PSA:
The Benefits of Screening

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The discovery and clinical application of tumour markers in oncology has significantly enhanced our ability to diagnose, treat and follow patients with a variety of neoplasms. By allowing for earlier detection before treatment and earlier evaluation of recurrences after definitive therapy, these markers have the potential to impact morbidity and mortality and allow physicians to alter the natural course of certain conditions. The research into new markers will undoubtedly continue to impact the care of cancer patients.

PSA utilization

The utilization of PSA in its association with carcinoma of the prostate has greatly impacted the ability to diagnose and treat this common urologic malignancy. Its discovery in 1979 and subsequent widespread usage starting in the early 1990s has led to significant stage migration of detected prostate cancers to lower the volume of organ-confined disease.

PSA and prostate cancer

Today, the majority of prostate cancers diagnosed in North America are incidental and clinically localized, with serum PSA measurements between 2.5 ng/ml and 10 ng/ml. This is in stark contrast to the 1980s, in which clinically palpable disease on a digital rectal exam (DRE) was most common, with a significant proportion of men presenting with locally-progressive disease. In the Surveillance, Epidemiology and End Results (SEER) database, the percentage of prostate cancer patients with metastatic disease at the time of diagnosis decreased from 16% in the period between 1985 to 1989, down further to 4% in 2003.

In addition, more recent SEER data demonstrated relative five-year survival rates of 100% for local/regional prostate cancer, compared to 33.5% for distant disease. The overall five-year survival was 99.8%, demonstrating that a large proportion of prostate cancers are now diagnosed earlier. This is evident in the overall relative five-year survival rate, which has increased from 75% in 1983 to 1985 to > 99% in 1999 and 2000.

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Experts agree that PSA-based screening is a major contributory factor for this survival improvement. A 32.5% decrease in the age-adjusted prostate cancer mortality rate has also been documented in the US since the introduction of PSA screening. A similar 33% decline in prostate cancer mortality rate was reported by Bartsch, *et al* 10 years after the introduction of free PSA screening in Austria.

Several recent studies have demonstrated that the stage migration can be translated into a prostate cancer mortality reduction.

Population screening and PSA

Although the utilization of serum PSA in men with prostatic disease is widely practiced, population screening in asymptomatic men remains a controversial topic, largely due to the low specificity of PSA in detecting cancer. While modern-day oncology research has yet to uncover a tumour marker as efficient and reliable as PSA in prostate cancer patients, the risk of identifying men with conditions such as benign prostatic hyperplasia (BPH), as well as those with indolent non-life-threatening prostate cancer is real. There is also an inherent risk of subjecting men to unnecessary prostate biopsies which carry with them the risks of physical discomfort as well as psychological and emotional trauma.

Benefits of PSA screening

The benefit of PSA screening is that it addresses a serious and growing healthcare concern, with a well-understood latent phase, in a minimally invasive and cost-effective way. As the course of prostate cancer from latency to declared disease is well understood, it offers men with a good life expectancy the opportunity for earlier diagnosis in order to treat aggressive disease early on in its stages to limit disease-related morbidity and mortality.

The American Cancer Society and the American Urological Association have published statistics demonstrating a 35% decrease in prostate cancer mortality since the onset of PSA screening in the early 1990s. The PSA-induced stage migration has allowed for earlier cancer detection, with a 50% reduction of metastatic disease at presentation. Additionally, a recent analysis documented a 50% reduction in disease specific mortality.

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Despite this aforementioned data, the use of PSA for screening has led to focus on the inherent lead-time bias. Secondary to this aspect of PSA-based cancer detection, patients with indolent, non-life-threatening disease may be subjected to significant and unnecessary treatment-related morbidity. This over-detection has been supported by autopsy studies documenting significant rates of prostate cancer in men in the fifth and sixth decades of life. The emotional burden of diagnosis and difficult decisions, coupled with no proof of overall survival (despite a clear disease-free survival advantage) further complicates this debate. To avoid this, several series have tried to define preoperative factors that could limit over-diagnosis. The vast array of cancers can (with 100% certainty) be differentiated between those cancers that will behave indolently and those that, if left untreated, might progress to a clinically relevant disease. Nevertheless, numerous studies have confirmed the prognostic significance

of the PSA level at diagnosis, especially when used in conjunction with and other clinical and pathological prediction tools.

Controversy

Much controversy exists regarding the threshold serum PSA level at which biopsy might be recommended to rule out the possibility of prostate cancer. The concern is that too low a value might increase the number of negative biopsies performed. In one study, using data from the National Health and Nutrition Examination Survey, reducing the PSA threshold from > 4 ng/ml to > 2.5 ng/ml was demonstrated to have increased the number of men labelled abnormal by 1.8 million. Although many of these men would have PSA rises over time that would ultimately lead to biopsy anyway, moving the PSA values to a lower cut-off would move the time of biopsy up, thereby increasing the chance of detecting organ-confined disease ripe for cure. This fact may be crucial for those with low PSA producing high-grade disease, as the cancer might present incurable with a PSA of 4 ng/ml. Further randomized controlled trials (*i.e.*, European Randomized Study of Prostate Cancer [ERSPC] and the Prostate, Lung, Colorectal and Ovarian cancer [PLCO] screening trial) whose results are expected in 2008 to 2009, will further elucidate if PSA screening has a mortality benefit and cost effectiveness.

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PSA kinetics: Is there an appropriate cut-off level?

Classically, the 4 ng/ml mark was used as a threshold for the recommendation of transrectal prostate biopsy. However, recent evidence revealed poor sensitivity in those < 60-years-old. A further decrease of the threshold to 2.6 ng/ml increases sensitivity to 36%. Attempts at improving these numbers migrated into the utilization of age-specific PSA ranges, in which the increasing prostatic size and contribution of BPH to serum PSA is taken into account. Other factors that contribute to elevated PSA levels are a recent vigorous DRE, in which the PSA can rise 2.5 times the baseline value for 24 hours, as well as recent cystoscopy. Transrectal prostatic biopsy, transurethral prostatic resection as well as infectious prostatitis can all increase serum PSA by as much as 50% above baseline. Ejaculation can also lead to a temporary 15% increase in PSA values, which normally returns to baseline within several hours (mean of one hour). The half-life of PSA is known to be 2.2 ng/ml, give or take 0.8 days.

Recent evidence from the Prostate Cancer Prevention Trial (PCPT) concretely demonstrated that there is no PSA value at which a man is guaranteed not to have prostate cancer. Participants from the placebo group with a normal DRE and a PSA level of < 4.0 ng/ml for the duration of the seven-year study were offered an end-of-study biopsy. Prostate cancer was detected in 15.2% of these men. Refer to Table 1 for the percentage of those studied that were detected with prostate cancer.

These results illustrate the difficulty in selecting a threshold PSA level to define what constitutes an abnormal PSA and that the measurement of PSA over time might constitute the most useful parameter as a continuous variable, providing a spectrum of prostate cancer risk.

PSA parameters

The effort to refine PSA-based diagnostics has led to the utilization of several PSA kinetic parameters, including:

- PSA velocity
- Free PSA
- PSA density

These measurements have recently gained considerable attention in their ability to predict rises of PSA attributable to cancer vs. benign prostatic disease. PSA doubling time is an alternative measurement of PSA kinetics, representing the amount of time necessary for the serum PSA level to double.

Free/total PSA measurement

PSA circulates in the bloodstream in both free and complex forms that can be individually detected by serum assay. Evidence suggests that in patients with prostate cancer, a greater proportion of PSA is bound; thus, a lower proportion circulates in free form. Catalona subsequently reported that measurements of the percentage of free PSA could be used to improve the accuracy of PSA testing, specifically in men with a total PSA level between 4.0 ng/ml and 10 ng/ml. He demonstrated that if the percentage of free PSA was > 25%, only 8% of patients were found to have cancer on biopsy; whereas, if the percentage of free PSA was < 10%, 56% of men were found to have cancer. He also showed that 75% of men with prostate cancer had a percentage of free PSA > 15%, having favourable pathological features at radical prostatectomy, compared to only 34% of men with a lower percentage of free PSA. Based upon these studies, in 1998, the Food and Drug Administration approved the free PSA test for prostate cancer detection. Further studies evaluating both free and complex PSA revealed that it can be found in significantly higher concentrations in men with prostate cancer and a complex PSA of > 3.75 ng/ml and is more specific for prostate cancer diagnosis compared to a total PSA of > 4.0 ng/ml.

Table 1

Results of the Prostate Cancer Prevention Trial (PCPT)

PSA	Detection of prostate cancer
0 to 0.5	6.6%
0.6 to 1.0	10.1%
1.1 to 2.0	17.0%
2.1 to 3.0	23.9%
3.1 to 4.0	26.9%

More recently, various isoforms of free PSA have been evaluated as a means to increase the specificity. Thus, the relative proportions of free and complex PSA can be used to enhance the specificity of PSA testing for prostate cancer. Additional research is underway to further elucidate the relationships between free PSA isoforms with prostate cancer aggressiveness and potentially with treatment outcomes.

PSA density

The underlying concept supporting the use of PSA density is that a given rise of serum PSA is more likely to be caused by a cancer in a smaller gland than in a patient with significant BPH. Previous studies denoted that the utilization of PSA density increases the specificity of diagnosis in large glands and increased the sensitivity in larger glands, both in patients with normal DREs and PSAs between 4 ng/ml and 10 ng/ml. Several studies have indicated that a higher PSA/prostate volume ratio correlated with a higher rate of prostate cancer. Catalona examined PSA density in the setting of treatment outcome and demonstrated that 74% of patients with a preoperative PSA density of 60.15 had a favourable pathology, compared to 36% of patients with a higher PSA density.

A major limitation of the technique is its dependence of the prostate gland measurement via transrectal ultrasound. While sonographic imaging of the prostate has correlated well with actual prostatic size, it is highly operator dependent.

Recently, this modality has been demonstrated to be unreliable, having an unacceptably high rate of false-negative diagnoses.

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PSA velocity

Further research into PSA parameters identified PSA velocity as a potential tool to refine PSA prognostication. It was observed that the rate of PSA change is greater in those that have underlying prostate cancer. Initially, it was demonstrated that the risk of death with a PSA velocity of > 2 ng/ml per year is significant, even in the face of treatment such as radical prostatectomy. Recently, it was found that a PSA rise in the order of 0.75 ng/ml per year, with at least three measurements over a two year period, can correlate with an increase in prostate cancer detection on transrectal biopsy. Carter first reported on longitudinal PSA changes in a non-screening clinical setting. Subsequent analyses have further supported its continued use.

Several investigators have established the link between total PSA and PSA velocity and have demonstrated that patients with higher total PSA values are more likely to have elevated and worrisome PSA velocities. The National Comprehensive Prostate Cancer Network suggests using a PSA velocity cut-off of 0.5 ng/ml per year for recommending a prostate biopsy. PSA velocity was also studied by D'Amico and he demonstrated that men with a preoperative PSA velocity of > 2.0 ng/ml per year had a 9.8-fold increased relative risk of death from prostate cancer than men with a lower velocity.

A significant limitation of PSA velocity is the normal physiologic fluctuation in serum PSA levels. This becomes even more of an issue when different assays are used.

PSA doubling time

PSA doubling time (PSADT) is a parameter that has found use in both the diagnosis of prostate cancer as well as in the surveillance of patients after primary therapy. Due to the dependence of doubling time on the baseline PSA, its use has been described in patients who begin with similar PSA levels, habitually after treatment. D'Amico reported on a significant association between post-radiation PSADT less than six months and survival. Pound, *et al* demonstrated that men with a PSADT of > 10 months were more likely to remain free of metastatic disease for a five year period. In the pre-treatment population, Sengupta reported that men with a preoperative PSADT of < 18 months had an approximately six-fold risk of cancer-specific death after radical prostatectomy. PSADT is most used for post-treatment prognostication after PSA velocity failures.

Current recommendations

Despite much emphasis on PSA kinetics, the utilization of PSA in general cannot be used as the sole method to diagnose prostate cancer. Considering

that there is much controversy in the medical community about the use of PSA, both an annual DRE and a thorough history are vital adjuncts to the diagnosis of prostate cancer. Conflicts in recommendations of PSA usage play a large part in the misunderstanding of PSA in the clinical and screening settings. In 1997, the American College of Physicians recommended informed usage of PSA in men, rather than the screening of all men. This attempt to individualize the usage of PSA relies on the patient-physician relationship to define who might benefit from PSA screening. Conversely, the American Cancer Society recommended annual prostate cancer screening with both PSA and DRE beginning at the age of 50 and even earlier in men with strong risk factors, such as a positive family history. The American Urological Society supported this latter position, with the added expectation of a life expectancy of > 10 years, along with a discussion about the benefits of early detection. Catalona recommended screening at age 40, with strict recording of data in order to define appropriate PSA parameters. Comparison of initial values with age appropriate men can be used to define those patients whose PSA values should be repeated and those who should proceed to further work. If the PSA velocity is > 0.5 ng/ml per year, or the per cent of free PSA is < 10%, then the patient should be referred for transrectal biopsy.

Conclusion

PSA is arguably the most important tumour marker in modern-day oncology. It is an extremely powerful diagnostic test, as evidence by the general increase in PSA-related prostate cancer diagnoses guidelines for managing patients with elevated PSA values. These guidelines were created with the goal of maximizing the diagnosis and treatment of patients with aggressive forms of the disease, while limiting diagnostic and treatment morbidity for those patients with more indolent forms of cancer.

For many years, regulating boards have utilized PSA as a means of detection of prostate cancer as well as monitoring response to treatment. It continues to be a useful serum marker in oncology and specifically, prostate cancer risk. PSA parameters can serve as successful adjucts to total serum PSA in refining the cancer specific goal of the marker.

Further research will continue to redefine PSA usage, as well as introduce newer prostate cancer markers, such as proPSA and other PSA isoforms.

Intelligent and deliberate use of PSA for prostate cancer will continue to reduce prostate cancer mortality rates and should be a part of routine discussions and screening programs. Dx

Take-home message

- The utilization of PSA has positively impacted the ability to diagnose and treat carcinoma of the prostate
- Though PSA has proven disease specific reduction in mortality, population screening in asymptomatic men remains controversial due to the low specificity of PSA in detecting cancer
- PSA screening needs to accompany a discussion regarding the implications of receiving an abnormal value
- The PCPT trial has demonstrated that prostate cancer can be present at any level of PSA
- The use of PSA should accompany an annual digital rectal exam and history in men > 50-years-of-age and in African American men > 45-years-of-age

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