Need for biomarkers in active surveillance of prostate cancer

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Although about one in every seven men will be diagnosed with prostate cancer in their lifetime, the mortality rate remains low with a 99% five-year survival rate for low to intermediate grade disease [1]. Aggressive treatments may not necessarily be required for indolent disease. Following diagnosis, surgery (radical prostatectomy), radiation therapy, hormonal therapy and chemotherapy either singly or in combinations are currently regular options for initial treatment. However, active surveillance may be a more appropriate option for less advanced and low grade disease. Active surveillance is a form of expectant management where disease progression is carefully monitored until such time as an intervention should be required. Careful, informed decision-making between the patient and his clinician is needed to determine the most suitable treatment choice. At present a diagnosis of prostate cancer is initially and most commonly made on the basis of three investigations: the prostate specific antigen (PSA) test, digital rectal examination (DRE) and biopsy-based grading of the tumour by histopathology. For many men it is accepted that these tests do not provide adequate information to support the decision of whether to pursue immediate treatment or active surveillance. Hence, there is a serious unmet need for specific and sensitive biomarkers to guide the decision between treatment and active surveillance, and for regular monitoring of disease progression in men on active surveillance. PSA is not sufficiently sensitive to inform this important decision; and biopsy is an invasive imperfect procedure with potential health risks, especially where repeat biopsies are undertaken.

We outline here the use of active surveillance in prostate cancer treatment and how new biomarkers might be developed in a patient-centered approach to guide it.

Active Surveillance

Prostate cancer is the second most common non-cutaneous cancer among men, second only to lung cancer. An estimated 180,000 men will be diagnosed this year in the UK, and about 26,000 of them will die from the disease [1]. These figures show that the majority will die with, not necessarily from prostate cancer [Figure 1]. This raises questions about whether, when and how to treat them. Men with low-risk disease have up to 100% relative five-year survival and would be good candidates for active surveillance. Conversely, men with aggressive metastatic disease have significantly worse outcomes, and require definitive treatment. As noted above, these four major interventions are initially used to treat prostate cancer; although these treatments (alone or in combination) can be curative, the disease recurs in many instances and becomes resistant to them. It is in this context that there have been some significant improvements in the armoury of treatments available in recent years. Significantly, these front-line treatments bring with them several side effects. Impotence, incontinence, and bowel dysfunction are common consequences

Table 1: Summary of Eligibility Criteria for Different Active Surveillance Guidelines

Guidelines	Risk Category	Tumour Features	Patient Profile
AUA	Low	Tumour stage T1c or T2a – Serum PSA ≤10ng/ml – Biopsy Gleason score ≤6	Not reported
	Intermediate	Tumour stage T2b – Serum PSA 10-20ng/ml – Biopsy Gleason score 7	
	High	Tumour stage T2c – Serum PSA >20ng/ml – Biopsy Gleason Score 8–10, ≤2 tumour positive biopsy core samples, ≤50% of tumour positivity per biopsy core, 10 cores sampled	
EAU	Low	Tumour stage T1c-T2 – Serum PSA >10ng/ml – Biopsy Gleason score ≤6, ≤2 tumour positive biopsy core samples, ≤50% tumour positivity per core	Life expectancy >10 years
NCCN	Very Low	Tumour stage T1c – Serum PSA <10ng/ml, PSA density <0.15 – Biopsy Gleason Score ≤6, <3 tumour-positive biopsy core samples, ≤50% tumour positivity per biopsy core	Life expectancy >10 years
	Low	Tumour stage T1-T2a – Serum PSA <10ng/ml – Biopsy Gleason score ≤6	
NICE	Low	Tumour stage T1-T2a – Serum PSA <10ng/ml – Biopsy Gleason score ≤6	Not reported
	Intermediate	Tumour stage T2b – Serum PSA 10-20ng/ml – Biopsy Gleason score 7	
PCFA	–	Tumour stage T1-T2 – Serum PSA ≤20ng/ml – Biopsy Gleason score 6	Not reported
NCCS	Low	Tumour stage ≤T2a – Serum PSA <10ng/ml, serum PSA density 0.15 – Biopsy Gleason score ≤6 (no Gleason grade 4 or 5), <3 tumour positive biopsy core samples, ≤50% tumour positivity per biopsy core	Life expectancy <10 years

of treatment that reduce the patient's quality of life [2]. It is in this complex interplay between the functional outcomes of the disease and treatments, social and psychological pressures that the patient and physician come together following diagnosis of prostate cancer to make the key decision of whether to accept active surveillance.

Active surveillance involves regular testing to monitor disease progression. Investigations can include PSA, DRE, biopsy and magnetic resonance imaging (MRI). While active surveillance seems an attractive prospect for the majority of men whose prostate cancer will not prove fatal, the key issue lies in determining those men that will succumb. Furthermore, current guidelines regarding patient suitability (Table 1) and methods for active surveillance vary widely [3], leading to large discrepancies in their use worldwide. In the US, only 9.6% of men opt for active surveillance [4] as opposed to Sweden where 59, 41 and 16% of those with "very low", "low", and "intermediate" risk prostate cancer, respectively, chose to defer any treatment [5]. A number of other factors influence this decision - age, comorbidities and personal lifestyle choices. Active surveillance has increased in recent years [6] and the trend appears to be moving towards greater reliance on this expectant management strategy of prostate cancer.

There is considerable debate about the classification of low-grade cancer, with some advising that Gleason grade 3+3=6 cancer be reclassified to reflect its limited pathological implications [7]. This will serve to increase the proportion of men kept under active surveillance and limit the undesirable side effects of any intervention. As the International Society of Urological Pathology (ISUP) has proposed changes to the Gleason grading structure [8], so do the clinical guidelines for AS need to be reviewed and consolidated to keep up to date with the present circumstances. Consensus on the inclusion criteria, the testing intervals, and intervention thresholds need to be defined and applied if active surveillance is to become a preferred strategy for indolent prostate cancer.

Current Biomarkers and Available Tests

There is a significant, and as yet unmet, need for better biomarkers to support the clinical decisions relating to active surveillance [9]. Despite their promise of better biomarkers, the -omics research approach to finding them has brought little help to the clinic [10]. This, however, is an unsatisfactory situation that is about to change in the case of prostate cancer, where (as outlined above) the need for better biomarkers for selecting patients for active surveillance is well recognised and advances are being made. The tests currently used for diagnosis – PSA, DRE, biopsy – are repeated in active surveillance to assess the potential risk re-stratification of the disease. In combination with imaging modalities and other patient characteristics, these remain the mainstay for active surveillance monitoring.

Prostate-specific antigen (PSA), a protein produced by cells of the prostate gland (not specifically tumour cells) was initially discovered in the 1970's by Richard Ablin, which was subsequently developed by others into a diagnostic test. The PSA test was approved by the FDA in 1986 and quickly adopted as a screening test for prostate cancer. Despite its widespread use, there is no definitive diagnostic level of PSA and the test is not specific to prostate carcinoma [11]. Significant variability is found in assay results [12], which can (and do) combine to have profound implications regarding decisions on treatment. Around 25 million PSA tests and >1 million prostate biopsies are carried out annually in the US. Biopsies have inherent risks and complications [13]; a 12-core biopsy procedure samples only a fraction of the

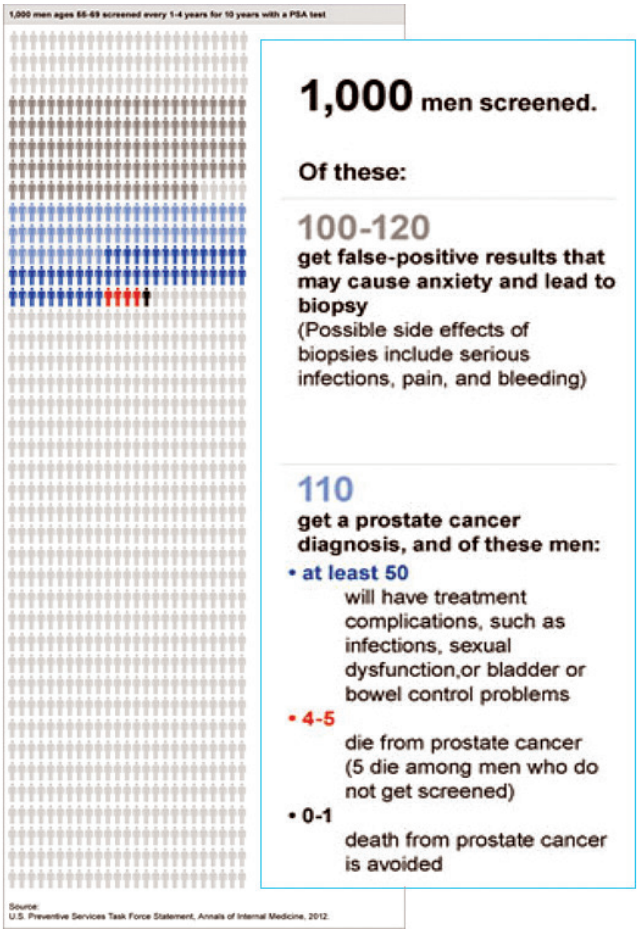

Figure 1: Screening for prostate cancer (adapted from http://prostatecanceruk.org)

prostate and incomplete sampling can influence the Gleason grading [14]. Efforts are being made to improve accuracy using multi-parametric magnetic resonance imaging (mp-MRI) to reduce over-diagnosis and unnecessary biopsying. MRI can also be used to detect more aggressive lesions and less accessible tumours [15]. MRI or MRI-ultrasonography fusion at the time of the initial diagnostic biopsy has greater sensitivity and negative predictive value than TRUS-guided biopsy [7]. Four international guidelines provided by NCCN, NICE, KCE and CCO consider the use of mp-MRI in active surveillance, but under varying conditions [3]. Increasing adoption of mp-MRI imaging methods worldwide could potentially allow urologists to monitor disease in an easier (less invasive) and more reliable manner.

In addition to traditional diagnostic investigations, there are a growing number of newer commercially available prostate cancer diagnostic and prognostic tests. ConfirmMDx (MDxHealth), Decipher (GenomeDx), OncotypeDx (Genomic Health), and Prolaris (Myriad Genetics Inc.) use prostate biopsy tissue to make measurements of disease severity and risk stratification. Starting at $1,800 (per test), these are relatively expensive. They also come with the well-established issues of biopsy sampling and logistical problems of transporting patient tissue. Less invasive tests using blood and urine samples, such as the 4K Score (OPKO Health, Inc.), Prostate Health Index (Beckman Coulter) and the recently reported ExoDx Prostate IntelliScore (Exosome Diagnostics) [16] aim to improve screening methods and predict which patients will develop aggressive disease. None of these tests are indicated for use in active surveillance, and thus there remains a serious need for non-invasive biomarkers for disease monitoring.

View from the Clinic – A Patient's Perspective

Here we have discussed the need for improved biomarkers and their swift translation into clinical tests for active surveillance in prostate cancer. Reliable tests to detect and monitor low to intermediate grade prostate cancer in a primary care setting are important for patients for a number of reasons. We discussed this issue with prominent prostate cancer patient advocates who had these views to offer:

- The current standard active surveillance treatment plan requires repeat visits to urologists, regular blood tests every 3-6 months, repeat DRE every 6 months, and biopies every 3 years.
- The initial alarm of prostate cancer is raised by an elevated PSA level. The PSA blood test was initially developed as a prognostic test to monitor the continued presence and activity of prostate cancer tissue left behind following radical prostatectomy – for which it is very effective. However using PSA to identify low-grade prostate cancer is likely to be unreliable.
- DREs are only accurate when carried out by an experienced urologist. A GP may be unreliable regarding this test when it is only done on an occasional basis.
- A biopsy completes the diagnostic testing and can confirm the presence of cancer cells and grade the tissue with a Gleason score. Because the biopsy is normally based on 12 samples, it is possible that, after an initial diagnosis of low-grade cancer, a repeat biopsy might show no sign of cancer. Does that mean the cancer is no longer there, or can it have progressed without this being picked up by a second biopsying?
- A man diagnosed at 60 years may be expected to have a biopsy 5-6 times by the time he is 75 years old.
- Each biopsy carries a risk of serious infection; repeated biopsies over a number of years can result in significant scar tissue in the prostate gland. Should the prostate cancer become more aggressive to the point that radical prostatectomy is required, the surgery to remove the prostate is more complex, with a much higher risk of incontinence.
- All this unpredictability can give rise to significant anxiety in a patient, and lead to increased costs.

Future Directions

Biomarker tests are needed that facilitate continuous testing and close monitoring of prostate disease. The tests have to be sensitive, specific and, when combined with other data, have a defined standard threshold to clearly indicate when intervention is required. Ideally such biomarkers should help to determine the most suitable treatment. Notably, companion diagnostics that measure the expression of an androgen receptor variant (AR-V7) are currently being developed to predict patients' responses to treatment with enzalutamide and/or abiraterone [17].

Proteomics based strategies - including the use of mass spectrometry - are being used for greater understanding of prostate cancer protein networks [18], and protein biomarker discovery and evaluation [19]. Mass spectrometry offers end-to-end control of the biomarker development pipeline and a sufficiently sensitive and robust platform for incorporation into clinical diagnostics laboratories. It is for these reasons that interest in mass spectrometry methods that allow targeted measurement of multiple protein biomarkers simultaneously is growing rapidly.

Conclusions

Establishing a consensus on inclusion criteria, testing intervals and intervention thresholds will strengthen the choice of active surveillance as a management modality for prostate cancer. At the same time, as we move towards a more personalized medicine framework for healthcare in general, clinical context-specific and patient-focused research are likely to be important factors in the success of future biomarker discovery and development efforts. In this setting there is significant optimism that much needed biomarkers indicating less invasive behavior, and hereby support active surveillance, will be developed. In our view, such biomarkers may include proteins discovered and measured by new mass spectrometry methods that are increasingly amenable to clinical diagnostic use.

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