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WHAT EVERY DOCTOR WHO TREATS MALE PATIENTS SHOULD KNOW

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Prostate cancer diagnosis clinical practice guidelines:

Every man should have an annual PSA and DRE starting at forty years of age even though current guidelines suggest fifty as appropriate. Men at risk due to race or a family history of prostate cancer (brothers, fathers),1-3 and men with a family history of breast cancer (mothers, sisters, aunts)1,4-6 should begin annual screening at age 35. Racial factors also contribute to risk of prostate cancer. Black men seem to have the highest incidence of prostate cancer, followed by Hispanic men.

U.K. National Cancer Programme guidelines advise that a PSA of 3.0 and over at any age should be investigated to rule out prostate cancer (PC), although some prostate cancer experts advocate 2.0 as being more appropriate.

A first step in an investigation of an elevated PSA should be the determination of the free PSA percentage.

• A free PSA percentage of over 25% is associated with a low risk of prostate cancer.

· A free PSA percentage of under 15% is associated with a higher risk of prostate cancer.7

• A benign cause of an elevated PSA and a correspondingly low free PSA percentage could be prostatitis. Four to six weeks of ciprofloxacin or similar antibiotic should be prescribed prior to recommending a biopsy if prostatitis symptoms are noted and/or if expressed prostatic secretions (EPS) are consistent with prostatitis. At the end of the antibiotic therapy, a repeat PSA determination should be made. If there is significant lowering of the PSA, an element of prostatitis is most likely present. The PSA value after antibiotic therapy will more aptly reflect the status of the patient in the situation where PC is subsequently established. It should also be emphasized that although the PSA may significantly decrease after antibiotic therapy, it is still important to do further PSA testing at regular intervals to determine if a serial progressive rise in PSA is occurring. It is the nature of the PSA kinetics, i.e. change in PSA over time, that is very helpful in discerning whether or not a malignant process is likely present.

• BPH (benign prostate hyperplasia) does not cause a low free PSA percentage. It may cause an elevated PSA, however. Therefore, in the case of an elevated PSA but a high free PSA percentage (equal to or greater than 25%), an estimate of gland volume by DRE or via transrectal ultrasound of the prostate may reveal findings consistent with a diagnosis of BPH. A general rule of thumb is that an accurate gland volume (best determined by transrectal ultrasound of the prostate) x 0.066 will equal the amount of benign-related PSA. Therefore, assuming only the presence of BPH, a 60-gramme or 60 cubic centimetre prostate is entitled to secrete approximately 3.96 ng of PSA into the blood.

Blood sampling for PSA determinations, done at least three months apart, and by the same laboratory using the same testing procedure, is necessary to establish PSA velocity (PSAV) and PSA doubling time (PSADT). The validity of such determinations is increased if such testing involves at least three determinations over an 18-month span of time. However, a progressive and serial increase in PSA values should raise flags of concern that prostate cancer is present and a greater degree of vigilance is mandatory.

· A PSAV that exceeds 0.75 ng/ml/yr is associated with a higher probability of PC.8

· A PSADT of less than 12 years is associated with a higher probability of PC.

A PSA value that bounces up and down is more indicative of a benign process than a malignant process.

A PSA that shows a persistent rise over time, particularly three consecutive rises, three months apart is suspicious for PC regardless of the level of the PSA. As mentioned above, gland volume in cubic centimetres (cc) multiplied by 0.066 yields the amount of PSA produced by the benign-related epithelial cell population of prostate cells. Any amount of PSA in excess of this should be considered to be produced by a malignant process, until proven otherwise. Systematic biopsies of the prostate under ultrasound guidance, however, must be considered mandatory when clinical &/or laboratory findings suggest the possibility of prostate cancer.

An approach using biological detection techniques such as those described above would eliminate advanced presentations of PC. Annual screening in this manner presents us with an opportunity to detect localised PC in over 95% of men.9 Such statistics offer an outstanding chance for a curative approach to this disease.

An approach involving these profiling techniques allows the patient-physician team to discern the very slow growing (indolent) presentations of PC that may be monitored using watchful waiting as opposed to the standard PC cases for which local treatments typically result in long term biological non-evidence of disease. Most importantly, attention to PSA kinetics accomplished by monitoring the PSA and PSA derivatives such as free PSA percentage, PSADT, PSAV and other calculations, should result in an almost total disappearance of highly aggressive presentations of PC. It is the latter that is associated with rapidly progressive disease and fatalities.

These opposite extremes in the clinico-pathological nature of PC, i.e. the indolent "pussycats" variants versus the aggressive "tigers" ones, are important to differentiate due to the highly different evaluation and management recommendations advised for each circumstance.

Indolent versus Aggressive PC ("Pussycats" Versus "Tigers")

Pussycats in general, have low PSA values (under 10) and long doubling times (greater than 24 months and often 48 months or longer), as well as low PSA velocities ($0.75 \text{ ng/ml/yr} \pm 10\%$). If a biopsy is done on a patient with a PSA that is under 10, the Gleason score often turns out to be (3,3). Depending on the calculated tumour volume, clinical stage, PSA doubling time, and other factors, these objectified biologic parameters may allow many such patients to be candidates for objectified observation ("watchful waiting"). Of course, these patients are also candidates for any of the currently available local therapies. Patients who choose to monitor their illness rather than seek immediate local therapy must be cognisant of the significance of change over time, or trend. They need to be aware that if manifestations of disease progression become evident, re-evaluation of their situation is warranted. In such circumstances, consideration must be made for some form of local treatment-before the window of opportunity for successful local therapy is lost.

Tigers in general, have high PSAs (over 10), OR very low PSAs associated with very aggressive, high Gleason score [(4,3), (4,4), (4,5), (5,4), (5,5)] cancers. These are very dangerous because they often escape investigation for long periods of time since the PSAs appear to be in the so-called normal range. Investigating all PSAs at 2.0 and over will help to catch these prostate cancers while they are still organ-confined and treatable with local therapies. The probability of spotting these low PSA/high Gleason score cancers is enhanced if patients and doctors monitor PSA levels over time. Such a practice will detect persistent increases in PSA, even if the absolute value of PSA is very low. High Gleason score cancers often have reverted to such a primitive state that they no longer secrete PSA into the blood. Checking the serum for elevations in other markers such as CGA (Chromogranin A), NSE (Neuron Specific Enolase), CEA (Carcino-Embryonic Antigen) and PAP (Prostatic Acid Phosphatase) is important to discern PC activity secondary to de-differentiated tumor cell populations. Although many physicians consider PAP to be an obsolete test, three contemporary peer-reviewed publications have concluded that PAP testing is of major prognostic value in the newly diagnosed man with PC.10-12

Therefore, in cases designated as "tigers", the normal guidelines for PSA velocity and doubling time may not be applicable. However, the concept of slope or trend in a biomarker of disease activity remains valid, and

any biomarker elevation should be tracked at regular intervals to determine the presence of abnormal growth of primitive tumor cell clones.

CONCLUSIONS:

If we scientifically observe the biological manifestations of prostate health or disease, we can detect PC at a time when currently available therapies are most likely to cure the most common malignancy facing man. If we ignore these biological communications that are red flags to alert us to the presence of a threat to our life, a vital opportunity to change the course of an illness is missed. The loss of life, productivity, and the extreme costs to the health care system-all of which result from a late-stage diagnosis of this disease-should provide impetus for all of us to be proactive when it comes to an early diagnosis of a malignant condition. This fundamental concept has been heralded for many malignancies, such as cancer of the cervix, lung cancer, colorectal malignancy and breast cancer. When will we make the same connection when it comes to men with PC?13 Aren't the almost 100,000 lives lost each decade in the U.K. too great a price to pay?

RESOURCES FOR PHYSICIANS AND PATIENTS:

In the U.K. and on the Web:

The Prostate Cancer Charity is a source of good prostate cancer literature and has an excellent helpline. Address: 3 Angel Walk, London W6 9HX. Confidential Helpline Tel. +44 (0)845 300 8383, Web site: www.prostate-cancer.org.uk.

Prostate Research Campaign, UK, 10 Northfields Prospect, Putney Bridge Road, London SW18 1PE. Tel. +44 (0)208 582 0248. Web site: http://www.prostate-research.org.uk/. Email: infor@prostate-research.org.uk.

The Prostate Cancer Research Institute (PCRI) Web site at http://www.pcri.org. This site has a wealth of information including the Prostate Cancer Address Book, which lists expert prostate cancer physicians, software tools, and articles and downloadable issues of the publication PCRI INSIGHTS.

Us TOO! INTERNATIONAL at http://www.ustoo.org/. This is the world's largest independent, charitable network of education and support groups for men with prostate cancer and their families, with groups worldwide.

In print:

"A Primer on Prostate Cancer, The Empowered Patient's Guide" by Stephen B. Strum, MD, FACP and Donna Pogliano, Second Edition, copyright 2005, now also available in the German language. The Primer is available at web booksellers such as www.amazon.com, http://www.barnesandnoble.com, and www.lefprostate.org. It can also be ordered through the Life Extension Foundation (+1-866-820-7457) and at Barnes & Noble, Borders, and other fine bookstores everywhere. This is an in-depth guide about prostate cancer that presents a comprehensive approach to the diagnosis, evaluation and selection of therapies currently available to the prostate cancer patient. It consists of 368 pages of fully indexed text with 168 full color graphics to enhance a clear understanding of prostate cancer. It is intended to bring the patient-partner-physician team involved with prostate cancer from a basic understanding of this disease to a highly sophisticated level of understanding.

Working together, we can achieve vast inroads into the diagnosis, evaluation and treatment of this illness.

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