cancer or to die of it (the higher the PSA velocity, the greater the risk). PSA doubling time (the period it takes for the PSA to double) correlates with the prognosis both before and after treatment (the shorter the doubling time, the worse the prognosis).

An internet Prostate Cancer Risk Calculator is available which calculates a man's risk by taking into account his age, race, family history, PSA level, findings on rectal examination and prior negative biopsy. Although this is a very convenient tool, it should be used with caution, especially at low PSA values, because there is a real risk of overdiagnosis.

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Introduction

The use of prostate specific antigen (PSA) in the diagnosis of prostate cancer remains a topic of considerable controversy. It is especially problematic for busy family practitioners who do not have the time to peruse the vast literature on this topic.[1,2] Currently, entering the words "prostate specific antigen" into an electronic literature index such as Pubmed produces more than 15 000 articles. The aim of this review is to provide the general practitioner with a brief but comprehensive update on the use of PSA testing in clinical practice.

What is PSA?

Prostate specific antigen (PSA) is an enzyme, a serine protease (molecular weight 33 kilodalton) that is produced almost exclusively by the prostatic epithelial cells. It is secreted into the prostatic ducts and forms part of the seminal fluid. Its function is possibly to lyse the semen coagulate formed a few minutes after ejaculation, although the physiological role of clotting and lysing of the ejaculate remains unknown.

Why all the fuss about PSA?

The protein now known as PSA was first identified in seminal plasma in 1966 and was given the name gamma-seminoprotein. It proved useful as a forensic marker in rape cases.[2] PSA was biochemically characterised in seminal fluid and a serum assay was developed in 1979.[3,4] During the 1980s it was realised that serum PSA levels correlate with the tumour burden in men with prostate cancer. Its

clinical use gained rapid momentum worldwide during the 1990s and it has become the most clinically useful of all serum tumour markers. It has a higher specificity for prostate cancer than the mammogram does for breast cancer, so it is somewhat ironic that its use should remain controversial.[5]

PSA testing of asymptomatic men has enabled the diagnosis of localised or early-stage prostate cancer. The widespread clinical use of PSA has led to a dramatic 'stage migration' in the USA and Europe – whereas previously about 80% of men were diagnosed with advanced prostate cancer (incurable), nowadays more than 80% are diagnosed with localised cancer (potentially curable). However, the availability of PSA testing has created new risks for both doctor and patient. There have been several cases of litigation where practitioners were sued for millions because of failure to diagnose prostate cancer at a curable stage. For patients there is the risk of overdiagnosis and overtreatment of non-significant prostate cancer, incurring costs and possible complications of treatment without any significant benefit.

What determines serum PSA levels?

PSA is secreted into the prostatic ducts and very little PSA enters the bloodstream, so its concentration is about a million times higher in seminal fluid than in serum. Elevated serum PSA results from disruption of the cellular architecture within the prostate gland, with loss of the normal barrier formed by the basal layer and basement membranes, so that PSA 'leaks' into the circulation.

Conditions that increase serum PSA:

- Prostate cancer
- Benign prostatic hyperplasia (BPH)
- Prostatitis
- Acute urinary retention (AUR)
- Prostatic biopsy, transurethral resection of the prostate (TURP)
- Digital rectal examination (DRE)
- Ejaculation

Prostate cancer cells usually make less rather than more PSA compared with normal prostate cells, so the elevated PSA associated with prostate cancer is due to more 'leakage' of PSA into the bloodstream rather than to increased production. In general there is a good correlation between PSA and cancer volume, i.e. the higher the PSA the larger the cancer. However, the correlation is not absolute and there are exceptions to the rule, i.e. high PSA with a small cancer, or metastatic cancer with a low PSA.

PSA increases with age and with increasing prostate volume, mainly due to BPH, which becomes more prevalent with age. AUR is often precipitated by urinary tract infection (UTI), prostatitis or prostatic infarction, which can all cause an elevated PSA. Catheterisation or cystoscopy in a normal man does not cause a clinically significant PSA elevation. Catheterisation in someone with AUR is often associated with an elevated PSA, most probably because of underlying UTI, prostatitis or infarction that precipitated the AUR. DRE may increase the PSA, but usually within the laboratory error of the assay, so it is not clinically significant. Nonetheless, it is preferable to draw blood for PSA before doing a DRE.
Ejaculation may cause a statistically (but not clinically) significant PSA elevation.

The half-life of serum PSA is two to three days. Prostatic trauma, e.g. biopsy or TURP, will dramatically elevate the PSA, which takes about four weeks to return to baseline. Therefore it is very important not to repeat PSA testing within four to six weeks after any event that is known to elevate the PSA, otherwise a false high value will be obtained.

Factors that decrease serum PSA:

- Decreased serum testosterone (hypogonadism)
- Androgen deprivation therapy (ADT)
- Finasteride and dutasteride

Low serum testosterone is associated with a relatively low PSA. The risk of finding prostate cancer on biopsy at any given PSA is higher in men with a low serum testosterone (hypogonadism) than in men with a normal testosterone.[6,7]

ADT, whether surgical (bilateral orchidectomy) or medical (oestrogens, luteinising hormone-releasing hormone agonists, anti-androgens) will almost always cause a dramatic decrease in PSA.

Finasteride and dutasteride are 5-alpha-reductase inhibitors (5ARI) used in the treatment of BPH. They inhibit the action of 5-alpha-reductase which converts testosterone to dihydrotestosterone (DHT). They reduce the PSA level by about 50% after six to 12 months of treatment. In patients on 5ARI treatment a PSA increase of more than 0.3 ng/ml over the nadir (lowest) value should raise suspicion of prostate cancer.[8]

What is a normal PSA?

Initial studies suggested that a PSA of 4.0 ng/ml indicates a high risk of prostate cancer and should be used as a threshold value (cut-off) for recommending a prostate biopsy. Later studies suggested that a cut-off value of 3.0 ng/ml or even 2.5 ng/ml should be used. However, it is now recognised that PSA reflects a continuous 'range of risk' for prostate cancer, rather than normal or abnormal values.

The Prostate Cancer Prevention Trial, which evaluated finasteride for the prevention of prostate cancer, provided information about the prevalence of prostate cancer in several thousand men with PSA below 3 ng/ml who underwent biopsy.[9] Other studies have investigated the risk of finding cancer in men with high PSA values (Table I).[10]

Table I: Cancer yield at different PSA levels*

Serum PSA (ng/ml)	Cancer yield on biopsy (approximate %)	High-grade cancer (approximate %)
0–1	10%	1%
1–2	15%	2%
2–4	20%	5%
4–10	35%	10%
10–20	75%	
> 30	90%	
> 60	98%	

* Cancer yield is the total number of cancers detected divided by the total number of men undergoing biopsy with a PSA in the given range.[9,10]

The relatively high cancer yield on biopsy in men with low PSA levels is not really surprising, because it has long been known that there is a high prevalence of prostate cancer that can be detected histologically in young men aged 30 to 50 years who died as a result of trauma.[11] However, the proportion of high-grade cancer is relatively low, ranging

from about one in ten cases diagnosed with a PSA below 1 ng/ml to one in four cases at a PSA of 2–4 ng/ml to approximately one in three cases with a PSA of 4–10 ng/ml (Table I).

The problem in choosing a single PSA cut-off for recommending biopsy is that there is an inverse relationship between sensitivity and specificity, and it is difficult to decide where the balance should be. The higher the PSA cut-off that is chosen, the more specific it is (because the higher the PSA, the more likely that prostate cancer is present, so few unnecessary biopsies will be done) but the less sensitive it is (because it will miss many cancers which are present with a PSA below the high cut-off).

The lower the PSA cut-off that is chosen, the more sensitive it is (it will detect almost all cancers, including those which are present with a low PSA) but the less specific it is (many more biopsies will be done unnecessarily in men with a low PSA who do not have cancer). For example, using a PSA threshold of 4.0 ng/ml, about 25% of prostate cancers are not detected (false-negative rate) whereas about 65% of biopsies will not show cancer (false-positive rate).[8]

Another problem is that lowering the PSA threshold, e.g. from 4 ng/ml to 2.5 ng/ml, would double the number of men requiring biopsy. Many of these men harbour low-grade, small-volume cancers that will not cause the patient's death, so there is a high risk of overdiagnosis and overtreatment.[12]

How reproducible are PSA assays?

Serum levels of PSA are very low, so the assay has to measure a tiny quantity of protein – in nanogram per millilitre or microgram per litre – and the risk for laboratory error is larger than with assays measuring proteins at higher concentrations. There is normal physiological variation. Also, there are different types of PSA assays which may give slightly different results on the same specimen. Variation in PSA assay results can be as high as 20 to 40%.[13]

It is very important to use the same laboratory and the same assay when doing sequential PSA tests in the same person. It is also important not to base a major clinical decision on a minor change in PSA, unless it has been confirmed with a repeat test.

What are age- and race-specific PSA ranges?

PSA increases with age, mainly due to the development of BPH. This means that, for any given PSA value, the chance of finding cancer on biopsy is higher in younger than in older men.

It is more important to diagnose early-stage prostate cancer in a younger than in an older man, because the cancer is more likely to be the cause of death in the younger man, whereas the older man may die of some other condition. A lower PSA cut-off value in younger men will reduce the risk of underdiagnosis (missing prostate cancer) and a higher PSA cut-off in older men will reduce the risk of overdiagnosis (finding cancer which is unlikely to cause death).[14,15]
Studies from the USA have indicated that prostate cancer may occur at a younger age in African-American men and that PSA at diagnosis in black men is higher than in white men. Therefore it has been suggested that a younger age and lower PSA cut-off value should be used as indication for prostate biopsy in black men. However, there is a lack of studies to show whether this also applies to black men living in Africa.[16]

Who should be offered PSA testing?

Prostate cancer is rarely diagnosed in men younger than 50 years, accounting for less than 0.1% of all patients. About 85% of cases are diagnosed after the age of 65 years. It is usually recommended that PSA testing be offered from the age of 50 onwards, and perhaps earlier (age 45) for those at higher risk (family history of prostate cancer, black African race).[9]

It has also been recommended that all men be offered baseline PSA testing at age 40 years and that the frequency of follow-up testing should depend on this baseline level. The relative risk of developing prostate cancer during the next 10 years is strongly correlated to the baseline PSA.[17]

The recommended upper age limit for PSA screening varies from 70 to 75 years. It is generally accepted that PSA screening of asymptomatic men should be limited to those with a life expectancy of more than 10 years. This is because early stage prostate cancer is unlikely to cause the patient's death in less than 10 years. It has been shown that if PSA testing were discontinued in men aged 65 years with PSA levels below 1 ng/ml, it is unlikely that a prostate cancer would be missed later in life.[18]

How often should PSA testing be repeated?

Long rescreening intervals may miss detecting curable cancer in those with fast-growing cancers, and short intervals may lead to unnecessary testing, overdiagnosis and overtreatment of those with slowly growing cancers. The problem is to define a screening interval that will minimise the risks of both underdiagnosis and overdiagnosis.

It has been recommended that all men older than 50 should have annual PSA screening regardless of risk. Some authors have suggested biennial screening (once every two years) for men with PSA levels of 2 ng/ml or less and annual screening for those with PSA levels of 2 ng/ml or above. It has also been suggested that men with PSA levels of less than 1 ng/ml can safely be scheduled for a three-year testing interval. The large European screening study has shown that a rescreening interval of four years may be reasonable.[19–22]

However, it has also been suggested that a two- or four-year PSA screening interval in men with initial serum PSA less than 2 ng/ml would result in substantial delays in prostate cancer detection, although the extent to which these delays would affect treatment outcomes remains undetermined.[23]

In summary, the following recommendations appear reasonable:

- PSA testing should be offered to all men aged 50 years or more (45 years in those with a family history of prostate cancer and – possibly – African men);
- Alternatively, PSA testing should be done at 40, 45 and 50 years and then every two to four years, depending on the baseline PSA value;
- PSA testing should be repeated annually if PSA is more than 2 ng/ml and every two years if it is less than 2 ng/ml;
- Stop PSA testing in asymptomatic men over 75 years or with less than 10 years' life expectancy, and in those aged over 65 years with PSA less than 0.5 to 1 ng/ml.

In men with a diagnosis of prostate cancer, whether treated or not, it is virtually never necessary to repeat the PSA at intervals of less than

three to six months, because PSA changes over shorter intervals are very unlikely to have major implications.

Can PSA replace digital rectal examination (DRE)?

In a man with lower urinary tract symptoms (LUTS), haematuria or other symptoms that may indicate advanced prostate cancer (back pain, weight loss, anaemia), a DRE is essential. The question is whether DRE should be performed in all asymptomatic men aged 50 to 70 years, because the majority who have prostate cancer do not have a palpable abnormality.

Most screening studies have shown that prostate cancer detection rates are significantly higher using PSA alone than using DRE alone, but is highest when a combination of the two is used. An abnormal DRE has been shown on multivariate analysis to be a predictor of high-grade (life-threatening) prostate cancer, independent of PSA.[24] However, the large European screening study has shown no additional benefit in using DRE or transrectal ultrasound (TRUS) rather than PSA alone.[25]

Nonetheless, examination of the external genitalia and DRE should continue to form part of a thorough clinical examination in all men with symptoms, and in asymptomatic men aged 50 to 70 years, just as dipsticks urinalysis should form part of the clinical examination, because in some patients (albeit a small minority) an unexpected but important abnormality may be detected.

Who should have a prostate biopsy?

An internet Prostate Cancer Risk Calculator is available on the National Cancer Institute website. (It can be found by simply typing "prostate cancer risk calculator" into a search engine such as Google). The complete address is: http://www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp?t=prostate&sub=s1&m=&v=prostate&x=Prostate%20Cancer

This computer programme uses data from large PSA-based cancer detection studies to calculate a man's risk of having cancer diagnosed on prostate biopsy by taking into account his age, race, family history of prostate cancer, PSA level, DRE result and whether he had a prior negative biopsy.

A representative sample of risk estimates for a 60-year-old white man with no prior prostate biopsy is shown in Table II. It can be seen that the risk increases with increasing PSA, and at each level of PSA the risk is higher if there is a family history of prostate cancer and if the DRE is abnormal.

It should be noted that the risk of finding high-grade (i.e. life-threatening) cancer is much lower than the risk of finding any cancer, especially with a PSA of 1–4 ng/ml, where high-grade cancer constitutes only one in 14 to one in five of cases, whereas with a PSA of 20 ng/ml about half of cases will be high-grade cancer (Table II).

Therefore, the computerised risk calculator should be used with caution, especially at low PSA values, because there is a real risk of overdiagnosis and overtreatment. It is estimated that lowering the PSA cut-off value for biopsy to levels below 4 ng/ml may lead to overdiagnosis rates of 30 to 50%, with a huge impact on costs of treatment and morbidity due to complications and side effects of treatment.[26–29]

Table II: Risk of finding prostate cancer on biopsy in a 60-year-old white man with no prior prostate biopsy*

	Family history negative, DRE normal		+ Family history positive	+ DRE abnormal
PSA ng/ml	Cancer (%)	High-grade cancer (%)	Cancer (%)	Cancer (%)
1	14	1	18	35
2	23	3	28	49
3	30	5	36	58
4	35	7	41	64
5	39	9	46	68
10	54	19	61	75
20	68	37	73	75

* According to the Prostate Cancer Risk Calculator which can be accessed on the National Cancer Institute website at http://www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp?t=prostate&sub=s1&m=&v=prostate&x=Prostate%20Cancer

How is a prostate biopsy done?

Prostate biopsy is usually done under TRUS guidance with an 18-gauge needle inserted through the rectum or (less commonly) the perineum. It can be done under general anaesthesia, but local anaesthesia is usually sufficient. Prophylactic antibiotic treatment is essential to prevent bacteraemia. Complications of prostate biopsy include pain or discomfort, bacteraemia or septicaemia, urinary tract infection, prostatitis, haematuria, haematospermia, rectal bleeding and acute retention.

Traditionally six biopsy cores were taken, three on each side ("sextant" biopsy). Subsequent studies showed that taking more cores produced a higher rate of positive biopsies ("the more holes you drill, the more oil you find") and currently there is controversy as to whether eight, 10, 12 or 18 cores should be taken. There are even centres advocating "saturation biopsy" where an average of 24 (and up to 45) cores are taken.[30] It has also been recommended that the number of cores should be determined by the size of the prostate and the age of the patient (more cores taken in larger prostates and in younger men).[31]

However, it should be kept in mind that increasing the number of biopsy cores increases the risk of diagnosing small-volume cancers which may not require treatment, i.e. it increases the risk of overdiagnosis and overtreatment.

Is informed consent necessary for PSA testing?

PSA testing in asymptomatic men may have far-reaching consequences in terms of the costs and complications of treating prostate cancer, without guaranteed benefits in terms of improved quality of life or longer survival. On the other hand, failure to diagnose prostate cancer at a curable stage may have serious medico-legal repercussions. Therefore it is important for practitioners to discuss the option of PSA testing with all asymptomatic men over the age of 45 to 50, and up to the age of 75 years, provided they have a life expectancy of 10 years.

The patient should be given the following basic information:

- Prostate cancer is one of the most common types of cancer in men.
- The risk is higher with age, and when there is a family history of prostate cancer (father, brothers, uncles).
- It can be diagnosed at an early stage with the aid of DRE and PSA testing.
- If diagnosed early, it can be cured.
- However, there are costs and risks involved in the diagnosis and treatment.
- The potential benefit of early diagnosis is that later suffering and death due to prostate cancer may be avoided.
- However, there may be a loss in quality of life without guaranteed benefit of longer survival.

If the patient declines the offer of PSA testing, it should be recorded in the clinical notes.

Should there be state-funded PSA screening?

There are several reasons why screening for prostate cancer makes good sense. It has a high prevalence, there is no effective prevention, it does not cause symptoms before it is advanced and incurable, it causes significant morbidity and mortality, there is a screening test which is more sensitive and specific in detecting early cancer than most screening tests for other cancers, a definitive diagnosis can be made relatively easily and reliably, and there is effective curative treatment.

The problems are that prostate cancer occurs in elderly men with competing causes of mortality, not all prostate cancers are life-threatening, its natural course is prolonged (even if untreated), so that the potential benefit of curative treatment must be weighed against the costs and complications of potentially unnecessary treatment in men who will die of some cause other than prostate cancer.[5] In short, the potential gain (living longer) has to be weighed up against the potential pain (losing quality of life).

Whether the term screening or early detection is used, PSA has already made a significant impact on prostate cancer. In the USA, the percentage of men with metastatic cancer at diagnosis has steadily decreased since 1991 and organ-confined disease found at radical prostatectomy has increased from less than 50% to more than 70% (stage migration). A decline in prostate cancer mortality is beginning to become evident in the USA and elsewhere, but it is not yet clear whether this is the effect of curative treatment or due to other factors.

Two large-scale randomised trials of PSA screening for prostate cancer in men aged 50 to 74 years are currently under way: the Prostate, Lung, Colorectal and Ovary Cancer trial in the USA, and the European Randomised Study of Screening for Prostate Cancer. The PLCO and ERSPC trials are designed to establish whether PSA screening will decrease prostate cancer specific mortality, but it will take several years before the final results of these studies are known.[2]

Widespread PSA screening should not be implemented before there is proof that it does more good than harm. However, it is strongly advised that doctors should give their patients information about the potential risks and benefits of early detection and treatment of prostate cancer, and assist them in making informed decisions about testing.[5]

What is the free/total PSA ratio (f/t PSA)?

PSA in the serum may be bound (complexed) to three different proteins. The bound PSA is enzymatically inactive but remains immunoreactive and can therefore be measured by immuno-assay.

Men with prostate cancer have a greater fraction of total PSA bound to serum proteins and a lower percentage that is free compared with men who do not have prostate cancer.

The free and total PSA values can be measured separately and expressed as a free to total PSA (f/t PSA) ratio or as the percentage free PSA. The lower the f/t ratio, the higher the risk of prostate cancer.

There is some controversy, but if the f/t PSA ratio is below 0.15 (free PSA below 15%) the risk of prostate cancer is considered sufficiently high to warrant biopsy or re-biopsy (if there is a previous negative biopsy).[32] Some authors recommend that a biopsy should be done in everyone with a percentage free PSA lower than 23%.

The f/t PSA ratio is only useful in men with a PSA less than 10 ng/ml in whom there is uncertainty as to whether a biopsy should be done or repeated. If the PSA is over 10 ng/ml the risk of prostate cancer is so high that a biopsy should be recommended, and repeated if the first biopsy is negative. There is no reason to do f/t PSA in all men, or in those with a total PSA over 10 ng/ml.

What is complexed PSA (cPSA)?

There is an assay that measures only the complexed forms of PSA bound to serum proteins; therefore cPSA gives the total minus free PSA in one assay. It provides the same information as the f/t PSA ratio, and its clinical usefulness is in better selecting which men should have a prostate biopsy.[33]

However, just as f/t PSA should not be routinely done, because it has no clinical relevance in the majority of men with a PSA outside the 4–10 ng/ml range, the routine use of cPSA is questionable. In the vast majority of cases it is of no importance what the free versus bound fractions of PSA are (the PSA is either too low to warrant biopsy, or it is so high that biopsy is mandatory).

What is PSA density (PSAD)?

PSA density (PSAD) is the serum PSA divided by the prostate volume as measured by TRUS. Any given volume of prostate cancer will elevate serum PSA about 10 times more than the same volume of BPH, i.e. the 'leakage' of PSA into the serum is 10 times higher with any volume of cancer than with the same volume of BPH.

The higher the PSAD, the greater the risk of prostate cancer, and the lower the PSAD, the lower the risk of cancer. In men with a normal DRE and PSA between 4 and 10 ng/ml, a PSAD greater than 0.15 indicates a higher risk of prostate cancer, so a biopsy should be advised or, if there is a prior negative biopsy, re-biopsy should be recommended.[34]

What is PSA velocity (PSAV)?

PSA velocity (PSAV) is the increase of PSA per year. This is calculated by using three or more PSA values taken over 18 months or more.

It has been shown that a PSAV of greater than 0.75 ng/ml/year indicates a very high risk of developing prostate cancer more than five years later.[35, 36] Subsequent studies have suggested that a PSAV of greater than 0.5 ng/ml/year indicates an increased risk of prostate cancer. PSAV can also predict the response to treatment and the cancer-specific survival.[36–38]

What is PSA doubling time (PSADT)?

PSA doubling time (PSADT) is the time that it takes for the serum PSA to double in value. The pre-treatment PSADT predicts the outcome after radical prostatectomy as well as radiotherapy – the shorter the PSADT, the worse the prognosis. With PSA recurrence after treatment, the shorter the PSADT, the shorter the patient's survival. In general, a PSADT less than six to 12 months denotes a poor prognosis, whereas a PSADT of 18 to 24 months or more indicates a good prognosis.[39–42]

What is meant by PSA kinetics?

It is now well recognised that the changes in PSA values over time (PSA kinetics) are much more valuable than single PSA values.[43] PSAV is usually calculated by simple linear regression, and PSADT is calculated by log linear regression using all available PSA values.[42,44]

PSAV and PSADT can be easily determined by using a calculator such as that available on the website of the Memorial Sloan Kettering Cancer Centre (MSKCC) at http://www.mskcc.org/.

How useful is PSA testing?

The greatest clinical value of PSA is in predicting and following the response to treatment of patients with prostate cancer.[28] The higher the pre-treatment PSA, the worse the prognosis, regardless of therapy.[45] After radical prostatectomy an increasing PSA is an early indicator of treatment failure. The time to PSA recurrence (biochemical failure) after radical prostatectomy is an important prognosticator – the shorter the time to PSA recurrence, the shorter the survival.

The PSA nadir (lowest level) as well as the time to PSA increase after radiotherapy are important prognosticators – the higher the nadir and the shorter the time to PSA increase, the worse the prognosis.[45] With androgen-deprivation therapy the prognosis correlates with the PSA nadir (lower nadir indicates longer survival), the time to reach PSA nadir (shorter time equals longer survival) and the time to PSA increase (shorter interval indicates poorer prognosis).

Although PSA generally correlates well with prognosis, an increasing PSA does not mean that the patient will die when the PSA has reached a certain level. Laboratory assays have an upper limit, and measuring PSA levels above this limit requires serial dilution of the specimen, therefore laboratories sometimes only report the PSA as 'more than 100 ng/ml' when it exceeds the detection limit. However, with serial dilution very high PSA levels can be measured – the highest in this author's experience is a reported value of 157 000 ng/ml (almost 40 000 times more than the traditional 'normal' value of 4 ng/ml).

Therefore, patients can be reassured that PSA is of secondary importance compared with symptoms, so that they do not become obsessively anxious about a rising PSA and do not insist on repeated testing at intervals less than six to three months. As long as the patient is symptom-free and feels well, he should forget about his PSA and let his doctor worry about it.

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