EDITORIAL

Diagnosis and overdiagnosis of prostate cancer: a personal view

The diagnosis of prostate cancer has been changed by the introduction of prostate-specific antigen (PSA) and transrectal ultrasound (TRUS)–guided spring-driven biopsies. Most prostate cancers develop in the peripheral zone of the prostate, and may then be palpated before becoming symptomatic and early enough to be curable. However, digital rectal examination (DRE) is notoriously inaccurate and its relevance in the PSA era may be decreasing. Whereas DRE has a roughly 30% positive predictable value for prostate cancer, case control studies have found that up to 25% of cancer may be found only by such examinations and result in a 20% to 30% reduction in corresponding cancer mortality.[1] Therefore, despite its low positive predictive value, DRE is still recommended as part of the routine screening regimen.

Transrectal ultrasound is the most common approach for imaging the prostate, and has the advantage of being able to visualise lesions in the prostate that are not palpable. In general, TRUS of the prostate is a readily accepted, fairly simple procedure that affords excellent visualisation of the gland. However, the procedure is hampered by its poor performance characteristics with respect to sensitivity and specificity for detecting carcinoma, and has led most investigators to conclude that TRUS as a 'stand-alone' screening tool has little usefulness for initial diagnostic workup. Nevertheless, TRUS is a necessary instrument for accurately spaced systematic biopsies. Guided TRUS biopsies, using spring-driven instruments, can remove multiple (8-12) cores of prostate tissue in a relatively painless, highly accurate and safe way. When volume of cancer is measured in each biopsy core, along with the percentage that is Gleason grade 4 and 5, TRUS represents a powerful tool for predicting extracapsular cancer and microscopic metastases in the pelvic lymph nodes.[2]

Prostate cancer tissue elevates serum PSA levels of about 3.5 ng/mL per gram of cancer tissue while in benign prostatic hyperplasia (BPH) they increase only about 0.3 ng/mL per gram of BPH tissue.[3] Since its discovery in 1979 to its clinical application in the late 1980s through 1990s, PSA has evolved into an invaluable tool for the detection, staging and monitoring of men diagnosed with prostate cancer. Although PSA is widely accepted as a prostate cancer tumour marker, it is organ specific and not disease specific. There is an overlap in the serum PSA levels among men with cancer and those with benign disease. Early studies established the reference range of ≤4.0 ng/mL to define normal serum PSA levels. Catalona and associates[4] detected prostate cancer in 22% of a group of men who underwent biopsy at PSA levels of 2.6 to 4.0 ng/mL and had non-suspicious prostate examinations. The choice of a PSA cut-off point above which one would recommend further evaluation to rule out prostate cancer is controversial. Currently, serum PSA levels as low as 2.6 ng/mL are used as a threshold to perform prostate biopsy. Although up to 30% of men presenting with an elevated PSA may be diagnosed with prostate cancer following this invasive procedure, as many as 70% are not found to have cancer.

Measurable PSA exists either as complexed form (cPSA) or as a free form (fPSA). Although the majority of serum PSA is found complexed to proteins, 5% to 35% exists as fPSA. Men with prostate cancer have a greater fraction of serum PSA complexed to proteins and a lower percentage of total PSA that is free compared with men without prostate cancer. Using this important observation led to the measurement of the ratio of free to total PSA (% fPSA) and has since provided an additional degree of specificity for prostate cancer detection.[5] Application of PSA derivatives such as molecular derivatives have attempted to improve the specificity, but this will undoubtedly impair its sensitivity. For the time being it seems sensible to continue using cut-off values of PSA.

Because of PSA's low positive predictive value, up to 75% of men with levels in the range of the 2.5-10 ng/mL and/or suspicious DRE findings still have negative biopsies. These biopsies must be viewed not only from an economic point of view, but also from the perspective of the anxiety and discomfort they generate, and the severe complications they may give rise to. Thus, there is a need for additional tests to increase the probability of detecting prostate cancer and reducing the number of unnecessary biopsies. In this respect, the Prostate CAncer gene (PCA-3) assay, a new prostate cancer gene-based marker, has shown promising results.

Expression of PCA-3 protein has been localised to prostatic tissue and de Kok and colleagues[6] showed a 66-fold up-regulation of this protein in cancerous as opposed to normal control tissue. Using a real-time quantitative reverse transcriptase polymerase chain reaction assay, it is possible to detect PCA-3 in

urine specimens from men with prostate cancer. To enhance the sensitivity of such assays, urine samples have to be collected after DRE, which conceptually will loosen and shed the cells within the prostate and therefore enhance the chance of detection. Several clinical studies have evaluated the utility of PCA-3 to serve as a prostate cancer biomarker. However, despite supporting evidence for the beneficial role of PCA-3 in diagnosing prostate cancer in the western population, information regarding its utility in the Chinese is scanty. Thus, in this journal issue, Ng and associates[7] provide some insight on the role of PCA-3 in diagnosing prostate cancer in a Chinese population.

Notably, PSA testing continues to be one of the most controversial topics in cancer screening. The potential benefits include prevention of prostate cancer morbidity and mortality, but men may be harmed through overdiagnosis and overtreatment. Two important studies demonstrated a mortality benefit: the European Randomized Study of Screening for Prostate Cancer (ERSPC[8]) and the overlapping Göteborg trial.[9] The other large randomised controlled trial, Prostate, Lung, Colorectal, Ovarian (PLCO) cancer screening trial[10] showed no mortality benefit for organised annual screening compared to opportunistic screening. Many explanations account for the discrepancy in results between these studies, including high rates (52%) of opportunistic PSA screening in the control arm of PLCO trial and differences in treatment between two arms in the ERSPC study. Investigators in the ERSPC trial estimated that 37 men would need to be screened and treated (NNT) to prevent one prostate cancer death after a median 11 years of follow-up; in the Göteborg trial,[9] the NNT was 12 after 14 years. Based on the best available evidence, screening with PSA testing is associated with modest improvement in mortality.

The harms of PSA screening include false-positive test results in up to 13% of screened men[8] and can be associated with significant psychological distress, in addition to the potential adverse effects of biopsy (bleeding, urosepsis, and acute urinary retention). Many men diagnosed with prostate cancer by screening have low-risk disease, which is associated with a low risk of prostate cancer–specific death after 15 years. Currently available screening tests are not able to identify which individual requires treatment and which men have disease that is truly clinically insignificant. Overdiagnosis means either non-progressive or very slow–growing cancers are identified, they pose no real threat to the patients. The problem is that it can be difficult to determine with confidence when a cancer diagnosis amounts to overdiagnosis. Attention is now turning to the questions of how to limit the harms that result from PSA screening, namely, how to mitigate the conversion of overdiagnosis into overtreatment.

Active surveillance has emerged in recent years as an option for initial treatment for low-risk disease. In this management strategy, men with low-risk prostate cancer are followed closely after diagnosis, and treated with curative intent only if their disease exhibits more aggressive behaviour. This approach differs significantly from watchful waiting, in which men, usually older men with significant co-morbidities, are offered only palliative treatment if they develop symptoms from their cancer. Prospective studies of active surveillance have entailed only limited follow-up; 30% of the men involved had been treated, and enjoyed a prostate cancer–specific survival of 97.2% at 10 years.[11] In the public mind, cancer is a lethal disease to be destroyed at all cost. This reaction can lead to overtreatment, with significant side-effects and costs. Patient education is a key solution to the problem of overtreatment.

Screening for prostate cancer appears to be based on the best data from randomised trials to reduce cancer mortality. However, reducing over-treatment in patients diagnosed with insignificant disease is critical to the success of screening. Active surveillance is a major step forward in addressing that concern. Genomics and biomarkers hold the promise of more accurate prediction of individual tumour behaviour. In 2012, however, these still have not achieved widespread application and acceptance.

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